

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (Review of TA95 and TA120)

This overview is a summary of:

- the assessment report
 - clinical effectiveness, section 4 , pages 12-37
 - cost effectiveness, section 6.21 onwards, pages 52-74
- evidence and views submitted by the manufacturers (joint industry submission)
 - clinical and cost effectiveness, section 6.5-6.20 pages 41-52
- evidence and views submitted by non-manufacturer consultees and their nominated clinical specialists and patient experts, section 5 pages 37-40.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- The joint industry submission and the Assessment Group take different approaches to this appraisal.
 - The manufacturers use individual patient level data from trials, and ask the questions which subgroups are those in which the devices are effective (The manufacturers approach is described in **sections 6.5 to 6.20.**)
 - The Assessment Group uses study level data, and asks the question whether the devices are effective in the populations defined in the scope.
- What are the advantages and disadvantages of each approach?

- The evidence included in the Assessment Group report includes all clinical evidence, that is evidence reviewed in TA95 and TA120, and new evidence.

What evidence is new and important since the previous NICE appraisal of these devices?

- When deciding whether patients should receive an ICD or CRT, which of the following clinical characteristics should clinicians take into account: NYHA criteria, presence or absence of atrial fibrillation, presence or absence of documented 'dyssynchrony', presence or absence of left bundle branch block, ejection fraction, and /or QT interval on ECG?
- Is an ischemic aetiology important in determining which devices are appropriate for which patients?
- Is it possible to identify patients at high risk for sudden death (who have never had a cardiac arrest), how would this be done, and what level of risk of sudden death is deemed 'high'?
- Trials used in the Assessment Group's study-level meta-analyses differed in population and design. Does the Committee consider that results from the assessment Group's meta-analyses are robust?
- The manufacturers presented network meta-analyses based on patient-level (rather than study-level data). The Assessment Group noted a limited evidence network, partial reporting of the exploratory analyses, lack of long term data and modest power to detect characteristics of patients more or less likely to respond to treatment. Does the Committee consider that results from the manufacturers' network meta-analyses are robust? Does the Committee have enough information about possible interactions between clinical criteria?
- Some of the trials compare the devices to optimal pharmacological therapy which the Assessment Group considers to be not always 'optimal'. Does this bias the results associated with the effectiveness of the devices?

Cost effectiveness

- In the Assessment Group's base-case analyses, patients could crossover and receive a device (or different device) if hospitalised because of heart failure or arrhythmia, using estimates of the risk from trials. Does the Committee consider that this is an appropriate approach to establish the cost effectiveness of the devices? Does the Committee consider that an analysis that explicitly explores a series of the potentially available treatment sequences is required?
- The Assessment Report addendum describes scenario analyses which exclude crossover from the OPT only arm to a device. However, these analyses resulted in slight increases in ICERs for devices compared with OPT. This is because the increased relative benefits were counterbalanced by increase relative costs. What is the Committee's view on these counter-intuitive results?
- The manufacturers' model did not allow crossover. Does the Committee consider that this is an appropriate approach?
- In the Assessment Group model the QALYs accumulated with OPT alone for population 3 were higher than in population 2 although population 3 has a worse prognosis than population 2 (see table 4 and 8, appendix C). Does the Committee consider that these counter-intuitive results point to a lack of robustness of the Assessment Group results?
- The Assessment Group has listed a number of limitations of the manufacturers' cost-effectiveness analyses (see section 6.20). Does the Committee consider that the results from the manufacturers' cost-effectiveness analyses are robust and that the sensitivity analyses provide enough information on what factors drive the model results?
- What factors does the Committee think drive the differences in results based on the Assessment group and manufacturers' models?

1 Background: clinical need and practice.

Arrhythmias

- 1.1 Arrhythmias occur when the heart contracts irregularly or at a faster or slower pace than normal, caused by an abnormality in the myocardial tissue of the atria or ventricles, or in the electrical conduction system. Arrhythmias that originate from above the ventricles (supraventricular or atrial) are generally not life threatening, but are associated with an increased risk of embolic stroke. Arrhythmias that arise from ventricles (ventricular arrhythmias) can happen suddenly and unexpectedly, and can sometimes be fatal. Ventricular arrhythmias include, among others, ventricular tachycardia and ventricular fibrillation. In ventricular tachycardia the ventricles beat faster than normal (between 120 and 200 beats per minute). In ventricular fibrillation electrical impulses rapidly start firing from multiple sites in the ventricles, resulting in an irregular rhythm and no effective output from the heart to sustain life.
- 1.2 Ventricular arrhythmias most commonly occur in people with underlying heart disease, including people who are having or had a myocardial infarction (heart attack), people with cardiomyopathy (a disease of the heart muscle), and people who have heart failure. Coronary heart disease, causing myocardial infarction leading to the ventricular tachycardia or ventricular fibrillation, is the most common clinical finding associated with sudden cardiac deaths, accounting for 80% of such deaths. Cardiomyopathies account for a further 10% to 15% of sudden cardiac deaths and there is likely to be significant overlap between this group and those with coronary heart disease. The remaining 5-10% of sudden cardiac deaths are associated with either structurally abnormal congenital cardiac conditions or structurally normal hearts with electrical abnormalities. People at higher risk of

sudden cardiac deaths include those who have previously survived a life-threatening arrhythmia, hemodynamic abnormalities including heart failure and acute coronary syndromes such as myocardial infarction and angina pectoris. However, in over 30% of sudden cardiac deaths, heart disease had either not been previously diagnosed or people were known to have cardiac disease but were considered to be at low risk for sudden cardiac death.

- 1.3 The Assessment Group estimate that around 75-80% of the estimated 70,000 sudden cardiac deaths in England and Wales in 2010 could be attributed to ventricular arrhythmias. The average survival of adults with an out of hospital cardiac arrest has been reported as low as 7%. With appropriate treatment and secondary preventive strategies, recent studies have reported 5 year survival of 69 to 100%. Preventing sudden cardiac death in someone who has never had a cardiac arrest or ventricular arrhythmia (primary prevention) is challenging in clinical practice because it requires identifying people with a sufficient level of risk, and an optimal strategy for risk stratification is currently lacking.
- 1.4 Treatment of ventricular arrhythmias acutely can consist of shocking a patient with an external defibrillator and then offering anti-arrhythmic drug therapy and other drug treatments specific to the underlying heart disease. Prophylactic anti-arrhythmic drug therapy aims to suppress the development of arrhythmias, but does not terminate an arrhythmia once it is initiated. People with arrhythmias at risk of sudden cardiac death may be given an implantable cardioverter defibrillator (ICD) device to detect and treat such arrhythmia. NICE technology appraisal guidance 95 recommends ICDs for both secondary prevention (that is, prevention of a further life-threatening event in survivors of a sudden cardiac episode or patients with recurrent unstable

rhythms) and primary prevention (that is, prevention of a first-life threatening arrhythmic event). For secondary prevention an ICD is recommended in people who have survived a cardiac arrest because of ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation) and in people with spontaneous sustained ventricular tachycardia causing syncope or significant hemodynamic compromise or who have LVEF of less than 35% but clinically are no worse than New York Heart Association (NYHA) class III of heart failure. For primary prevention it is recommended in people with a familial cardiac condition with a high risk of sudden death (for example long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia), or in people who have undergone surgical repair of congenital heart disease. It is also recommended as primary prevention in people with previous (more than 4 weeks) myocardial infarction (MI) who also have either LVEF of less than 35% but clinically are no worse than NYHA class III of heart failure and non-sustained VT on Holter monitoring plus inducible VT on electrophysiological testing or LVEF of less than 30% but clinically are no worse than NYHA class III of heart failure and have a QRS duration of equal to or more than 120 milliseconds.

Heart Failure

- 1.5 Heart Failure is a condition caused by any structural or functional cardiac disorder that impairs the heart's ability to function efficiently as a pump to support circulation. It is characterised by breathlessness, fatigue and fluid retention. Clinically it is classified using the NYHA functional class, ranging from Class I (no limitation of physical activity) to Class IV (symptomatic at rest and discomfort from any physical activity). Heart failure is also classified based on which heart function or which side of the heart is most affected:

some patients have heart failure due to left ventricular systolic dysfunction (LVSD) which is associated with a reduced left ventricular ejection fraction (left heart failure or biventricular failure); while others have only right heart failure with a preserved ejection fraction. The scope for this appraisal focuses on left and biventricular heart failure.

1.6 Heart failure is a chronic condition predominantly affecting people over the age of 50 years. The incidence of heart failure in the UK is 140 per 100,000 men and 120 per 100,000 women. Approximately 900,000 people in England and Wales have heart failure, of which at least half have LVSD. The incidence and prevalence of heart failure increases with age and the average age at first diagnosis is 76 years. People with heart failure are at risk from sudden cardiac death, which is the most common cause of death in people with mild to moderate heart failure. Progressive failure of the heart's ability to pump is usually the cause of death in case of severe heart failure.

1.7 Treatment of heart failure aims to improve life expectancy and quality of life. NICE clinical guideline 108, "Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care" recommends treating heart failure due to LVSD with angiotensin converting enzyme (ACE) inhibitors and beta-blockers. If a person then remains symptomatic, the guideline recommends adding one of the following as second-line treatment: an aldosterone antagonist licensed for heart failure (e.g. spironolactone) (especially NYHA class III–IV) or has had a recent MI] or an angiotensin II receptor antagonist (ARB) licensed for heart failure [especially if NYHA class II–III] or hydralazine in combination with nitrate [especially if the patient is of African or Caribbean origin and has NYHA class III–IV]. Other drugs recommended for heart failure include diuretics, calcium channel

blockers, amiodarone, anticoagulants, aspirin and inotropic agents (such as dobutamine, milrinone or enoximone. However, as the condition becomes more severe, cardiac function and symptoms may no longer be controlled by pharmacological treatment and require invasive procedures. Cardiac function and heart failure symptoms may be improved by the implantation of a cardiac rhythm device which can sense and stimulate the atria, right and left ventricles independently. The devices are known as cardiac resynchronisation pacemaker (CRT-P) or cardiac resynchronisation defibrillator (CRT-D). The decision to implant CRT is also guided by left ventricular ejection fraction. NICE technology appraisal 120 'Cardiac resynchronisation therapy for the treatment of heart failure' recommends CRT-P as a treatment option for people with heart failure who fulfil all the following criteria: are currently experiencing or have recently experienced NYHA class III–IV symptoms; are in sinus rhythm - either with a QRS duration of 150 ms or longer estimated by standard ECG or with a QRS duration of 120–149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography; have a LVEF of $\leq 35\%$; are receiving OPT. CRT-D may be considered for people who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD device as recommended in NICE technology appraisal guidance 95.

2 The technologies

Implantable cardioverter defibrillators (ICDs)

- 2.1 ICDs are small, battery powered devices that are implanted under the skin, typically just below the collarbone, with leads (tiny wires) into the heart. The devices operate by sensing and analysing the electrical activity of the heart thereby monitoring for arrhythmia and delivering electrical pulses or shocks to restore normal sinus rhythm. Based on average selling prices aggregated across all

manufacturers of ICDs sold in the UK to the NHS, the cost for ICDs was estimated at £9,692 for the whole system.

Cardiac resynchronisation therapy pacing device (CRT-P)

- 2.2 Cardiac resynchronisation therapy (CRT-P), also known as biventricular pacing, involves implanting a pulse generator in the upper chest to resynchronise the contraction of the ventricles, thereby improving pumping efficiency and increasing blood flow to the body. Based on average selling prices aggregated across all manufacturers sold in the UK to the NHS, the cost for CRT-P is at £3,411 for the whole system.

Cardiac resynchronisation defibrillators (CRT-D)

- 2.3 CRT-Ds combine CRT-P and ICD devices. A CRT-D defibrillates the heart internally in an acute arrhythmic event and improves ventricular efficiency and blood flow. Based on average selling prices aggregated across all manufacturers sold in the UK to the NHS, the cost for CRT-D is at £12,293 for the whole system.
- 2.4 Adverse events are mostly related to implantation-related complications and include coronary vein dissection, coronary vein perforation, lead dislodgement, infection and death. For details of adverse events related in the trials please see section 4.10, 4.30 and 4.43 and 4.55.

3 Remit and decision problem(s)

- 3.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of implantable cardioverter defibrillators in the treatment of arrhythmias and biventricular pacing (cardiac resynchronisation) to restore synchronous cardiac contraction in patients with advanced heart failure.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	<p>People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment</p> <p>People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment</p> <p>People with both conditions described above</p>	<p>This group includes and expands on the population considered in TA 95. For the present assessment this population is not restricted by NYHA classification and there is no specified cut-off for LVEF.</p> <p>The second group includes and expands on the population considered in the previous TA 120. As in the TA120, this population is not restricted by NYHA classification but unlike it there is no specified cut-off for LVEF.</p> <p>The third group, people with both conditions, were not considered in the previous technology appraisals.</p>

People with cardiomyopathy are not excluded from consideration in this assessment.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Intervention	<p>Implantable cardioverter defibrillators (ICDs) in addition to optimal pharmacological treatment</p> <p>Cardiac resynchronisation therapy (CRT-P or CRT-D) in addition to optimal pharmacological treatment</p> <p>Cardiac resynchronisation therapy with a defibrillator device (CRT-D) in addition to optimal pharmacological treatment</p>	<p>No additional comments or specifications.</p>

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Comparators	<p>For People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment:</p> <ul style="list-style-type: none"> • standard care (optimal pharmacological treatment without ICD) <p>For people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment:</p> <ul style="list-style-type: none"> • CRT-P and CRT-D will be compared with each other • standard care (optimal pharmacological treatment without CRT) <p>For people with both conditions:</p> <ul style="list-style-type: none"> • ICD • CRT-P • standard care (optimal pharmacological treatment alone) 	<p>The Assessment Group noted that a standard definition of optimal pharmacological treatment (OPT) was difficult because the concepts of OPT have changed over time and also depend on the patient population being treated, for example patients with previous ventricular fibrillation, post MI, or heart failure receive different pharmacological treatment.</p> <p>The Assessment Group included all studies that compared ICDs or CRTs with the different types of medical therapy and reported the details of the pharmacological therapy.</p> <p>The clinical-effectiveness section of this report therefore describes this as 'medical therapy', specifying where the Assessment Group noted this to be 'optimal' by current standards.</p>

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Outcomes	<ul style="list-style-type: none"> • mortality (may include progressive heart failure mortality, non heart failure mortality, all cause mortality and sudden cardiac death) • adverse effects of treatment • health related quality of life • symptoms and complications related to tachyarrhythmias and/or heart failure • heart failure hospitalisations • change in NYHA class • change in left ventricular ejection fraction 	No additional comments or specifications.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	No additional comments or specifications.

4 Clinical-effectiveness evidence

4.1 The Assessment Group conducted a systematic review of the literature and identified 26 relevant randomised controlled trials (RCTs): 13 trials comparing ICD with medical therapy in people at increased risk of sudden cardiac death as a result of ventricular arrhythmias (population 1); 4 trials comparing CRT-P (and CRT-D in one trial) with medical therapy in people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony, (population 2) and 9 trials comparing CRT-D with ICD in people with both of these conditions (population 3).

People at risk of sudden cardiac death as a result of ventricular arrhythmias (population 1)

4.2 The Assessment Group highlighted that all 13 RCTs identified were unblinded and therefore at high risk of bias, particularly in the context of quality of life outcomes. The trials used different criteria to identify groups at 'high risk' of sudden cardiac death from ventricular arrhythmia as categorised below:.

People with ventricular arrhythmia/cardiac arrest (secondary prevention)

4.3 The AVID (n=1016), CASH (n=288), CIDS (n=659) and DEBUT (n=66; pilot – 20 and main study – 46) trials evaluated ICD in combination with medical therapy compared with medical therapy

alone, as in people who had previous ventricular arrhythmia or had been resuscitated from cardiac arrest (secondary prevention). The DEBUT trial included people of Thai origin who had survived sudden unexplained death syndrome with otherwise normal hearts. The average length of follow-up varied from 18 months to 57 months across the trials. All participants in the CASH trial, 90% in the CIDS trial and 60% in the AVID trial had congestive heart failure, with more than 80% (CASH) and 50% (AVID, CID) classed as NYHA I and II. All participants in the DEBUT trial had NYHA class 1 congestive heart failure, and were also younger with a mean age of 40-48 years compared with a mean age of 56 to 65 years in the other trials. LVEF varied from 30% to 70% across the trials.

4.4 All four trials assessed all-cause mortality as the primary outcome measure. The Assessment Group noted that only the CASH trial was adequately powered to detect a difference in all-cause mortality and reported a risk ratio of 0.82 (95% CI 0.60 to 1.11) for ICDs compared with medical therapy. The AVID and the main DEBUT trials reported all-cause mortality risk ratios of 0.66 (95% CI 0.51 to 0.85) and 0.09 (95% CI to 1.57) respectively for ICDs compared with medical therapy. The CIDS trial reported a risk ratio of 0.85 (95% CI 0.67 to 1.10) for ICD compared with medical therapy. The Assessment Group conducted a meta-analysis of the results from the AVID, CASH, CIDS and 20 people in the pilot DEBUT trial and results indicated a benefit for ICDs compared with medical therapy, with a risk ratio of 0.75 (95% CI, 0.61 to 0.93; $p=0.010$).

4.5 The AVID and CIDS trial reported total cardiac death risk ratios of 0.67 (95% CI 0.50 to 0.90) and 0.81 (95% CI 0.61 to 1.08) respectively for ICDs compared with medical therapy. The Assessment Group's meta-analysis of the two studies indicated

that a benefit on cardiac death of ICDs compared with medical therapy with a risk ratio of 0.74 (95% CI, 0.61 to 0.91; $p=0.004$). The AVID and CIDS trials found no differences between the ICDs and medical therapy for non-arrhythmic cardiac deaths and a meta-analysis conducted by the Assessment Group supported these findings reporting a risk ratio of 0.97 (95% CI 0.72 to 1.31; $p=0.83$). Results from the Assessment Group's meta-analysis found no effect of ICDs on non-cardiac deaths 0.79 (95% CI 0.45 to 1.37; $p=0.40$).

4.6 The rates of sudden cardiac death were lower with ICDs compared with medical therapy in all 4 trials and a meta-analysis conducted by the Assessment Group indicated a benefit for ICDs compared with medical therapy with a risk ratio of 0.49 (95% CI, 0.34 to 0.69; $p<0.0001$). The AVID trial reported a benefit on overall survival at 3 years (difference 11%, $p<0.02$), survival free of cardiac death at 2 years (difference 4%, $p=0.004$) and survival to arrhythmic death at 2 years (difference 5%, $p=0.0002$) for ICDs compared with medical therapy. The CASH trial also reported a benefit on survival free of sudden death at 57 months with a HR of 0.42 ($p=0.005$) and trends towards benefits on overall survival (HR 0.77, $p=0.081$) and survival free of cardiac arrest (HR 0.48, $p=0.072$) for ICDs compared with medical therapy.

4.7 The AVID trial reported the proportion of patients re-hospitalised during follow up finding higher rates for the ICD group compared with the medical therapy group at 3 years (83% compared to 75.5%; $p=0.04$).

4.8 The AVID and CIDS trials assessed quality of life through separate sub-studies using a range of generic and condition-specific measures of quality of life. The AVID trial reported that there were no statistically significant differences in SF-36 scores between groups at 12 month follow-up. The Assessment Group noted that,

at baseline, the ICD group reported worse score on the mental component of the SF-36 compared with the medical therapy group, but there was no difference between groups at 12 month follow-up. Adverse symptoms and ICDs shocks were reported to have a negative impact on quality of life scores for ICD across the different measures. A sub-study of the CIDS trial reported that quality of life improved significantly for the ICD group, between baseline and 12 month follow up, on 3 domains of the Mental Health Inventory (MHI) and 5 out of 7 domains on the Nottingham Health Profile (NHP), while there was no improvement in the medical therapy group and the domains of energy level and physical mobility deteriorated. The quality of life of those experiencing more than 5 ICD shocks did not differ significantly on the MHI and the NHP from the medical therapy group. Those experiencing no shocks and between 1 and 4 shocks reported significant improvements on the MHI and NHP with ICDs compared with medical therapy.

4.9 While all 4 trials reported adverse events, the events reported differed, therefore limiting comparison across trials. Direct comparisons of adverse events between the ICDs and medical therapy were also limited: the DEBUT trial reported that that 30% of people with ICDs and 14% of people with medical therapy experienced adverse events; the AVID trial compared deaths within 30 days of initiation of therapy or by hospital discharge if 30 days after initiation of therapy, and reported no statistically significant differences between the ICDs and medical therapy. In contrast, the CASH trial reported statistically significantly higher mortality rates during the perioperative period for ICDs (5.1%) compared with medical therapy (1.1%).

4.10 The AVID trial presented four pre-specified subgroup analyses for all-cause mortality based on age, LVEF, cause of arrhythmia and

qualifying arrhythmia. The results for all-cause mortality did not differ from the overall population for any of the subgroups.

- 4.11 The most frequently reported adverse events with ICDs included defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia (19%, DEBUT); T-wave oversensing (8%, DEBUT); product discomfort (7.6%, CIDS); ICD permanently or temporarily explanted due to infection, heart transplantation or patient preference (5%, DEBUT); device dysfunction (5%, CASH); pocket erosion requiring removal of ICD (3%, DEBUT); dislodgement or migration of system leads (3%, CASH); ICD dislodgement/fracture (2.4%, CIDS); bleeding requiring reoperation or transfusion (1.2%, AVID); and, unsuccessful first attempt at ICD implantation without thoracotomy (1.0%, AVID). Other adverse events included: haematoma or seroma (6%, CASH); serious haematoma (2.6%, AVID); pleural effusion (3%, CASH); infection (2.0% [AVID] to 4.6% [CIDS]); and, pneumothorax (1.6%, AVID).

People with a recent myocardial infarction (primary prevention)

- 4.12 The DINAMIT (n=674) and IRIS (n=898) trials compared ICD in combination with medical therapy with medical therapy alone in people with a myocardial infarction within the previous 6 to 40 days, or within 5 to 31 days respectively. The Assessment Group highlighted that medical therapy in both trials, which included antiplatelet agents, beta-blockers and lipid lowering agents including statins, met current standards of optimal management. The Assessment Group stated that the block randomisation in the unblinded DINAMIT trial could have lead to a prediction of allocation and bias. In addition, in the IRIS trial the ICD group had a higher proportion of people with left-bundle-branch block (10.1% vs. 6.4%, p=0.05) and diabetes mellitus (37.2% vs. 30.2%, p=0.03) than the medical therapy group. Average length of follow-up was 30

and 37 months respectively. Approximately 60% of people in both trials were in NYHA class II, Most of the remaining were NYHA class III in the DINAMIT trial and NYHA class I in the IRIS trial Mean LVEF was 28% in the DINAMIT trial and 35% in the IRIS trial.

- 4.13 Result from both trials were supported by results from a meta-analysis of the two trials conducted by the Assessment Group which reported no benefit in all-cause mortality (RR 1.04, 95% CI, 0.86 to 1.25; $p=0.69$), total cardiac deaths (RR 0.97, 95% CI, 0.79 to 1.20; $p=0.8$) or non-cardiac deaths (RR 1.39, 95% CI, 0.86 to 2.27; $p=0.18$) with ICDs compared with medical therapy. However, people receiving ICDs had a lower risk of sudden cardiac death (RR 0.45, 95% CI, 0.31 to 0.64; $p<0.0001$), but a higher risk of non-arrhythmic cardiac death (RR 1.77, 95% CI, 1.30 to 2.40; $p=0.0002$) compared with people receiving medical therapy. The IRIS trial found no statistically significant difference between groups for cumulative mortality. Quality of life was not reported in either study. In the IRIS trial, 15.7% patients in the ICD group experienced clinically significant complications requiring hospitalisation, surgical correction, or intravenous drug administration and 1.7% patients died within 30 days of implantation surgery. In 3.4% of patients, ICD was explanted or permanently deactivated because of complications. No participant in DINAMIT died because of a complication with the device but 8.1% of patients experienced device-related complications.
- 4.14 The IRIS trial included 13 pre-specified subgroup analyses for all cause-mortality. Statistically significant differences were found in favour of medical therapy for people who received thrombolytic therapy for early reperfusion of ST-elevation MI and statistically significant differences were found in favour of ICD in combination with medical therapy for people with left main artery disease.

People with remote myocardial infarction (primary prevention)

- 4.15 The MADIT I (n=196 and MADIT II (n=1232 trials compared ICD in combination with medical therapy with medical therapy alone, in people who had an episode of myocardial infarction at least three weeks or one month prior to study entry respectively. Average length of follow-up was 27 months for MADIT 1 and 20 months for MADIT II. Approximately 70% of people in both trials had NYHA class II or III symptoms and the remaining had NYHA class I symptoms. Mean LVEF was approximately 26% in MADIT 1 and 23% in MADIT II.
- 4.16 Both the MADIT I and MADIT II trials reported a reduction in all-cause mortality with ICDs compared with medical therapy reporting hazard ratios of 0.46 (95% CI 0.26 to 0.82, p=0.009) and 0.69 (95% CI, 0.51 to 0.93; p=0.016) respectively and these results were supported by a meta-analysis conducted by the Assessment Group. Post-trial follow-up of MADIT II found continued benefit with ICDs at 8 years with a HR of 0.66 (95% CI 0.56 to 0.78, p=0.001). The meta-analysis also supported the finding from the trials with regard to some secondary outcomes for ICDs compared with medical therapy, reporting a RR of 0.59 (95% CI, 0.42 to 0.83; p=0.003) for total cardiac deaths, a RR of 0.36 (95% CI, 0.23 to 0.55; p<0.00001) for sudden cardiac death. No differences between groups were found in the trials for non-arrhythmic cardiac deaths or for non-cardiac deaths, supported by results from the meta-analysis which reported RR of 0.95 (95% CI, 0.41 to 2.18; p=0.9) and 1.06 (0.58 to 1.95; p=0.84) respectively. The MADIT II trial reported a similar hospitalisation rate per 1000 months follow-up (ICDs 11.3, OPT 9.4, p=0.09). It also reported that the proportion of hospitalisations due to heart failure was higher with ICDs (ICDs 19.9%, OPT 14.9 %,) but the statistical significance was not stated.

4.17 The MADIT II trial assessed quality of life through the Health Utility Index (HUI3), reporting that scores were lower (worse) in people in the ICD group (0.637) compared with medical therapy (0.646) at baseline and that differences were not statistically significant between groups at 3 years follow-up (ICD 0.019, medical therapy 0.013, p value not reported). The MADIT II trial also reported 12 pre-specified subgroup analyses for all-cause mortality. The Assessment Group stated that the hazard ratios were similar in all subgroups, with no statistically significant interactions.

People with non-ischemic or idiopathic dilated cardiomyopathy (primary prevention)

4.18 The AMIOVIRT (n=103), CAT (n=104) and DEFINITE (n=458) trials compared ICD in combination with medical therapy alone with medical therapy in people with non-ischemic or idiopathic dilated cardiomyopathy, with follow-up ranging from 24 months to 29 months. The Assessment Group stated that the medical therapy in all the AMIOVIRT and DEFINITE trials met current standards for optimal management (see table 15 on page 75 of the Assessment Report for further details). The medical therapy in the CAT trial was not considered optimal by current standards due to low beta-blocker use. The CAT trial enrolled people with recently diagnosed with heart failure. However, despite participants not having suffered ventricular arrhythmias, the Assessment Group highlighted that a low LVEF of <30% indicates risk of ventricular arrhythmias and sudden cardiac death, so the trial was considered eligible for inclusion. Participants in CAT had a median duration of symptoms of 3 months, compared to around 3 years in AMIOVIRT and DEFINITE. They were also younger with a mean age 52 years compared with 58 and 59 years in DEFINITE and AMIOVIRT. The majority of participants in all 3 trials were in NYHA class II or III,

with none in NYHA class IV. Mean LVEF ranged from 21% to 25% across the trials.

4.19 None of the trials reported a statistically significant difference in all cause mortality with ICD in combination with medical therapy compared with medical therapy, with a risk ratio of 0.87 (95% CI 0.32 to 2.42) in the AMIOVIRT trial, a risk ratio of 2.16 (95% CI 0.41 to 11.28) in the CAT trial and a risk ratio of 0.70 (95% CI 0.45 to 1.09) in the DEFINITE trial. These results were supported by a meta-analysis by the Assessment Group which reported an all-cause mortality risk ratio of 0.77 (95% CI, 0.52 to 1.15). The meta-analysis also found no statistically significant differences between groups for non-arrhythmic cardiac death (RR 1.13, 95% CI, 0.42 to 3.03). In addition, a meta-analysis of the AMIOVIRT and CAT trials found no statistically significant differences between groups for total cardiac deaths (RR 2.03, 95% CI, 0.17 to 23.62), or non-cardiac death (RR 0.65, 95% CI, 0.13 to 3.29;). The CAT trial reported substantially worse outcomes in the ICD group for non-arrhythmic cardiac death as well as total cardiac death, but these results were not statistically significant. A meta-analysis of the AMIOVIRT and DEFINITE trials found a statistically significant reduction for sudden cardiac death with ICDs, with a risk ratio of 0.26 (95% CI, 0.09 to 0.77; $p=0.02$).

4.20 The AMIOVIRT and CAT trials reported no statistically significant difference in survival. The AMIOVIRT trial assessed changes in quality of life using the Quality of Well Being Schedule (QWBS) and the State Trait Anxiety Inventory (STAI) and reported no statistically significant difference between the groups at 1 year follow up. Although the DEFINITE trial assessed quality of life using the SF-12 mental (MCS) and physical (PCS) component scores and MLHFQ, and stated that no statistically significant differences were

found between groups, the Assessment Group stated that no data were reported.

- 4.21 The DEFINITE trial reported six pre-specified subgroup analyses for all-cause mortality. The differences were statistically significant for the subgroups of men, in people with NYHA class III heart failure and in people with LVEF $\geq 20\%$ for ICD compared with medical therapy.

People scheduled for CABG surgery (primary prevention)

- 4.22 The CABG Patch trial (n=900) compared ICD combined with medical therapy compared with medical therapy alone in people who were scheduled for coronary artery bypass graft surgery and were at risk of sudden cardiac death. The Assessment Group noted that the medical therapy in this trial would have been considered optimal when the trial was conducted, but that it was not optimal by current standards and the excess use of anti-arrhythmic drugs in the ICD arm may have offset some of the benefits from ICD. The mean follow-up was 32 months and mean LVEF was 27%. The majority of participants were in NYHA class II or III.
- 4.23 The results showed risk ratios of 1.08 for all-cause mortality (95% CI 0.85 to 1.38), of 0.98 for total cardiac deaths (95% CI 0.74 to 1.30), of 1.26 for non-arrhythmic cardiac death (95% CI 0.87 to 1.82), of 1.50 for non-cardiac death (95% CI 0.82 to 2.73) and of 0.55 for sudden cardiac death (95% CI 0.30 to 1.01) for the ICD group compared with medical therapy.
- 4.24 The CABG Patch trial assessed health related quality of life using measures of perception of health, ability to function and psychological well-being at 6 months follow-up. Health related quality of life scores were lower with ICDs compared with medical therapy for all measures, and the results were statistically

significant for measures of perception of health transition, emotional role function, mental health, satisfaction with appearance and satisfaction with scar.

- 4.25 The CABG Patch trial evaluated 10 pre-specified subgroups (age, gender, heart failure, NYHA class, LVEF, diabetes mellitus, QRS complex duration, use of ACE inhibitors, use of class I or class III antiarrhythmic drugs, and use of beta-adrenergic-blocking drugs). It reported that the hazard ratios for all-cause mortality with ICDs compared with medical therapy were similar among the subgroups. However, the Assessment Group noted that the actual data were not reported.

People with mild to moderate heart failure (secondary prevention)

- 4.26 The SCD-HeFT three-arm trial (n=2521) compared ICD in combination with medical therapy, medical therapy and placebo in combination with medical therapy alone, in a broad population of patients with mild-to-moderate heart failure due to ischaemic or non-ischaemic causes. The Assessment Group highlighted that the medical therapy in this trial could be considered optimal by current standards. Mean follow-up was 46 months and mean LVEF was 25%. Over 70% of participants were in NYHA class II, and the remaining were in NYHA class III.
- 4.27 The primary outcome of all-cause mortality was reduced with ICDs compared with the combined placebo and medical therapy group with a hazard ratio of 0.77 (97.5% CI, 0.62 to 0.96; p=0.007). Reductions in total cardiac death were also found with ICDs compared with the combined placebo and medical therapy groups with a hazard ratio of 0.76 (95% CI, 0.60 to 0.95; p=0.018) and for sudden cardiac death with a risk ratio of 0.44 (95% CI 0.31 to 0.61; p<0.00001). For non-arrhythmic cardiac death or deaths from non-

cardiac causes, there were no differences between ICDs and the control arm with risk ratios of 1.14 (95% CI 0.88 to 1.48) and 0.92 (95% CI 0.66 to 1.27) respectively.

- 4.28 The SCD-HeFT trial reported health related quality of life scores at baseline, 3, 12 and 30 months follow-up using the Duke Activity Status Index (DASI), Mental Health Inventory 5 (MHI-5), Minnesota Living With Heart Failure (MLHFQ) and the global health status. The only statistically significant differences between ICDs and placebo were in median MHI scores and global health status at 3 and 12 months, but these differences were not maintained at 30 months; and the MLHFQ score at 3 months but this benefit was not maintained at 12 months. A significant decrease in perceptions of quality of life was found using the SF-36 among people who had received an ICD shock within the previous month compared with those who had not received a shock.
- 4.29 The SCD-HeFT trial reported pre-specified subgroup analyses for all-cause mortality and cause of death according to cause of congestive heart failure and NYHA class (class II or III). There was no interaction of ICD therapy ($p=0.68$) with the cause of congestive heart failure (ischaemic or non-ischaemic) for all-cause mortality or other specified modes of death. However, there was an interaction between ICD therapy and NYHA class ($p<0.001$). Compared with placebo, ICDs reduced the risk of all-cause mortality, cardiac mortality and sudden cardiac death in people with NYHA class II but not in those with NYHA class III.). The interaction between ICD therapy and NYHA class was not statistically significant for heart failure ($p=0.29$) or non-cardiac ($p=0.11$) deaths.
- 4.30 The 9RCTS evaluating ICDs for primary prevention reported adverse event rates between 5% (SCD-Heft) and 61% (CABG Patch) in people with an ICD, depending on the definition of adverse event and length of follow-up. Adverse event rates for the

comparator treatment were between 12% to 55% in the three RCTs reporting it. Lead, electrode or defibrillator generator related problems affected 1.8% (MADIT II) to 14% (CAT) of people in the five trials that reported it.

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony (population 2)

4.31 The Assessment Group identified 4 multicentre RCTs comparing CRT-P with medical therapy in people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony. The CARE-HF (n=813) and COMPANION (n=1520) trials were unblinded, and therefore at high risk of bias. The MIRACLE (n=453) and MUSTIC (n=58) trials were blinded as investigators implanted all participants with a CRT-P device, but inactivated the device in the control group. The MUSTIC trial used a randomised crossover design, with 3 months follow-up for each of the two cross-over periods and the Assessment Group stated that the crossover design was appropriate. The details of randomisation methods and allocation concealment methods were not reported in the COMPANION, MIRACLE and MUSTIC trials. The Assessment Group stated that the medical therapy included in all 4 trials was optimal by current standards (page 149 of the Assessment Report). The COMPANION trial also compared CRT-P with CRT-D and CRT-D with medical therapy; however, the Assessment Group stated that the trial was not powered for the comparison of CRT-P with CRT-D. All trials included people with NYHA class III or IV heart failure, with the majority of participants in NYHA class III (82% [CARE-HF] to 100% [MUSTIC]) and with LVEF less than 35%. Average LVEF was about 22% in MIRACLE and COMPANION, and 25% in CARE-HF. Though the QRS duration criteria differed across trials, (that is for CARE-HF and COMPANION ≥ 120 ms, MIRACLE ≥ 130 ms and MUSTIC ≥ 150 ms)

the mean QRS interval was approximately 160 ms across all 4 trials.

- 4.32 Studies differed in the timing of implantation, baseline evaluation and randomisation. In particular, the Assessment Group noted that only those participants with a successful implantation underwent randomisation in the MUSTIC and MIRACLE trials, limiting the generalisability of these studies. Although an intention to treat analysis was performed in the trials, the proportion of patients in the medical therapy group who switched to a CRT was high ranging from 4% in MIRACLE to 42% in COMPANION.. The primary outcomes in the COMPANION and CARE-HF trials were composite endpoints of all-cause mortality and all-cause hospitalisation in COMPANION, and all-cause mortality and unplanned hospitalisation for a major cardiovascular event in CARE-HF. The primary outcome of MIRACLE and MUSTIC was distance walked in 6 minutes. Changes in NYHA class and quality of life were also primary outcomes in MIRACLE. The results reported from the trials are summarised below.

CRT-P compared with medical therapy

- 4.33 The CARE-HF trial reported a difference in all-cause mortality after a mean follow-up of 37.4 months, with a risk ratio of 0.60 (95% CI 0.47 to 0.77, $p < 0.0001$) for CRT-P compared with medical therapy. This difference persisted during long-term follow-up of 343 of 813 people originally enrolled despite implantation of CRT devices in more than 95% of those originally assigned to the medical therapy group (HR 0.77, 95% CI 0.63 to 0.93, $p = 0.007$). Differences in all cause mortality observed in the other 3 trials were not statistically significant. A meta-analysis of the results of all 4 trials conducted by the Assessment Group found that CRT-P statistically significantly reduced the risk of all-cause mortality compared with

medical therapy with a risk ratio of 0.75 (95% CI 0.58 to 0.96, $p=0.02$).

- 4.34 The COMPANION and MUSTIC trials measured total cardiac death and reported no statistically significant difference between the CRT-P and medical therapy groups. The COMPANION trial also found no statistically significant differences between groups for non-cardiac deaths. All trials reported sudden cardiac death, although the Assessment Group noted uncertainties with the MIRACLE trial data because the numbers in each arm were not reported and the total sample size in the FDA report ($n=536$) differed from the number randomised in the main publication ($n=453$). In the CARE-HF trial, fewer patients randomized to CRT-P experienced sudden cardiac deaths compared with medical therapy with a risk ratio of 0.59 (95% CI 0.39 to 0.89). The COMPANION and MUSTIC trials did not report any statistically significant difference between groups. The Assessment Group conducted a meta-analysis which demonstrated no difference in risk of sudden cardiac death between the CRT-P and medical therapy groups with a risk ratio of 0.97 (95% CI 0.44 to 2.14).
- 4.35 In the CARE-HF trial, fewer patients randomized to CRT-P died from heart failure compared with medical therapy with a risk ratio of 0.59 (95% CI 0.40 to 0.86). The COMPANION trial, however, found no statistically significant differences between groups reporting a risk ratio of 0.78 (95% CI 0.52 to 1.17). A meta-analysis by the Assessment Group found that CRT-P relative to medical therapy delayed the time to death with a risk ratio of 0.67 (95% CI 0.51 to 0.88, $p=0.004$).
- 4.36 All 4 trials measured hospitalisations attributed to heart failure and all except MUSTIC reported lower rates of hospitalisation from heart failure with CRT-P compared with medical therapy. The Assessment Group's meta-analysis showed a risk ratio for

hospitalisation due to heart failure of 0.61 (95% CI, 0.44 to 0.83; $p=0.002$). Data on the number of events of hospitalisation attributed to heart failure and/or number of days of hospitalisations due to heart failure were reported in three trials (CARE-HF, COMPANION and MIRACLE) but no statistical analyses were reported. The Assessment Report calculated the rate of hospitalisation due to heart failure for each trial and combined these in a meta-analysis. This demonstrated a significant reduction in the rate of heart failure hospitalisations with CRT-P compared to medical therapy (RR 0.58, 95% CI 0.35 to 0.96, $p=0.03$). Three trials (CARE-HF, MIRACLE and MUSTIC) reported a benefit with CRT-P for 'worsening of heart failure', the criteria for which differed across the trials. When the trials were combined in a meta-analysis, the risk of worsening heart failure was lower with CRT-P (RR 0.71, 95% CI 0.63 to 0.80, $p<0.00001$) than with medical therapy. These trials (CARE-HF, COMPANION and MIRACLE) also reported a greater proportion of participants with improvement in NYHA class with CRT-P than with medical therapy. The Assessment Group conducted a meta analysis which showed an increase in the proportion of people with an improvement in one or more NYHA class with CRT-P compared with medical therapy (RR 1.68; 95% CI, 1.52 to 1.86; $p<0.00001$).

- 4.37 The CARE-HF trial reported that the risk of arrhythmias was higher with CRT-P compared with medical therapy with a risk ratio of 1.54 (95% CI 1.07 to 2.23, $p=0.02$). The CARE-HF, COMPANION and MIRACLE trials reported a statistically significant greater proportion of patients with an improvement in NYHA class with CRT-P compared with medical therapy. The Assessment Group's meta-analysis of these trials for an improvement in one or more NYHA class with CRT-P compared with medical therapy, estimated a risk ratio of 1.68 (95% CI 1.52 to 1.86, $p<0.00001$). The MIRACLE trial measured change in LVEF and reported an improvement with

CRT-P at 6 months, with an increase of 4.6%, compared with a decline of 0.2% with medical therapy.

- 4.38 The COMPANION, MIRACLE and MUSTIC trials reported that CRT-P improved exercise capacity more than did medical therapy, as measured by the distance walked in 6 minutes. A meta-analysis of these trials showed a change from baseline to final reported walking distance, with a mean difference of 38.14 m, 95% CI 21.74 to 54.54, ($p < 0.00001$).
- 4.39 All 4 trials assessed change in the health related quality of life using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ). CARE-HF also reported EQ-5D, mean QALYs and mean life-years. All trials found that CRT-P improved MLWHFQ score compared with medical therapy and a meta-analysis by the Assessment Group indicated a mean difference of -10.33 (95% CI, -13.31 to -7.36, $p = 0.00001$). CARE-HF also reported improvements in EQ-5D, with a mean increase of 0.13 in the EQ-5D scores for CRT-P compared with medical therapy (95% CI 0.08 to 0.18, $p = 0.0001$). In addition, the mean number of QALYs was higher with CRT-P at 18 months (CRT-P 0.95 vs. medical therapy 0.82, $p < 0.0001$) and also at the end of the study (1.45 vs. 1.22, < 0.0001).
- 4.40 Only CARE-HF reported pre-specified subgroup analyses. Of 17 subgroups, the investigators reported a significant interaction only between CRT-P and the presence of absence of ischaemic heart disease: people without ischemic heart disease experienced a greater improvement in LVEF than people with ischaemic heart disease.

CRT-D compared with medical therapy

- 4.41 Data from the COMPANION trial were available for a comparison of CRT-D with medical therapy. Results from this trial reported

reductions or delays with CRT-D compared with medical therapy for the outcomes of all-cause mortality (HR 0.64, 95% CI 0.48 to 0.86, $p=0.003$), total cardiac deaths (RR 0.68, 95% CI 0.50 to 0.93, $p=0.02$), sudden cardiac deaths (HR 0.44, 95% CI 0.23 to 0.86, $p=0.02$) and heart failure hospitalisations (RR 0.77, 95% CI 0.63 to 0.93, $p=0.008$). In addition, the proportion of people with an improvement of one or more NYHA class (57% vs. 38%, $p<0.001$), improvements in exercise capacity (change in 6 MWT 46 m vs. 1 m, $p<0.001$), and health related quality of life scores at 6 months measured by MLWHFQ score (-26 vs. -12, $p<0.001$) were statistically significantly greater with CRT-D compared with medical therapy. There were no differences between the CRT-D group and the medical therapy group for the outcomes of heart failure deaths (HR 0.73, 95% CI 0.47 to 1.11, $p=0.143$) and non-cardiac deaths (CRT-D 2.3% vs OPT 3.6%, $p=0.717$).

CRT-P compared with CRT-D

4.42 Data from the COMPANION trial were available for a comparison of CRT-P with CRT-D. However, the Assessment Group highlighted that the trial was not powered for to compare CRT-P with CRT-D and therefore all results for this comparison should be interpreted with caution. The results indicated that total cardiac deaths and sudden cardiac deaths were higher with CRT-P compared with CRT-D with risk ratios of 1.38 (95% CI 1.06 to 1.81, $p=0.02$) and 2.72 (95% CI 1.58 to 4.68, $p=0.0003$) respectively. The results were for all-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, $p=0.12$), heart failure deaths (RR 0.98, 95% CI 0.68 to 1.42, $p=0.93$), heart failure hospitalisations (28% vs. 29%). Changes in NYHA class, exercise capacity and health related quality of life scores were not statistically significantly different between CRT-P and CRT-D.

4.43 The Assessment Group stated that the reporting of adverse events was limited in all 4 trials. The MIRACLE and MUSTIC excluded

patients with unsuccessful implantation (7.5% and 7.8% of enrolled patients) while the rate of unsuccessful implantation was 6% in CARE-HF and 12.6% in COMPANION. Device-related deaths reported in the trials varied between 0.2% (MIRACLE and CARE-HF) and 0.8% (COMPANION) for those with CRT-P and 0.5% for those with CRT-D (COMPANION). In COMPANION moderate or severe adverse events related to implantation procedure was 10% with CRT-P and 8% with CRT-D, with 13% and 9% of CRT-P and CRT-D implantations unsuccessful. Reported complications included lead displacements, infections and coronary-sinus dissections.

People with heart failure as a result of LVSD and cardiac dyssynchrony who are also at risk of sudden cardiac death as a result of ventricular arrhythmias (population 3)

4.44 The Assessment Group identified 9 trials comparing CRT-D with ICDs in people at risk of sudden cardiac death due to ventricular arrhythmia and with heart failure as a result of LVSD and cardiac dyssynchrony. In 6 trials (CONTAK-CD [n=490], MIRACLE ICD [n=369], MIRACLE ICD II [n=186], Pinter [n=72], RethinQ [n=172] and Rhythm ICD [n=179]), all patients were implanted with a CRT-D, that is, a device that could provide both CRT and ICD therapy, but the CRT function was switched off in the comparator group, therefore providing active ICD therapy only. In 3 trials (MADIT-CRT [n=1820], RAFT [n=1798] and Piccirillo [n=31]), the comparator group received an ICD only device. Participants also received medical therapy (except in the Piccirillo trial) and the Assessment Group stated that, in general, the medical therapy was optimal by current standards (see page 195 of the Assessment Report). No trials comparing CRT-D with medical therapy or with CRT-P were identified for this population.

- 4.45 The Piccirillo trial was a single-centre study conducted in Italy. All other trials were multicentre trials with largely North American centres. Only the MADIT-CRT trial included a UK centre. The ReTHINQ and RHYTHM ICD trials were described as double-blind but the Assessment Group stated that details were not reported. The Assessment Group also stated that apart from the MADIT-CRT trial, no details were available on the methods of randomisation method or blinding. The MADIT-CRT trial was considered to be at high risk of bias because diagnosis of heart failure and decisions on therapy or hospital admission were made by physicians who were aware of study group assignments. The RAFT trial was considered to have a high risk of selective reporting bias because outcomes stated in the protocol were not reported in the publication. The study design of CONTAK-CD was modified from a randomised crossover design with crossover to occur after 3 months of randomised therapy (Phase I), to a parallel RCT design with 6 months of follow-up (Phase II) and data from both phases are reported.
- 4.46 The trials differed in their eligibility criteria for severity of heart failure. Most patients in MADIT-CRT, MIRACLE ICD II and RAFT were in NYHA class II while in CONTAK-CD, MIRACLE ICD, RethinQ and RHYTHM ICD majority of patients were in NYHA class III. NYHA class was not reported by Pinter, although the eligibility criteria specified mild to moderate heart failure. The majority of patients in Piccirillo were in NYHA class I. The proportion of patients with ischemic heart disease varied between the trials, from approximately 52% in the RethinQ trial to 100% in the Piccirillo trial. Average length of follow-up ranged between 6 to 40 months across the trials. Prolonged QRS duration on ECG (more than 120 ms to more than 150 ms in different trials) was used to define cardiac dyssynchrony in all the trials except in the RethinQ in which people with a narrow QRS interval (less than 130

ms) were included on the basis of mechanical dyssynchrony apparent on echocardiograph. Mean left ventricle ejection fraction ranged from 21% (CONTAK-CD) to 26% (RethinQ). Crossover between groups was reported by 6 the trials and crossover from the ICD to the CRT-D treatment arm ranged from 2.8% (Pinter) to 12.4% (MADIT-CRT) of patients, the most common reason for crossover was heart failure events. Crossover from CRT-D to ICD ranged from 0% (RethinQ) to 7.5% (MADIT-CRT) of patients, most commonly because of difficulties with the implanted device. The MADIT-CRT, Piccirillo and RAFT trials randomised participants before or at the time of implantation. The CONTAK-CD trial implanted the device first because of the immediate need for ICD therapy, then programmed the randomised therapy after a minimum 30 day period with no CRT, during which time investigators were permitted to optimise pharmacologic therapy. The other studies randomised only those participants in whom the implanted were successful and the time of randomisation varied between from 7 to 28 days after implantation.

- 4.47 The Assessment Group stated that only 4 trials were adequately powered to show a difference in their primary outcomes which were death or non-fatal heart-failure events (MIRACLE ICD), left ventricular end-systolic volume change from baseline (Pinter), composite outcome of death from any cause or heart failure leading to hospitalisation (RAFT) and proportion of patients with an improved peak oxygen consumption during cardiopulmonary exercise testing and survival from CRT-D system related complications (ReTHINQ) . However, the Assessment Group highlighted that the MIRACLE ICD trial was not powered to detect a morbidity or mortality difference. Of the remaining trials, the CONTAK-CD and MADIT-CRT trials were not considered to be adequately powered and the MIRACLE ICD II and RHYTHM ICD trials did not report sample size calculations. The Piccirillo trial was

a small study of 31 participants which did not report sample size calculations, and because mortality and NYHA were not primary outcomes the Assessment Group assumed that it was not powered for these outcomes.

- 4.48 All trials reported data on all-cause mortality, but not as a primary outcome, and only the MADIT-CRT and RAFT trials compared the results statistically. The MADIT-CRT trial found no statistically significant difference in all-cause mortality with a risk ratio of 0.94 (95% CI 0.67 to 1.32) while the RAFT trial found a statistically significant reduction in mortality with CRT-D compared with ICDs with a risk ratio of 0.80 (95% CI 0.67 to 0.94). The Assessment Group's analysis of reported data from the remaining trials suggested no statistically significant difference in all-cause mortality between groups in any of the trials. In the Piccirillo trial no deaths were observed in both groups. The Assessment Group also conducted a meta-analysis pooling data from the trials which found that compared to ICDs, CRT-D reduced the risk of all-cause mortality significantly with a risk ratio of 0.84 (95% CI 0.73 to 0.96, $p=0.01$). The Assessment Group commented that the results were strongly influenced by the RAFT trial and when this study was removed from the analysis the differences were no longer statistically significant.
- 4.49 All but the MADIT-CRT and Piccirillo trials reported data on total cardiac deaths, although only the RAFT trial compared results between groups statistically. It found that CRT-D was associated with a statistically significant reduction in cardiac deaths compared with ICDs with risk ratio of 0.76 (95% CI 0.60 to 0.96). When these trials were combined in a meta-analysis by the Assessment Group, the overall risk ratio was 0.82 (95% CI 0.67 to 1.00, $p=0.05$) in favour of CRT-D compared with ICDs. The results were no longer significant if the RAFT study was excluded from the meta-analysis.

The CONTAK-CD, MIRACLE ICD II, Piccirillo and ReTHINQ trials reported data on deaths from heart failure and sudden cardiac death. In addition, the MICRACLE ICD and RHYTHYM ICD trials reported data on sudden cardiac death. Deaths due to heart failure or sudden cardiac death were not statistically significantly different between the CRT-D and ICD groups in any of the trials reporting it as well as in the meta-analyses conducted by the Assessment Group. The pooled risk ratio for death due to heart failure, for CRT-D compared with ICD was 0.64 (95% CI 0.18 to 2.22, $p=0.48$) while for sudden cardiac death it was 1.45 (95% CI 0.43 to 4.92, $p=0.55$). No statistically significant differences between groups for 6-month cumulative survival was reported by the MIRACLE ICD or RethinQ trials with rates of 92.4% and 94.2% for the CRT-D group respectively and rates of 92.2% and 98.8%, for the ICD group respectively. The RAFT study indicated that the probability of event-free survival at 5 years was 57.6% with CRT-D and 48.7% with ICD but statistical significance was not reported.

- 4.50 The RAFT, CONTAK-CD and Piccirillo trials reported hospitalisations related to heart failure. The RAFT trial found a statistically significant reduction in heart failure hospitalisations with CRT-D compared with ICD with a risk ratio of 0.75 (95% CI 0.63 to 0.89; $p=0.0009$). The CONTAK-CD and Piccirillo trials found no significant difference between groups but combining all 3 trials in a meta-analysis demonstrated that CRT-D statistically significantly reduced the risk of hospitalisation by 25% compared with ICD with a risk ratio of 0.75 (95% CI 0.64 to 0.88, $p=0.0005$). The CONTAK-CD, MICRACLE ICD, MIRACLE ICD II and Pinter trials reported the number of participants experiencing at least one episode of ventricular tachycardia or ventricular fibrillation. The Assessment Group stated that the proportions were similar between groups across the trials and a meta-analysis demonstrated no statistically significant difference in the number of people experiencing at least

one arrhythmia with a risk ratio of 0.90 (95% CI 0.71 to 1.14, $p=0.38$).

- 4.51 All except the Pinter and RAFT trials reported change in NYHA class. The MIRACLE ICD, MIRACLE ICD II and RHYTHM ICD trials reported a statistically significant improvement in mean or median NYHA class among people with CRT-D compared with people with ICD. Combining these studies in a random effects meta-analysis resulted in a statistically significant mean difference of -0.19 (95% CI -0.34 to -0.05, $p=0.008$). The CONTAK-CD, ReTHINQ and Piccirilli trials reported the proportion of people who improved by one or more NYHA class; the RethinQ and Piccirillo trials found a statistically significant improvement with CRT-D compared with ICDs but the CONTAK-CD trial found no statistically significant difference between groups in the number of people with improvement in NYHA class. The meta-analysis of these studies showed no statistically significant difference between two groups with a risk ratio of 1.81 (95% CI 0.91 to 3.60).
- 4.52 Three trials (CONTAK-CD, MADIT-CRT, MIRACLE ICD II) reported a statistically significant improvement from baseline in mean LVEF among people with CRT-D compared with ICD, whereas three trials (MIRACLE ICD, Pinter, RethinQ) reported no statistically significant difference between the groups in change from baseline. The Piccirillo and RHYTHM ICD trials reported data but did not provide a statistical analysis of change in LVEF. The Assessment Group's own assessment of the data from the Piccirillo trial indicated a statistically significant improvement with CRT-D compared with ICD, but the results from RHYTHM trial did not indicate any statistically significant differences. The Assessment Group's meta-analysis indicated a statistically significant improvement in LVEF with CRT-D compared with ICD with a mean difference in mean LVEF of 2.15 (95% CI 0.45 to 3.86, $p=0.01$).

- 4.53 All except the RAFT and Piccirillo trials reported change in exercise capacity measured by either distance walked in 6 minutes, measuring exercise duration, measuring peak VO₂ (peak oxygen uptake), and by proportion of participants with an increase of at least 1.0 ml/kg body weight/minute in peak oxygen consumption. The Assessment Group's meta-analysis indicated that there was a greater improvement in exercise capacity with CRT-D than with ICD, as demonstrated by change from baseline in peak VO₂, with data pooled from 5 trials indicating a mean difference of 0.75 ml/kg body weight/minute between groups (95% CI 0.23 to 1.27, p=0.005) and as demonstrated by distance walked in 6 minutes, with data pooled from 6 trials indicated a mean difference of 14.5 meters between groups (95% CI 2.9 to 26.1, p=0.01).
- 4.54 All except the RAFT and Piccirillo trials reported changes in quality of life at 6 months using the MLWHF questionnaire. Meta-analysis of these trials indicated an statistically significant improvement in quality of life with CRT-D compared with ICD with a mean difference of -6.9 in MLWHFQ scores between groups (95% CI -10.4 to -3.4, p=0.0001). The Pinter trial also reported statistically significant improvements between groups for the General Health component of the SF-36 when comparing baseline to 6 month changes.
- 4.55 The Assessment Group stated that reporting of adverse events was inconsistent between the trials. The RAFT trial compared adverse events between groups statistically and found that device or implantation related complications within 30 days of implantation were significantly higher in the CRT-D group than the ICD group (13.3% compared with 6.8%, p<0.001), as was device-related hospitalisation (20% compared with 12.2%, p<0.001), lead-dislodgement requiring intervention (6.9% compared with 2.2%) and coronary sinus dissection (1.2% compared with 0). After the

first 30 days, MADIT-CRT reported 4.5 serious device-related adverse events per 100 device-months with CRT-D compared with 5.2 events with ICD.

- 4.56 Three trials (MADIT-CRT, RAFT and RethinQ) reported pre-specified subgroup analyses. The MADIT-CRT and RAFT trials reported that CRT-D was associated with a greater benefit in people with QRS duration 150 ms or more than in those with QRS duration of less than 150 ms with p-values of interaction of 0.001 in the MADIT-CRT trial and of 0.002 in the RAFT trial. The ReTHINQ trial found significant improvements in the proportion of people with an improvement in peak oxygen uptake with CRT-D in those with QRS \geq 120ms but not for those with QRS <120ms. CRT-D was also associated with greater benefit in women than in men (MADIT-CRT; p-value for interaction 0.01) and in people with left bundle branch block (LBBB) than in those with nonspecific intraventricular conduction delay (RAFT; p-value for interaction 0.046). The RethinQ trial found a statistically significant improvement with CRT-D in distance walked in 6 minutes for those with non-ischemic cardiomyopathy (55.0 m vs. 2.5 m, p= 0.01) but not for those with ischemic cardiomyopathy (4.2 m vs. 5.8 m, p=0.57). Other subgroups analyses did not show any statistically significant effects (see page 236 of the Assessment Report for further details).

5 Comments from other consultees

- 5.1 Consultees submitted a comprehensive review of the clinical effectiveness of ICD and CRT as well as a perspective of the place of the technology in current practice. It noted that many healthcare professionals are involved in the identification, treatment and follow-up of patients with indications for ICD and CRT therapy. These include primary and secondary care physicians to identify patients and cardiologists specialising in electrophysiology, device therapy or heart failure who are primarily responsible for

determining whether device therapy is indicated, subsequently implanting the devices and providing specialist clinical follow-up along with nurses who play a major part in the follow-up of patients. Consultees emphasised that long-term coordination of these healthcare professionals is essential for optimal care.

5.2 Consultees also commented that multiple trials have shown that anti-arrhythmic drugs may alleviate symptoms but do not improve prognosis in patients with life-threatening arrhythmias and the only effective treatment for these patients is an ICD. It was noted that ICDs have become safer to implant, that they have become more reliable in avoiding unnecessary therapy and also have significantly improved battery life. Indications for ICD implantation have evolved from purely secondary prevention after a resuscitated cardiac arrest, to include primary prevention in those at high risk of sudden cardiac death. In addition, it was noted that a simple assessment based on LVEF and underlying cardiac disease can predict those who benefit from ICD implantation. Similarly, it was noted that CRT has revolutionised the treatment of severe heart failure in those with cardiac dyssynchrony and a simple assessment based on LVEF and the duration of the QRS complex on the standard ECG can predict those who are likely to benefit.

5.3 Consultees stated that in the UK, implantation rates remain well-below rates in Western Europe or North America and analysis of the National Devices Database and other audits shows that access to device therapy is not uniform across the UK, suggesting that failure to identify patients suitable for device therapy was a reason for this disparity. Consultees suggested that simplification of indications and investigations in line with trial evidence and international guidelines would reduce this inequity of access.

5.4 Consultees noted that the main advantage of ICD implantation is that it reduces the risk of sudden death while CRT implantation

reduces the burden of heart failure symptoms and mortality. Disadvantages include the discomfort of implantation procedures, associated complications, regular device follow-up and social effects including restriction of driving. Consultees also mentioned that the clinical trials have demonstrated that the benefits of device therapy remain significant and sustained and highlighted that adverse events can be minimised by appropriate patient selection, highly competent implantation and follow-up services using remote technologies.

5.5 In the review of clinical effectiveness presented by a consultee, it was highlighted that superiority of ICD over medical therapy for secondary prevention has been well established and it is considered unethical to perform further clinical trials in this population. For primary prevention, it found that left ventricular function is a significant predictor of risk while non-sustained ventricular tachycardia, ventricular tachycardia induced by programmed electrical stimulation and QRS duration have limited sensitivity or specificity to predict those who will and will not benefit from ICD implantation. It also commented that since measurement of LVEF is not very accurate in clinical practice, a single threshold of equal or less than 35% should be used. For CRT it noted that patients with severe left ventricular impairment (LVEF \leq 35%) and evidence of dyssynchrony on ECG (QRS \geq 120ms) and heart failure symptoms despite optimal pharmacological therapy, benefit from CRT with improved symptoms, reduced hospitalisation and reduced all-cause mortality. Other measures of mechanical dyssynchrony have not shown sufficient sensitivity and specificity to be clinically useful in the identification of patients who will benefit from CRT.

5.6 Comments were received from one patient organization emphasising the importance of primary prevention, ensuring

screening for those who are at risk of arrhythmias that lead to sudden cardiac arrest and may require an ICD or CRT device.

6 Cost-effectiveness evidence

Assessment Group literature review

- 6.1 The Assessment Group conducted a systematic literature review to identify published health economic evaluation studies relevant to this appraisal. It identified that the cost effectiveness of ICD and CRT had been evaluated in 34 and 16 studies respectively, and that 2 of these studies included the evaluation of both ICD and CRT. These studies were published between 1990 and 2012, and most of them were conducted in North America. Most of these studies employed state transition models to estimate long term outcomes extrapolated from short-term outcomes in the trials and time horizons varied from 3 years to a lifetime. Most of the studies were based on a single trial, with MADIT II and SCD-HeFT being the most common trials for ICD evaluation and CARE-HF and COMPANION being the most common trials for CRT evaluation.
- 6.2 For ICD therapy, the Assessment Group stated that it considered only 5 studies to be of high methodological quality. Of these, it considered only one study (Buxton et al., 2006) relevant from a UK perspective. This study used a Markov model with a 20 year time horizon to evaluate the cost-effectiveness of ICD compared with medical therapy in people patients at risk of sudden cardiac death with previous CA or VT, using data from the CIDS, CASH and AVID trials and data from observational studies. It reported a mean ICER of £76,139 per QALY gained, and this decreased to £48,372 per QALY gained in people with low LVEF when the time horizon was extended to a lifetime. However, the Assessment Group highlighted that this study used data from before 2002 and therefore the results may not be generalisable to current practice.

- 6.3 For CRT, almost all studies reported that CRT was cost effective compared with medical therapy, with only two studies uncertain as to whether CRT was cost effective compared with medical therapy. The Assessment group considered 6 studies to be of high methodological quality, two of which were the studies reporting uncertainty about cost-effectiveness of CRT compared with medical therapy. Of these, one study (Fox et al.) was considered relevant from a UK perspective. This study reported a Markov model to compare CRT-P and CRT-D with medical therapy in people with heart failure in the UK over their lifetime. People were in NYHA class III and IV with LVEF $\leq 35\%$ and QRS duration >120 ms. It estimated an ICER of £16,735 per QALY gained for CRT-P compared with medical therapy, and an ICER of £40,160 per QALY gained for CRT-D compared with CRT-P. CRT-D was more likely to be cost-effective compared with CRT-P, in subgroups of people who are younger or those with high risk of sudden cardiac death who would qualify for CRT.
- 6.4 Bertoldi et al. 2011 evaluated the cost-effectiveness of CRT-D compared with ICD. The Assessment Group noted that this was conducted in Brazil using a Markov model and reported that in people with heart failure (NYHA class II-IV and LVEF less than 35%) CRT-D compared with ICDs was associated with an ICER of \$36,940 per QALY gained.

Manufacturer's submission

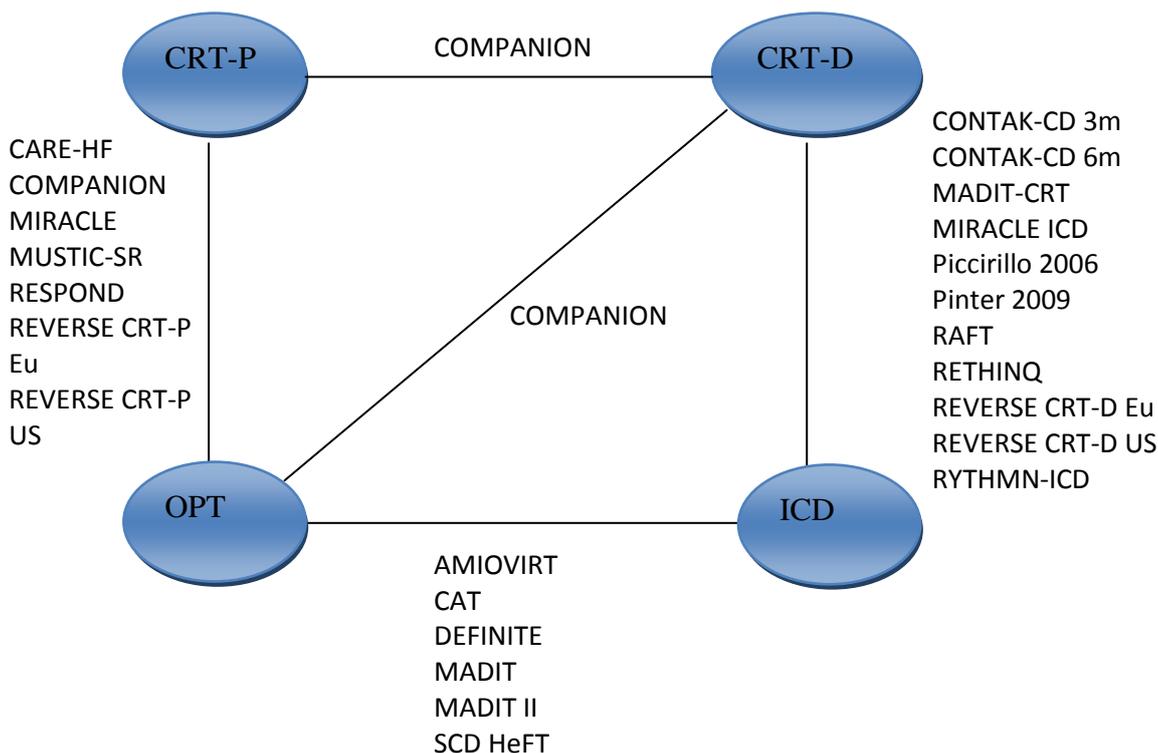
- 6.5 The Association of British Healthcare Industries (ABHI) submitted a joint submission on behalf of the five major device manufacturers relevant to this submission (Biotronik UK, Boston Scientific, Medtronic UK, Sorin Group and St Jude Medical). The submission included a systematic review of published studies of clinical effectiveness of OPT, ICD, CRT-P and CRT-D for the treatment of cardiac arrhythmias and heart failure, and an economic evaluation

with which to determine the patients, based on clinical parameters, in whom the different devices (ICD, CRT-P, or CRT-D) would be most cost-effective. The focus of this economic evaluation is different from the scope as it does not address the 3 populations specified in the scope. The manufacturers highlighted that they used individual patient characteristics to define the populations as the population in most of the trials did not match the groups defined in the scope. In addition, the manufacturers' submission focused solely on the use of ICD for primary prevention, commenting that people who meet the criteria laid in TA95 for secondary prevention (in particular having survived a cardiac arrest) have a strong clinical indication for an ICD, that there was a the reduction in implant costs, as well as the absence of new studies in this patient group. The Assessment Group stated that while the interventions compared in the submission were consistent with the NICE scope, not all of them were included as comparators for all patient subgroups in the submission because no patients were identified for these combinations: for example, ICD was excluded for NYHA class IV, CRT-P was excluded for NYHA class I/II and QRS <120ms and CRT-D was excluded for QRS <120ms. The Assessment Group stated that these exclusions appeared to be reasonable based on clinical opinion.

6.6 The manufacturers conducted a systematic review of the literature and identified 22 relevant trials. The manufacturers stated that this indicated that there is a large body of RCT evidence available confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with heart failure. The manufacturers also stated that no new evidence was identified relating to the use of ICD for secondary prevention of ventricular arrhythmia.

6.7 The manufacturers' presented an individual patient data network meta-analysis using meta-regression to assess the effectiveness of

ICDs, CRT-P and CRT-D in the different sub-groups of people who have heart failure. The results for the outcomes relevant to economic analysis, that is, all-cause mortality, all cause hospitalisation and health related quality of life were synthesised and incorporated in the modelling. The Assessment Group stated that with limited published evidence on the effectiveness of devices in different patient sub-groups with heart failure, the availability of individual patient data makes a network meta-analysis meta-regression possible and justified.



Network of randomised controlled trials

6.8 Individual patient data from 13 of the 22 trials identified in the systematic review was available to inform the individual patient

data network meta-analysis. These 13 trials included the COMPANION, CONTAK-CD, MADIT, MADIT II, MADIT-CRT, CARE-HF, MIRACLE, MIRACLE-ICD, RAFT, REVERSE, SCD-HeFT, DEFINITE and RethinQ trials. These trials included 95% of the total number of patients across all 22 trials. The Assessment Group commented that 7 trials identified in the Assessment Report (DINAMIT, IRIS, CABG Patch, AVID, CASH, CIDS, DEBUT) were not included in this analysis. However, the Assessment Group noted that issues concerning differences in the 13 trials relating to the effects of length of follow-up, trial cross-over, missing data and data handling were discussed in the submission. Length of follow-up was limited to that specified in the trials' protocols to limit the effects of trial cross-over at longest follow-up. Missing data for the covariables appeared limited, with data imputed through multiple imputations where necessary. In addition, the covariables used to capture baseline risk and treatment effect modifiers in the NMA were outlined for the different outcomes assessed, with the rationale for their inclusion and for any data manipulation discussed.

- 6.9 The data for all-cause mortality were aggregated from 13 trials, all-cause hospitalisation from 11 trials and health related quality of life from 3 trials. However, the Assessment Group noted that the submission outlined reasons for excluding specific studies from the overall evidence network, the approach taken to allocating trials to different comparisons and the basis for handling data. Different types of regression were used for analysing the three outcomes, and these are presented on pages 247 and 248 of the Assessment Report. The Assessment Group stated that although it was not possible to provide a detailed critique of each stage in the three analyses given the partial reporting of the exploratory and confirmatory analyses undertaken or to replicate the network meta-analysis, the steps taken and the results appeared to be

reasonable, noting that several concerns described in section 6.8 has been addressed in the submission.

6.10 The network meta-analysis found CRT-D to have the strongest effect on all-cause mortality with a hazard ratio of [REDACTED] compared with medical therapy. The hazard ratio for all-cause mortality was [REDACTED] for CRT-P compared with medical therapy and [REDACTED] for ICD compared with medical therapy. The hazard ratio for all-cause mortality for CRT-D compared with CRT-P was [REDACTED] and for CRT-D compared with ICD it was [REDACTED]. For all cause-hospitalisation, the network meta-analysis indicated that across all NYHA classes, device therapy was associated with a reduction in admission rates. In NYHA class I to III, ICD was associated with a [REDACTED] reduction in admission rates, and CRT with a [REDACTED] reduction. The effect in NYHA class IV was more pronounced, with CRT associated with a [REDACTED] reduction in admission rates (although the data used to inform this result are sparse). Baseline estimates of health related quality of life using the EQ-5D from the network-meta-analysis showed that patients in NYHA I and II had similar values to the population norms, while patients in NYHA III and IV had values that were progressively lower. Some of the treatment estimates showed counter-intuitive results, for example results for CRT-D for NYHA III and IV class showed a decrease in health related quality of life, in contrast to those for CRT-P, possibly reflecting the limited individual patient data available. As a consequence, adjustments were made that assumed that CRT-P and CRT-D had the same effect on EQ-5D values and that ICDs had an effect on the quality of life of NYHA I and II only. The Assessment Group noted that for all-cause mortality, network meta-analyses were produced to compare outcomes with those using aggregate data from all trials in the network, finding no significant

differences. Similar comparisons were not produced for the other outcomes.

6.11 The manufacturers' submission included a survival-based model to estimate the relative cost-effectiveness of OPT, ICD, CRT-P and CRT-D, compared with each other. The UK NHS and PSS perspective was adopted and the model had monthly cycles and a lifetime time horizon. Costs and health benefits were discounted at 3.5%. The model has two health states: alive and dead. The manufacturers stated that death is the main clinical event for the patient population considered in this appraisal and by modelling death directly via a series of covariate based regression equations (for baseline risk and treatment effect), the long term data available could be used to explore the impact of patient-level heterogeneity. The manufacturers stated that this approach would also allow for a coherent regression-based approach to modelling health related quality of life and all-cause hospitalisation that was aligned with the mortality analysis, and that the alternative approach to capture the effect on health related quality of life using time-dependent progression through NYHA classes was technically difficult and less accurate. The Assessment Group stated that the fundamental features of the condition and the impact of the interventions seem to be captured in the manufacturers' model structure and while no assessment of internal validity of the model was included in the submission, it appeared to be intuitive.

6.12 Individual patient data from 12,638 patients were used to inform the manufacturers' economic model. Modeled patients were adults with heart failure with LVEF $\leq 35\%$, and/or at risk of sudden cardiac death. This heterogeneous group of patients was split into 48 subgroups according to their NYHA class, QRS duration, left bundle branch block (LBBB) status and aetiology of heart disease, and cost-effectiveness results are reported for each subgroup. In

order to model baseline mortality risk, a parametric survival curve (Weibull) was fitted to a pooled data set of all patients randomised to medical therapy in the included trials. The base-line probability of all-cause hospitalisation was estimated in a similar manner using individual patient data from 11 clinical trials. The relative effectiveness of the devices was estimated from individual patient data network meta-analysis as discussed in section 6.9. UK device longevity estimates were derived from NHS data from the Central Cardiac Audit Database on all implants with verified life status from 2000 to 2011 (around 40,000 implants). Device specific median survival estimates were obtained by fitting Weibull curves to this data. Median time to device failure in the model was 7.1 years for ICD, 10.4 years for CRT-P and 5.8 years for CRT-D.

- 6.13 The manufacturers' model does not include short-term device related adverse events as the costing approach used to derive total implant costs covered additional costs such as short term adverse events. Infection following device was included in the model for all procedures subsequent to the initial implant. The proportion of patients experiencing infection was estimated to be 0.8% and applied to all devices in the first cycle following battery replacement.
- 6.14 The resource use included device-related costs, medication, and resources related to disease progression. Individual patient data from the trials was used to estimate the mean number of all cause hospitalisation events per month and the mean number of days of hospitalisation per month. The hospital costs were derived from the NHS Schedule of Reference Costs and combined with the average mean length of hospital stay. The cost of hospitalisation because of heart failure was £2,295 and the non-heart failure hospitalisation cost was £2,448. Device costs were sourced from the average selling prices across the manufacturers for ICD, CRT-P and CRT-D

devices and leads sold in the UK to the NHS. The implantation costs were taken from the Healthcare Resource Group tariff values. . Device costs, including implantation costs, were estimated to be £15,248, £8,281 and £17,849 for ICD, CRT-P and CRT-D respectively. The Assessment Group stated that, overall, the derivation of costs and assumptions presented in the submission appeared to be appropriate and consistent with previous approaches.

- 6.15 The manufacturers' assumed that medical therapy which was considered optimal by current standards, that is, OPT was received by all patients for heart failure treatment, regardless of whether they received a device in addition. It was also assumed that the drug cost allocated in any given month to each patient was based on their baseline NYHA class. The proportion of patients using a range of medications, by NYHA class, was derived from a combination of the clinical studies identified in the systematic review and expert opinion. The recommended daily dose for each commonly used drug was sourced from the British National Formulary (BNF). The total cost of OPT treatment per 1 month cycle was £14.28 for NYHA class I and between £22.13 and £22.30 for NYHA class II-IV.
- 6.16 For modelling utility, general UK population utilities based on a study of 3,395 individuals resident in the UK were used at baseline to which disease-specific decrements taken from the CARE-HF, MADIT-CRT and RAFT trials were applied. The impact of each intervention on patients' health related quality of life was incorporated as intervention-specific increments, calculated as the difference between baseline and the first follow-up period. These estimates were derived from published sources and individual patient data from the trials included in the manufacturers' systematic review of clinical effectiveness studies. It was assumed

that the health related quality of life benefit from the intervention observed at six months is maintained up to five years and thereafter begins to decrease in a linear manner over a time period of five to ten years. After ten years, the model assumed that a person with a CRT or ICD device will have no additional benefit compared with an identical person receiving OPT. The Assessment Group stated that the submission did not report a systematic review of health-related quality of life studies and the approach differs from that of most previous models (including Buxton et al and Fox et al) where no benefit from the intervention was assumed. In addition, the impact of treatment-related adverse events (such as infection and perioperative complications) on quality of life, which was considered in previous models, was not included in the submission.

6.17 The base case deterministic results are presented for 48 subgroups defined by NYHA class, QRS duration, LBBB status, and aetiology (ischaemic or non-ischaemic), but are not presented for the population as a whole or according to the population groups scoped by NICE, and the Assessment Group stated that it is unclear how these results could be aggregated. The base case results are summarised in Table 1 below.

Table 1: Summary of the manufacturer's base case deterministic results

Heart failure severity	QRS duration	ICERs (cost per QALY gained)
<i>NYHA class I/II</i>	QRS duration < 120ms	ICD vs. OPT: £23,884 to £25,110
	QRS duration 120-149ms	In patients with no LBBB: CRT-D is dominated by ICD ICD vs. OPT: < £17,000. In patients with LBBB:

		CRT-D vs ICD or OPT : <£25,000 (£20,608 to £24,343)
	QRS duration ≥ 150ms	CRT-D in all comparisons: < £28,000
<i>NYHA class III</i>	QRS duration < 120ms	ICD vs. OPT: <£30,000 (£26,923 to £29,402)
	QRS duration 120-149ms	CRT-P vs. OPT: <£20,000. CRT-D vs. CRT-P: £23,900 - £27,400. ICD is either dominated or extendedly dominated with the exception of patients who are non-ischaemic and without LBBB. The ICER for ICD vs. OPT in this group is £19,760 per QALY gained.
	QRS duration ≥ 150ms	CRT-P vs. OPT: < £20,000 CRT- D vs. CRT-P, < £30,000. ICD is either dominated or extendedly dominated.
NYHA class IV	QRS duration < 120ms	No comparative analysis was possible in this patient group, as no patients were identified for this combination.
	QRS duration ≥120ms	CRT-P vs. OPT: <£20,000 CRT-D vs. CRT-P: > £30,000.

6.18 The following scenarios were tested in sensitivity analyses: removal of mortality and health related quality of life effect tapering, use of alternative NYHA based individual patient data results, and increase in device longevity. The base case assumed that treatment effects on mortality or health related quality of life are not constant but diminish over time. When constant treatment effects for mortality and quality of life were explored, ICERs in all patient groups were lower than in the base case. According to the manufacturers' submission, there may be a lower mortality benefit in patients with NYHA class IV compared with NYHA classes I/II/III

for CRT-D. The economic model was run using the estimated all-cause mortality effects based on the grouping of NYHA class IV compared with NYHA class I-III patients. This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups were lower than in the base case. Device longevity was investigated by increasing time to device failure by 10% and this resulted in minimal changes to the cost effectiveness results.

- 6.19 Probabilistic sensitivity analyses were conducted for 4 subgroups, selected to reflect the baseline characteristics of the MADIT-CRT trial, but no overall population analysis was performed due to the complexity of individual patient level data. Results were presented graphically for 4 patient profiles, that is: men with and without LBBB, and women with and without LBBB. The baseline characteristics of the MADIT-CRT trial was an age of 65-years, NYHA class II, ischemic etiology, QRS >150ms, LVEF between 20 and 25% patients. For these subgroups, CRT-D and OPT showed similar probability of being cost-effective at a threshold of £20,000 per QALY gained.
- 6.20 The manufacturers stated that caution should be taken not to over-interpret individual subgroups since anomalies may arise as a result of patient level characteristics which have not been accounted for. In addition, the power of this analysis to detect treatment effect modifiers was likely to be low for relatively modest effect modifiers, the trial data on which this analysis is based extends to 7.5 years and treatment effect beyond this point was uncertain. The manufacturers highlighted that the CARE-HF and MADIT II trials reporting extensive long-term follow-up were available were available for consideration. The Assessment Group stated that the manufacturers' submission did not provide any details of the variables included in the probabilistic sensitivity

analyses, such as mean values, distributions and variability of those variables. Credible intervals for mean ICERs of the most cost-effective interventions were also not reported. The Assessment Group therefore noted that it was not clear whether the methods of assessment of parameter uncertainty are appropriate and whether the estimates of variation in the probabilistic sensitivity analyses are appropriate to reflect uncertainty in parameter estimates.

Assessment Group Model

- 6.21 The Assessment Group adapted the developed by Fox et al. for NICE technology appraisal 120, 'Cardiac resynchronisation therapy for the treatment of heart failure'. Population 1, that is, people at increased risk of sudden cardiac death from ventricular arrhythmias had not been included in the previous model and the Assessment Group adapted the pathways for this population based on reviews of previous models and expert opinion. The Assessment Group developed a Markov model with monthly cycles over a lifetime time horizon (figure 1) and discounted all future costs and benefits at a rate of 3.5%.

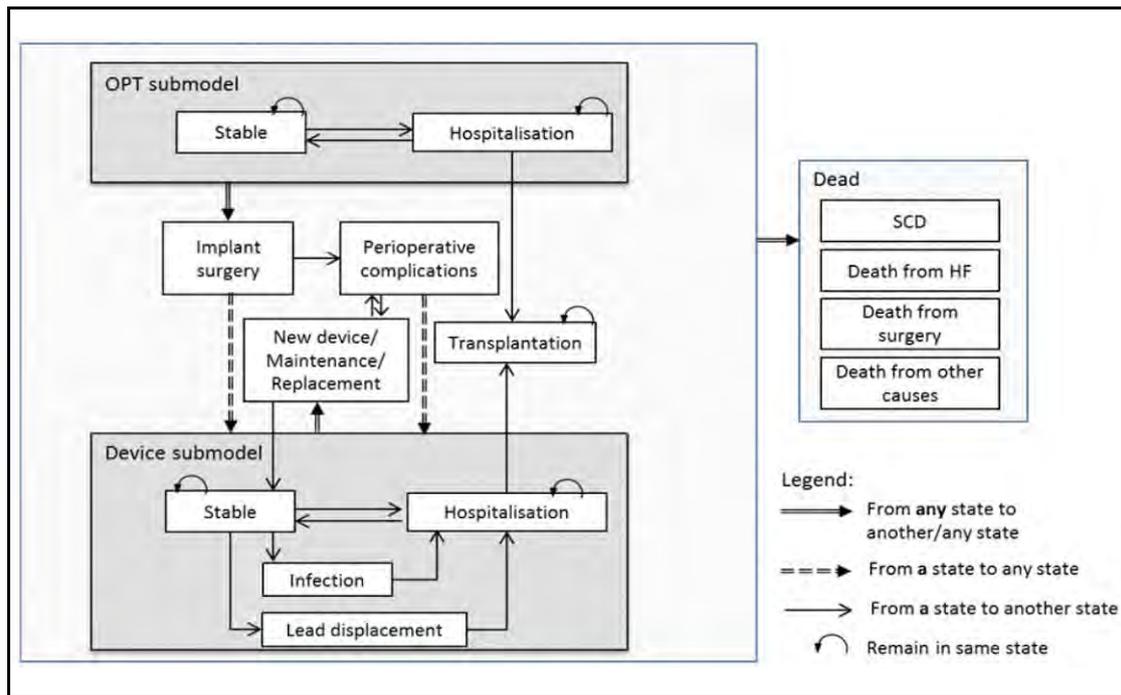


Figure 1: General schematic of the model

6.22 Patients in the comparator arm (managed with medical therapy) enter the model in the stable health state of the OPT sub-model, whereas patients with a device enter the model in the implant surgery state and will typically transition to the stable state in the device sub-model. Patients in a stable health state (either with OPT or with a device) can remain stable, be hospitalised because of heart failure or arrhythmia, or may die from causes other than heart failure of an arrhythmia. In addition, patients in a stable health state with a device may experience device-related adverse events (infection or lead displacement/ failure) or may require maintenance or replacement of their current device. Patients who are hospitalised because of heart failure may be referred for heart transplantation. Patients in any of the live health states (stable, hospitalised, and transplanted) can die from arrhythmia, heart failure, or any other cause (cardiac or non-cardiac). The 3 populations (1, 2 and 3) identified in the scope and described in the

clinical-effectiveness section were modelled. Transitions between health states vary according to the population group and the treatment received. Baseline characteristics (age, sex and, where relevant, proportion in NYHA class) for the modelled populations were based on values reported by relevant clinical trials.

- 6.23 For population 1, patients in the intervention arm enter the model undergoing ICD implantation surgery and therefore experience a risk of procedure-related death. Those who survive surgery and have a successful implantation can become stable with the device or be hospitalised because of heart failure, perioperative complications, lead displacement, infection, or battery failure. Patients who experience unsuccessful implantations are referred for re-implantation and are subject to the same risks as those who attempt implantation for the first time. Stable ICD patients can further be hospitalised because of heart failure, severe arrhythmia, lead displacement, infection, or battery failure. ICD patients who are hospitalised may continue to be hospitalised, return to the stable state after treatment, or may be referred for heart transplantation (if hospitalised for heart failure). Stable ICD patients are also subject to periodic battery replacement. As with initial implant surgery, and re-implantation, these routine replacement procedures expose the patient to risk of procedure-related death, perioperative complications and unsuccessful implantation.
- 6.24 In the comparator arm for population 1, patients enter the model in a stable health state where they are treated with OPT in order to prevent major ventricular arrhythmia. Stable OPT patients can remain stable, be hospitalised because of heart failure, or be hospitalised because of major arrhythmia and therefore referred for ICD implantation. Hospitalised patients can return to the stable health state after treatment, be referred for ICD implantation (if hospitalised for major arrhythmia), or be referred for transplantation

(if hospitalised for heart failure). The Assessment Group assumed that patients referred for ICD implantation follow the same pathway as those who enter the model in the ICD arm. The Assessment Group also presented a scenario analysis in which patients in the comparator arm were managed with OPT only, that is, without switching to ICD implantation.

- 6.25 The Assessment Group assumed that no risk of surgical failure is associated with lead displacements, that, if ICD was not successfully implanted, re-implantation would be attempted in the following cycle with the same risks of adverse events as the first implant. No risk of return to OPT alone was assumed after unsuccessful ICD implantation. The Assessment Group also assumed based on the Fox et al. model, that, people receiving OPT alone who are hospitalised because of a non-fatal arrhythmia receive an ICD and that people who are hospitalised because of heart failure (and had an arrhythmic event) receive an ICD and follow the ICD pathway in the following cycle.
- 6.26 For population 2, CRT-P in combination with OPT and CRT-D in combination with OPT were compared with each other as well as with OPT alone. For CRT-P, patients enter the model undergoing CRT-P implantation. Patients who survive the procedure with a successful CRT-P implantation may experience perioperative complications, lead displacement, infection, and hospitalisation due to heart failure or severe arrhythmia – those who do not experience any of these events transition to the stable state with CRT-P in combination with OPT. Patients who survive but have unsuccessful CRT-P implantations may return to the OPT stable health state or may be hospitalised because of heart failure or because of severe arrhythmia, and then progress in line with the pathway described below in section 6.28 for people receiving OPT alone. Stable CRT-P patients may be hospitalised if they experience heart failure, lead

displacement, infection, or battery failure. If hospitalised, they may return to a stable state after treatment, remain hospitalised, be referred for an upgrade to CRT-D if they experience serious arrhythmia, or be referred for a heart transplant if they experience worsening heart failure.

6.27 The treatment pathway for patients who received CRT-D is similar to patients who enter the model with CRT-P implantation surgery, except that patients who survive unsuccessful CRT-D implantations are assumed to receive ICD. Those who survive ICD implantation and have a successful implantation can become stable or be hospitalised because of heart failure or severe arrhythmia, perioperative complications, lead displacement, infection, or battery failure. Those who survive with unsuccessful ICD implantations are assumed to receive OPT alone and follow the pathway described below in section 6.28 for people receiving OPT alone.

6.28 For the comparator OPT arm, patients enter the model in a stable health state being treated with OPT in order to prevent heart failure. They may remain stable or be hospitalised because of heart failure or severe arrhythmia. If hospitalised, they may return to the stable health state after treatment, be referred for CRT-P implantation, CRT-D implantation, or transplantation. Patients referred for CRT devices follow a similar pathway to those described above for patients entering the model undergoing CRT-P or CRT-D implantation. The Assessment Group also explored a scenario where patients in the OPT arm were not assumed to receive any device despite failure of treatment with OPT.

6.29 The Assessment Group stated that the assumptions included those previously validated by clinical experts for TA120, as well as some additional assumptions based on clinical advice such as: people who survive unsuccessful CRT-D implantation are assumed to receive ICDs and, for consistency with unsuccessful CRT-P

implantation, patients who survive unsuccessful ICD implantation are assumed to return to receiving OPT alone.

6.30 For population 3, four cohorts were modelled initially receiving CRT-D in combination with OPT, CRT-P in combination with OPT, ICD in combination with OPT or OPT alone, with allowances for subsequent device implants and upgrades. The CRT-D cohort follows a pathway similar to that described for population 2 receiving CRT-D in combination with OPT above (section 6.27), except that if patients who received ICD because of unsuccessful CRT-D implantation, hospitalised because of heart failure are referred for CRT-D re-implantation. The CRT-P cohort follows a similar pathway to that described for population 2 receiving CRT-P in combination with OPT (see section 6.26). In the ICD cohort, patients enter the model undergoing ICD implantation surgery. Those who survive with successful ICD implantations can become stable or be hospitalised because of heart failure, serious arrhythmic event, perioperative complications, lead displacement, infection, or battery failure. Patients hospitalised for heart failure receive a CRT-D implant. Those who survive with unsuccessful ICD implantations are assumed to be managed with OPT alone and follow the OPT pathway described below (section 6.31).

6.31 In the OPT alone cohort, patients may remain stable or be hospitalised because of heart failure or severe arrhythmia. Patients hospitalised for heart failure may return to the stable health state after treatment, be referred for CRT-P implantation, CRT-D implantation, or transplantation. Patients who are hospitalised because of serious arrhythmia are referred for a CRT-D implant. Patients referred for CRT devices follow a similar pathway to those described above for population 3 patients entering the model receiving CRT-P or CRT-D (section 6.30).

- 6.32 The Assessment Group stated that some assumptions from the model by Fox et al. were maintained in their model, such as patients receiving OPT alone or CRT-P who experience a serious arrhythmic event are assumed to be referred for CRT-D implantation. Patients with an ICD who are hospitalised because of heart failure are also assumed to receive CRT-D and can either become stable with the device or be hospitalised because of heart failure, perioperative complications, lead displacement, or infection, in the following cycle. However, the Assessment Group made some additional assumptions, confirmed by clinical experts, that patients who survive unsuccessful CRT-D implantation would undergo ICD implantations and patients who survive unsuccessful ICD implantation would return to OPT alone.
- 6.33 In addition, several modelling assumptions were common across the 3 populations. These included: - patients hospitalised because of perioperative complications are assumed to have no risk of surgical death or surgical failure; patients hospitalised because of heart failure while receiving OPT are assumed to have a no risk of remaining hospitalised because of heart failure in the following cycle; only patients who are hospitalised because of heart failure are assumed to be at risk of heart transplant; patients referred to transplantation are assumed to remain in this health state until they die; that the probability of death post-transplant is assumed to be lower than that for non-transplanted patients, except in the first cycle; and that all patients undergoing surgery are assumed to have the same risk of surgery failure. Transition probabilities for moving between health states were based on the estimates of clinical effectiveness from the relevant trials identified in the systematic review.

Population 1

6.34 In population 1, survival data reported in the AVID trial was modelled for the base-case analysis. Survival data from the MADIT II trial was considered representative of a subgroup of patients who had increased risk of ventricular arrhythmia because of previous myocardial infarction. The results from the SCD-HeFT trial were used to inform a subgroup analysis of patients with mild-moderate heart failure. An additional subgroup analysis was conducted for patients with cardiomyopathy using data from a subgroup of patients with non-ischaemic congestive heart failure from SCD-Heft trial. Kaplan-Meier curves for overall survival for the medical therapy arms of the relevant trials were used to derive the baseline mortality risk of patients receiving OPT. Parametric (Weibull) models were fitted to these curves to derive approximate hazard functions and to estimate survival beyond trial follow-up. For patients in the ICD arm of the model, transition probabilities to death were estimated by applying the relative risks estimated in systematic review of clinical effectiveness to the baseline transition probabilities of the OPT arm. For the base case analysis, the pooled relative risk of ICDs compared with OPT 0.75 (95% CI 0.61 to 0.93) was used (section 4.4). For primary prevention in the subgroup of patients with remote myocardial infarction, a pooled relative risk from MADIT I and MADIT II of 0.57 (95% CI 0.33 to 0.97) was used (section 4.15). A relative risk of 0.77 (95% CI 0.66 to 0.89) reported in SCD-HeFT was used for patients with mild to moderate heart failure (section 4.27), and a pooled relative risk of 0.74 (95% CI 0.58, 0.93) was used for patients with cardiomyopathy (section 4.19).

6.35 A risk of hospitalisation because of heart failure of 0.0082 (95% CI 0 to 0.0202) per cycle from the MADIT II trial was incorporated in the model for patients at risk of sudden cardiac death being managed with ICD or OPT, assuming that ICDs have no effect on heart failure hospitalisations. As no robust estimation of

hospitalisation rate due to non-fatal arrhythmia for this population was available, the Assessment Group assumed, based on clinical advice, that the baseline probability of a patient receiving OPT to be hospitalised for a non-fatal arrhythmia to be the same as that of patients with heart failure (population 2) (0.0075, 95% CI 0.0002, 0.0148), derived from the number of events in both medical therapy and CRT-P arms of the MIRACLE trial. In addition, the probability of being referred for ICD implantation in patients who are hospitalised because of heart failure while on OPT alone was assumed to be the same as that for patients with heart failure (population 2) in the medical therapy arm of the CARE-HF trial who were referred for CRT-D implantation (0.0018 [95% CI 0 to 0.0059]).

- 6.36 Adverse events occurring with ICDs were categorised into those occurring at time of implantation (or during the initial in-patient stay) and longer term adverse events. Adverse events at the time of implantation included procedure-related mortality, surgical complications and implant failure while longer term adverse events included lead displacements, infections and device malfunctions and dislodgements. The probability of procedure-related death was taken from the pooled estimate from trials (MADIT II, DEFINITE, DINAMIT, DEBUT and CASH) reporting perioperative deaths related to the implantation procedure; a pooled probability of 0.003 (95% CI 0 to 0.055) per cycle was incorporated in the base case analysis, based on 5 procedure-related deaths among 1449 patients. Because the trials included in the Assessment Group's systematic review did not explicitly report data on implant failure, a probability of 0.011 (95% CI 0.009, 0.013) reported in a systematic review of randomised control trials and observational studies conducted by Ezekowitz et al. was incorporated in the model. Similarly, probabilities of peri-operative complications of 0.053 (95% CI 0.046 to 0.062), of post-operative complications of

0.0012 (95% CI 0.0010 to 0.0014) and of infection of 0.0005 (95% CI 0.0004 to 0.0006) were incorporated from this systematic review.

6.37 The distribution of patients by NYHA class was sourced from the baseline distribution of patients in the AVID trial for secondary prevention, and the MADIT II and SCD-HeFT trials for primary prevention of sudden cardiac death and majority of people were in NYHA class I and II (see page 309 of the Assessment Report for further details).

Population 2

6.38 For population 2, for time dependent transition to death, the model accounts for cardiac mortality and for non-cardiac mortality. Baseline time-dependent probabilities of sudden cardiac death and death due to heart failure were derived from survival curves in the medical therapy group of the CARE-HF trial after parameterization (Weibull fitting). For patients receiving devices (CRT-P, CRT-D, or ICD), time-dependent death probabilities were derived by applying device-specific hazard ratio or relative risk to the baseline probabilities. The relative effect on heart failure deaths of CRT-P was obtained from the meta-analysis of the CARE-HF and COMPANION trials which reported a risk ratio of 0.67 for CRT-P compared with medical therapy and for CRT-D compared with medical therapy, a hazard ratio of 0.73 (95% CI 0.47 to 1.11) was included from the COMPANION trial. No effect on sudden cardiac death was assumed in the model (a relative risk of 1) as this estimate was assumed to range between the relative risks reported in the most relevant trials (0.54 in CARE-HF and 1.13 in the COMPANION trial). The relative risk of sudden cardiac death for CRT-D compared to medical therapy was sourced from the COMPANION trial (HR=0.44, 95% CI 0.23 to 0.86). For patients who switched to ICD because of CRT-D implant failure, the relative

risks for sudden cardiac death for ICD compared with medical therapy of 0.44 (95% CI 0.31 to 0.61) was sourced from the SCD-HeFT trial. The SCD-HeFT trial also reported a relative risk of 1.14 (95% CI 0.88 to 1.48) for non-arrhythmic cardiac death which the Assessment Group incorporated as relative risk of death due to heart failure. Non-cardiac death rates were estimated from the 2010 Mortality Statistics for England and Wales and gender proportions of patients with heart failure were estimated based on the 2011 statistics for incidence of heart failure by gender reported by the British Heart Foundation.

- 6.39 For the hospitalisation baseline risk estimate, a pooled estimate of 0.037 (95% CI 0.025 to 0.049) per cycle was included based on the number of events reported for the medical therapy arm in the relevant trials (CARE-HF, MIRACLE, MUSTIC and COMPANION). The relative risk of hospitalisation because of heart failure with CRT-P compared with OPT alone was estimated to be 0.58 (95% CI 0.35 to 0.96) based on pooling data from the CARE-HF, COMPANION, MIRACLE, and MUSTIC trials. For CRT-D compared with OPT, a relative risk of 0.77 (95% CI 0.63 to 0.93, $p=0.008$) was included from the COMPANION trial. As per the assumption in the original model by Fox et al., the risk of hospitalisation because of heart failure for patients with ICD was assumed to be the same as for patients receiving OPT.
- 6.40 The probability of death related to CRT-P implant surgery included in the model was 0.048 (95% CI 0.0015 to 0.0081) per cycle, derived from the number of events reported in the 4 trials included for population 2 and a probability of 0.005 (95% CI 0 to 0.0107) per cycle was derived from the COMPANION trial for CRT-D. Similarly a probability of implant failure of 0.084 (95% CI 0.070, 0.097) per cycle was estimated for patients with CRT-P and of 0.087 (95% CI 0.064 to 0.109) per cycle for patients with CRT-D. The probability of

peri-operative complications related to CRT implantation for both CRT-P and CRT-D (0.1063 was sourced from Fox and colleagues model. For probability of lead displacement, a pooled risk of 0.0037 (95% CI 0.0004 to 0.0071) from 3 trials (CARE-HF, MIRACLE and MUSTIC) was used in the model for both CRT-P and CRT-D. The probability of device-related infections in patients with CRT-P of 0.0006 (95% CI 0 to 0.002) and for patients with CRT-D of 0.0006 (95% CI 0 to 0.0015) per cycle was derived from the trials reporting this outcome.

- 6.41 According to the treatment pathway (section 6.31) patients receiving OPT can be referred for CRT-P or CRT-D implantation, and patients with CRT-P can be referred for CRT-D following hospitalisation. These probabilities of device upgrade after hospitalisation were derived from the CARE-HF trial. Based on clinical opinion, the Assessment Group assumed that patients would receive ICD only in case of failure to implant CRT-D, and estimated this probability by multiplying the probability of upgrading from OPT to CRT-D by the probability of CRT-D implant. For patients who receive an ICD, the probabilities for ICD-related adverse events are considered to be the same as for those who received ICD in population 1 (see section 6.36).
- 6.42 The Assessment Group incorporated the same distribution of heart failure patients by NYHA class used in the model by Fox and colleagues. The Assessment Group noted that this was derived based on the distribution of patients per NYHA class at baseline and 90 days in the CARE-HF trial (for further details see page 315 of the Assessment Report).

Population 3

- 6.43 For population 3, base line mortality was modelled by parametrically (Weibull) fitting Kaplan-Meier curves for all-cause

mortality from the CRT-D arm of the RAFT trial which had the longest average follow-up period of 40 months. The survival data from the MADIT-CRT trial (average follow-up period of 28.8 months) was used in a scenario analysis. The Assessment Group estimated all-cause mortality for patients receiving OPT alone, ICD in combination with OPT, or CRT-P in combination with OPT by applying the hazard ratio or relative risk estimated in the systematic review. No trials for this population compared OPT alone with CRT-D in combination with OPT, therefore a hazard ratio from the COMPANION trial (for population 2) was used assuming that the same relative effect could be expected in this population. Also, since no direct estimates of relative effectiveness of CRT-P and CRT-D were available for this population, and the comparison reported in the COMPANION trial in population 2 was not statistically robust, the Assessment Group assumed the risk of all-cause mortality for patients with CRT-P to be the same as for those with CRT-D with a sensitivity analysis by varying the relative risk between 0.80 to 1.20.

- 6.44 The Assessment Group derived a baseline risk of hospitalisation because of heart failure of 0.0077, 95% CI 0.0027 to 0.0128) for patients in the CRT-D arm of the model from the number of patients experiencing at least one hospitalisation during the follow-up period in the CONTAK-CD, Piccirillo, and RAFT trials. This estimate was considered conservative as some patients in the trials may have experienced more than one episode of hospitalisation and hence it was likely to underestimate the total number of hospitalisations and consequently resource use. The relative risk for hospitalisation because of heart failure of patients with ICD compared with CRT-D was estimated to be 1.33 (95% CI 1.14 to 1.56) as the reverse of the risk ratio of 0.75 (95% CI 0.64 to 0.88) obtained by pooling data from the CONTAK-CD, Piccirillo, and RAFT trials. Since the COMPANION trial reported no significant differences in

hospitalisations because of heart failure between CRT-P and CRT-D for population 2, the Assessment Group modelled the risk of hospitalisation in CRT-P equal to the risk estimated for the CRT-D arm for population 3. The COMPANION trial also reported a statistically significant difference in heart failure hospital admissions per patient between CRT-D and OPT arms. The relative risk estimated for hospitalisations because of heart failure with OPT compared with CRT-D was used in the model for calculating risk of hospitalisation in the OPT arm of the model.

6.45 The baseline risk of hospitalisation for arrhythmia for the CRT-D arm of the model (0.029, 95% CI 0.015 to 0.042) was derived from trials (MIRACLE, MICACLE ICD II, CONTAK-CD1, and Pinter) reporting the number of patients with CRT-D experiencing at least one episode of ventricular fibrillation. The Assessment Group stated that this approach was likely to underestimate the total number of hospitalisations for arrhythmic events. For the ICD arm the inverse of the relative risk estimated in the meta-analysis was used, that is, 1.11 (95% CI 0.88 to 1.41) (section 4.49). In the absence of any robust evidence, the Assessment Group assumed that the risk for hospitalisation because of arrhythmia for patients managed with OPT alone or with CRT-P was the same as that of patients with CRT-D. Device-related adverse events were poorly reported in the trials included in the systematic review of population 3 and the Assessment Group assumed the same risks of device related adverse events for Population 3 as those for Population 2 (section 6.40).

6.46 The number of patients by NYHA class at baseline was reported in the RAFT trial but no evidence on the effect of the devices on heart failure progression was found; hence the model assumes no effect on patient's distribution by NYHA class. An alternative scenario explored the impact of accounting for the potential benefit of CRT

devices, assuming that 50% of patients with a CRT device improve 1 NYHA class at 6 months of treatment.

6.47 Some parameters were common to all populations; these include age-related mortality (same as in Fox and colleagues' model) , distribution of heart device implants by age (from a report commissioned by the British Cardiovascular Society, the British Heart Foundation and the Cardio & Vascular Coalition), rate of heart transplant surgery (from the MIRACLE trial), mortality associated with transplant surgery (from UK Cardiothoracic Transplant Audit) and in the post-transplant mortality (same as in Fox and colleagues' model). The utility value of patients in stable health states was modelled to vary according to their NYHA class. A utility value of 0.57 was used for hospitalisation and a decrement of 0.05 was applied to health states involving surgery (including initial device implantation, device-related complications and device replacement) and a decrement of 0.1 for infection was also included.. The distribution of patients by NYHA class reported at baseline in the relevant trials for Population 1 were used in combination with utility values by NYHA class by Gohler et al. to estimate a NYHA-class weighted average utility value. The Gohler et al. utility values were 0.855 for NYHA I, 0.771 for NYHA II, 0.673 for NYHA III and 0.532 for NYHA IV. For Population 2, the impact of CRT on health related quality of life over time was captured in the model by changes in the distribution of patients with heart failure by NYHA class derived from the relevant trials. For Population 3, no robust evidence of the effect of devices on heart failure progression was found and CRT and ICD devices were assumed to have no impact on the distribution of patients by NYHA class over time. The model assumed similar utility values for patients with CRT, ICD, or OPT alone for the same NYHA class. In addition, for all population groups, the utility estimates for transplantation were assumed to be similar to those for hospitalised

patients and post-transplanted patients were assumed to have similar utility estimates as NYHA class I patients.

6.48 To estimate resource use, the Assessment Group considered costs of devices, device implantation, device-related complications and maintenance, hospitalisation because of heart failure or severe arrhythmia, medication and heart transplantation. The model estimates resource use associated with each intervention based on event rates and patient transition probabilities among the different health states. Unit costs associated with each resource used were then applied for estimation of total cost per intervention. Estimates of device longevity were also sourced from the joint manufacturers' submission that reported the Kaplan-Meier plots of time to device replacement derived from data submitted to the Central Cardiac Audit Database and estimates of mean time to replacement were derived from the reported survival functions. Clinical advice indicated that the longevity might have been overestimated and shorter device longevity was explored in a sensitivity analysis. The mean device cost was estimated to be £3411, £12,293 and £9692 for CRT-P, CRT-D and ICD respectively (see page 332 of the Assessment Report for a complete breakdown of device related total costs used in the model). In the model, patients with heart failure in both the intervention and comparator arms were assumed to receive a combination of drugs according to their NYHA class, and this medical therapy was considered optimal by current standards. The drugs, their daily doses and proportions were included in the Assessment Group base-case analysis based on the joint manufacturers submission. Unit costs for the drugs were derived from the British National Formulary (BNF) 61. The cost of OPT management for Population 1 patients without heart failure was assumed to be the same as that for patients in NYHA I. For population 2 and 3, this cost was dependent on the number of patients in each NYHA class.

Table 2: Proportion of drugs (OPT) by NYHA class and associated cost

Drug (mg/day)	Proportion of patients by NYHA class (Cost £)			
	I	II	III	IV
Atorvastatin (10)	20% (0.38)	20% (0.38)	20% (0.38)	20% (0.38)
Simvastatin (20)	55% (0.50)	55% (0.50)	55% (0.50)	55% (0.50)
Warfarin (1)	10% (0.09)	15% (0.13)	25% (0.21)	40% (0.34)
Clopidogrel (75)	15% (0.35)	15% (0.35)	15% (0.35)	15% (0.35)
Ramipril (10)	90% (1.25)	90% (1.25)	90% (1.25)	90% (1.25)
Carvedilol (25)	85% (1.37)	85% (1.37)	75% (1.21)	70% (1.13)
Spironolactone (25)	0% (0)	30% (0.43)	30% (0.43)	30% (0.43)
Digoxin (125) ^a	5% (0.05)	25% (0.25)	25% (0.25)	25% (0.25)
Furosemide (60)	75% (1.8)	80% (1.92)	90% (2.16)	95% (2.28)
Eplerenone (25)	0% (0)	30% (12.82)	30% (12.82)	30% (12.82)
Total cost (£)	5.78	19.39	19.56	19.73

^a Dosing measured in µg per day.

Results of Assessment Group's economic analysis and sensitivity analysis

Population 1

6.49 In the base-case analysis, in a mixed gender cohort of 65 year old patients, ICD in combination with OPT arm were associated with incremental QALYs of 0.80, incremental costs of £15,492 and an ICER of £19,479 per QALY gained compared with OPT alone. These results presented by age group indicated that the ICER increases with age, ranging from £17,083 per QALY gained at 30 years to £28,211 per QALY gained at 80 years. The Assessment Group also presented results for a mixed age and gender cohort, using the distribution of ICD implants by age in the UK as proxy for the distribution of patients at increased risk of sudden cardiac death due to ventricular arrhythmia. The results indicated incremental

QALYs of 0.7, incremental costs of £15,279 and an ICER of £24,967 per QALY gained for ICD in combination with OPT compared with OPT alone.

- 6.50 The Assessment Group also presented subgroup analyses for ICD in combination with OPT compared with OPT alone. First, for patients with remote myocardial infarction, using MADIT II all-cause mortality for a cohort of 64-year old patients, the ICER was £14,231 per QALY gained. Second, for patients with mild-moderate heart failure, the ICER was £29,756 per QALY gained and third, for patients with cardiomyopathy, the ICER was £26,028 per QALY gained. Please refer to section 6.34 for details of the estimates incorporated in these analyses.
- 6.51 The Assessment Group conducted univariate sensitivity analyses on the key inputs in the model. The inputs which had most impact were using a time horizon of 3 years rather than a lifetime time horizon which increased the ICER for ICD in combination with OPT compared with OPT alone to £141,235 per QALY gained; using upper limit of 95% CI for risk ratio of all cause mortality for ICDs compared to OPT of 0.93 which resulted in an ICER of £78,268 per QALY gained; and increasing the risk of surgery-related death to 0.055 which resulted in an ICER of £32,605 per QALY gained (see page 339 of the Assessment Report for further details).
- 6.52 The Assessment Group also conducted a scenario analysis in an appendix to the Assessment Report where it was assumed that in the OPT alone arm, patients would not receive an ICD if they were not responding to OPT alone. This resulted in an incremental QALY of 1.16, incremental cost of £26,294 and an ICER of £22,710 for ICD in combination with OPT compared with OPT alone. In another scenario analysis, incorporating higher device related costs, that is using the upper limit of the 95% CI for device-related costs resulted in an ICER of £37,832 per QALY gained. Other scenario analyses

did not have a substantial impact on the ICER, please see page 341 and 342 of the Assessment Report.

6.53 The Assessment Group also performed a probabilistic sensitivity analysis for the base case to estimate the impact of joint parameter uncertainty on the model's cost-effectiveness results. The resulting probabilistic mean ICER was £20,479 per QALY gained. The addition of ICD to OPT for secondary prevention of sudden cardiac death has a 51% probability of being cost-effective at £20,000 per QALY gained, and a probability of 82% at £30,000 per QALY gained.

Population 2

6.54 For the base case analysis, the Assessment Group modelled a 70 year-old mixed-gender cohort of patients with heart failure. The comparison of CRT-P in combination with OPT with OPT alone resulted in incremental QALYs of 0.69, incremental costs of £18,845 and an ICER of £27,584 per QALY gained. The comparison of CRT-D in with CRT-P (both in combination with OPT) resulted in incremental QALYs of 0.41, incremental costs of £11,703 and an ICER of £28,420 per QALY gained. As for population 1, these results presented by age group indicated that the ICER increases with age, estimated at approximately £32,000 per QALY gained for both comparisons at 80 years. The Assessment Group also presented an ICERs for a mixed age and gender cohort which were estimated as £28,928 per QALY gained for the comparison of CRT-P with OPT and £30,321 per QALY gained for the comparison of CRT-D with CRT-P.

6.55 The Assessment Group conducted a scenario analysis reported in an addendum to the Assessment Report where it was assumed that in the OPT alone arm, patients would not receive any device even if they were not responding to OPT alone. This resulted in a

reduction in costs in the OPT alone arm from £7615 to £7300, resulting an ICER of £27,644 per QALY gained for CRT-P in combination with OPT compared with OPT alone and an ICER of £28,429 per QALY gained for CRT-D compared with CRT-P (both in combination with OPT). In other scenario analyses conducted by the Assessment Group, for the comparison of CRT-P with OPT alone, varying device related costs had the most impact on the ICER with estimates ranging from £20,977 to £48,486 per QALY gained and varying the utility assumptions reduced the ICER to £22,892 per QALY gained. For the comparison of CRT-D with CRT-P, incorporating higher device related costs resulted in a higher ICER of £61,967 per QALY gained and assuming a shorter device lifetime resulted in an ICER of £34,416 per QALY gained.

6.56 The Assessment Group conducted a range of sensitivity analyses. For the comparison of CRT-P with OPT alone, the inputs which had most impact were: using a lower risk of hospitalisation for non-fatal arrhythmia with CRT-P of 0.0002, instead of 0.0075, which reduced the ICER to £15,780 per QALY gained; assuming a greater relative risk of heart failure death with CRT-P of 0.88, rather than, 0.67, which increased the ICER to £36,019 per QALY gained; and assuming a greater relative risk of heart failure death with CRT-D of 1.11, rather than 0.73, which increased the ICER to £34,720 per QALY gained. Sensitivity analyses on inputs for the comparison of CRT-D with CRT-P had substantial impacts on the ICER and these are summarised in table 5, appendix C.

6.57 The Assessment Group conducted scenario analyses to assess the effect of change in assumption in the model on the base-case ICERs. Assuming shorter lifetime of devices as used in the previous model by Fox and colleagues results in slightly higher cost for all strategies with minimal effect on the QALYs and the overall effect was that both OPT and CRT-P strategies are either

dominated or extendedly dominated by CRT-D which is associated with a lower ICER of £23,690 per QALY gained compared to ICD. Other scenarios like use of utility values as in the Fox and colleagues' and assuming CRT devices improve NYHA class by 1 in 50% of patients at 6 months, have no substantial effect on the ICERs. Varying device cost to their upper and lower limits of 95% of confidence interval resulted in the ICERs associated with CRT-D ranging from £13,829 to £60,864 per QALY gained.

- 6.58 The Assessment Group's resulting probabilistic mean ICER for CRT-P compared with OPT alone was £27,434 per QALY gained while the probabilistic mean ICER for CRT-D compared with CRT-P was £27,899 per QALY gained. At £20,000 per QALY gained, OPT alone has the highest probability of being cost-effective (83%) while at £30,000 per QALY gained, CRT-D and CRT-P have 46% and 31% probability of being cost-effective, respectively compared to OPT alone (23%).

Population 3

- 6.59 CRT-P was associated in the model with a marginally higher cost and slightly fewer QALYs than CRT-D, and was therefore dominated by CRT-D. When compared with the next most cost-effective option, that is, OPT alone, the ICER was £41,414 per QALY gained and CRT-P was therefore extendedly dominated by CRT-D compared with OPT alone as this was associated with a smaller ICER of £35,193 per QALY gained. Therefore, the base-case analysis estimated incremental QALYs of 0.10, incremental costs of £287 and an ICER of £2824 for OPT alone compared with ICD therapy; and incremental QALYs of 0.31, incremental costs of £10,906 and an ICER of £35,193 per QALY gained for CRT-D compared with OPT only.

- 6.60 The Assessment Group's scenario analysis in which it was assumed that patients in the OPT arm cannot receive ICD or CRT devices even if they were not responding to OPT alone, resulted in a reduction in estimated costs by £30,580 and in estimated benefits by 0.88 QALYs compared with the base case OPT only arm so that OPT alone became the least costly and least effective strategy. As before, CRT-P was extendedly dominated by CRT-D, and ICD was also extendedly dominated by CRT-D. Therefore, for the relevant comparison of CRT-D with OPT alone, incremental costs were £41,485, incremental QALYs of 1.18 and the ICER was £35,010 per QALY gained. The Assessment Group stated that in this scenario analysis, though incremental costs of the interventions compared with OPT had substantially increased, a corresponding gain in incremental QALYs had resulted in similar ICERs as in the base case analyses.
- 6.61 In another scenario analysis, the Assessment Group included estimates of all-cause mortality reported for men in the CRT-D arm, and the respective hazard ratio for ICD for the whole population, from the MADIT-CRT trial (1.00, 95% CI 0.69, 1.44). The results showed that CRT-P and CRT-D are less effective and more costly than ICD and hence both CRT strategies were extendedly dominated by ICD compared with OPT alone. Therefore, the results obtained with MADIT-CRT data indicate that ICD as the most cost-effective strategy, with an ICER of £154 per QALY gained compared with OPT alone.
- 6.62 The Assessment Group reported results from sensitivity analyses only for those changes when variation between the 95% CI limits caused a change of more than £20,000 per QALY gained in the ICER. These are summarised in the table 9, appendix C for the relevant comparisons. Scenario analyses were conducted and these are described in table 10 of the appendix C. The ICERs

remained similar to the base case when it was assumed that 50% of patients with a CRT device would improve 1 NYHA class at 6 months of treatment and also when alternative utility estimates used by Fox et al. were incorporated.

- 6.63 The Assessment Group conducted probabilistic sensitivity analyses and these results are consistent with the deterministic results. At £20,000 per QALY gained, the probability of OPT alone being cost-effective was 57%, 37% for ICD, and approximately 3% for CRT-D and for CRT-P. At £30,000 per QALY gained, OPT alone, ICD, CRT-D, and CRT-P have 44%, 31%, 15%, and 10% probability of being cost-effective respectively.

7 Equalities issues

- 7.1 Consultees highlighted during scoping consultation and in the evidence submitted that there were significant differences in access to device therapy across the UK.

8 Innovation

- 8.1 No claims for innovation were presented. However, consultees commented that ICD and CRT devices had revolutionised the treatment of arrhythmias and heart failure.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Chronic heart failure. NICE clinical guideline 108(2010). Available from www.nice.org.uk/guidance/CG108
- Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120(2007). Available from www.nice.org.uk/guidance/TA120

Recommendations:

1.1 Cardiac resynchronisation therapy with a pacing device (CRT-P) is recommended as a treatment option for people with heart failure who fulfil all the following criteria.

- They are currently experiencing or have recently experienced New York Heart Association (NYHA) class III–IV symptoms.
- They are in sinus rhythm:
 - **either** with a QRS duration of 150 ms or longer estimated by standard electrocardiogram (ECG)
 - **or** with a QRS duration of 120–149 ms estimated by ECG **and** mechanical dyssynchrony that is confirmed by echocardiography.
- They have a left ventricular ejection fraction of 35% or less.
- They are receiving optimal pharmacological therapy.

1.2 Cardiac resynchronisation therapy with a defibrillator device (CRT-D) may be considered for people who fulfil the criteria for implantation of a CRT-P device in section 1.1 and who also separately fulfil the criteria for the use of an ICD device as recommended in [NICE technology appraisal guidance 95](#).

- Implantable cardioverter defibrillators for arrhythmias. NICE technology appraisal guidance 95 (2006). Available from www.nice.org.uk/guidance/TA95

Recommendations

1.1 ICDs are recommended for patients in the following categories.

1.1.1 'Secondary prevention', that is, for patients who present, in the absence of a treatable cause, with one of the following:

- having survived a cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF)
- spontaneous sustained VT causing syncope or significant haemodynamic compromise
- sustained VT without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF of less than 35%) (no worse than class III of the New York Heart Association functional classification of heart failure).
- 1.1.2 'Primary prevention', that is, for patients who have:
 - a history of previous (more than 4 weeks) myocardial infarction (MI)

either

- left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure), **and**
- non-sustained VT on Holter (24-hour electrocardiogram [ECG]) monitoring, **and**
- inducible VT on electrophysiological (EP) testing

or

- left ventricular dysfunction with an LVEF of less than 30% (no worse than class III of the New York Heart Association functional classification of heart failure) **and**
- QRS duration of equal to or more than 120 milliseconds
- a familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia (ARVD), or have undergone surgical repair of congenital heart disease.

NICE pathways

- There is a NICE pathway on chronic heart failure, which is available from <http://pathways.nice.org.uk/pathways/chronic-heart-failure>

Appendix B: Summary result of the systematic review and meta-analysis by the Assessment Group

People at risk of SCD as a result of ventricular arrhythmias (population 1)

Population	No. of included trial	Event rate (n/N)		Relative effect (relative risk or hazard ratio)	95% CI	Reference
		ICDs	Medical therapy			
All-cause mortality						
Population 1 overall	13 +1 pilot study	819/4200	1251/4935	0.81	0.71 to 0.93	Figure 4 (page 86 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	4 trials+1 pilot study	199/981	311/1068	0.75	0.61 to 0.93	Figure 4 (page 86 of AR)
Subgroup-people with a recent myocardial	2	178/777	175/795	1.04	0.86 to 1.25	Figure 4 (page

infarction (primary prevention)						86 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	120/837	136/591	0.57	0.33 to 0.97	Figure 4 (page 86 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	3	38/330	49/335	0.77	0.52 to 1.15	Figure 4 (page 86 of AR)
Subgroup-people scheduled for CABG surgery	1	102/446	96/454	1.08	0.85 to 1.38	Figure 4 (page 86 of AR)
Subgroup-people with mild to moderate HF	1	182/829	484/1692	0.77	0.66 to 0.89	Figure 4 (page 86 of AR)
Total cardiac deaths						
Population 1 overall	10	567/3825	845/4478	0.80	0.69 to 0.92	Figure 5 (page 88 of AR)
Subgroup of people with cardiac arrest	2	130/835	177/840	0.74	0.61 to 0.91	Figure 5 (page

(secondary prevention)						88 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	141/777	148/795	0.97	0.79 to 1.20	Figure 5 (page 88 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	90/837	107/591	0.59	0.42 to 0.83	Figure 5 (page 88 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	2	8/101	5/106	2.03	0.17 to 23.62	Figure 5 (page 88 of AR)
Subgroup-people scheduled for CABG surgery	1	76/446	79/454	0.98	0.74 to 1.30	Figure 5 (page 88 of AR)
Subgroup-people with mild to moderate HF	1	122/829	329/1692	0.76	0.63 to 0.92	Figure 5 (page 88 of AR)
Sudden cardiac deaths/arrhythmic deaths						

Population 1 overall	13 +1 pilot study	194/4200	540/4935	0.45	0.38 to 0.53	Figure 6 (page 94 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	4 trials+1 pilot study	67/981	167/1068	0.49	0.34 to 0.69	Figure 6 (page 94 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	39/777	89/795	0.45	0.31 to 0.64	Figure 6 (page 94 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	31/837	62/591	0.36	0.23 to 0.55	Figure 6 (page 94 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	3	4/330	16/335	0.26	0.09 to 0.77	Figure 6 (page 94 of AR)
Subgroup-people scheduled for CABG surgery	1	15/446	28/454	0.55	0.30 to 1.01	Figure 6 (page 94 of AR)

Subgroup-people with mild to moderate HF	1	38/829	178/1692	0.44	0.31 to 0.61	Figure 6 (page 94 of AR)
Non-arrhythmic cardiac deaths						
Population 1 overall	11	382/4054	377/4707	1.21	1.01 to 1.45	Figure 7(page 97 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	2	76/835	79/840	0.97	0.72 to 1.31	Figure 7(page 97 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	102/777	59/795	1.77	1.30 to 2.44	Figure 7(page 97 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)	2	50/837	34/591	0.95	0.41 to 2.18	Figure 7(page 97 of AR)
Subgroup- people with cardiomyopathy	3	16/330	14/335	1.13	0.42 to 3.03	Figure 7(page 97 of AR)

(primary prevention)						
Subgroup-people scheduled for CABG surgery	1	57/446	46/454	1.26	0.87 to 1.82	Figure 7(page 97 of AR)
Subgroup-people with mild to moderate HF	1	81/829	145/1692	1.14	0.88 to 1.48	Figure 7(page 97 of AR)
Non-cardiac deaths						
Population 1 overall	10	171/3825	216/4478	1.02	0.83 to 1.25	Figure 8 (page 101 of AR)
Subgroup of people with cardiac arrest (secondary prevention)	2	33/835	43/840	0.79	0.45 to 1.37	Figure 8 (page 101 of AR)
Subgroup-people with a recent myocardial infarction (primary prevention)	2	37/777	27/795	1.39	1.86 to 2.27	Figure 8 (page 101 of AR)

Subgroup-people with remote myocardial infarction (primary prevention)	2	26/837	18/591	1.06	0.58 to 1.95	Figure 8 (page 101 of AR)
Subgroup- people with cardiomyopathy (primary prevention)	2	2/101	4/106	0.65	0.13 to 3.29	Figure 8 (page 101 of AR)
Subgroup-people scheduled for CABG surgery	1	25/446	17/454	1.50	0.82 to 2.73	Figure 8 (page 101 of AR)
Subgroup-people with mild to moderate HF	1	48/829	107/1692	0.92	0.66 to 1.27	Figure 8 (page 101 of AR)
Hospitalisations						
Subgroup of people with cardiac arrest (secondary prevention)						
AVID trial (N=1011)	- at 1 year	59.5%	55.6%		p value; 0.04	Table 24 (page 106 of AR)
	- at 2 years	74.8%	64.7%			Table 24 (page

						106 of AR)
	- at 3 years	83.3%	75.5%			Table 24 (page 106 of AR)
Subgroup-people with remote myocardial infarction (primary prevention)						
Hospitalisation due to heart failure (MADIT II)	Hospitalisation due to heart failure, n (%)	148 (19.9)	73 (14.9)			Table 24 (page 106 of AR)
	Patients hospitalised, per 1000 months of active follow-up	11.3	9.4		p value; 0.09	Table 24 (page 106 of AR)

People with heart failure as a result of LVSD and cardiac dyssynchrony (population 2)

Comparison	No. of included trial	Event rate (n/N)		Relative effect (relative risk or hazard ratio)	95% CI	Reference
		Intervention	Comparator			
All-cause mortality						
CRT-P vs. medical therapy	4	247/1312	247/995	0.75	0.58 to 0.96	Figure 10 (page 157 of AR)
CRT-D vs. medical therapy	1	71/595	59/308	0.64	0.48 to 0.86	Table 34 (page 156 of AR)
CRT-P vs. CRT-D	1	131/617	105/595	1.20	0.96 to 1.52	Table 34 (page 156 of AR)
Total cardiac deaths						

CRT-P vs. medical therapy	MUSTIC	2/29	0/29	7.00	0.37 to 132.56	Table 35 (page 158 of AR)
	COMPANION	109/617	58/308	0.94	0.70 to 1.25	Table 35 (page 158 of AR)
CRT-D vs. medical therapy	COMPANION	76/595	58/308	0.68	0.50 to 0.93	Table 35 (page 158 of AR)
CRT-P vs. CRT-D	COMPANION	109/617	76/595	1.38	1.06 to 1.81	Table 35 (page 158 of AR)
Heart failure deaths						
CRT-P vs. medical therapy	2	91/1026	98/712	0.67	0.51 to 0.88	Figure 11 (page 161)
CRT-D vs. medical therapy	1	52/595	34/308	0.73	0.47 to 1.11	Table 36 (page 160)
CRT-P vs. CRT-D	1	53/617	52/595	0.98	0.68 to 1.42	Table 36 (page 160)

Sudden cardiac death						
CRT-P vs. medical therapy	3	82/1084	72/770	0.97	0.44 to 2.44	Figure 12 (page 160 of AR)
CRT-D vs. medical therapy	1	17/595	18/308	0.44	0.23 to 0.86	Table 37 (page 163)
CRT-P vs. CRT-D	1	48/617	17/595	2.72	1.58 to 4.68	Table 37 (page 163)
Number of people hospitalised due to heart failure						
CRT-P vs. medical therapy	4	272/1283	288/966	0.61	0.44 to 0.83	Figure 13 (page 167 of AR)
CRT-D vs. medical therapy	1	166/595	112/308	0.77	0.63 to 0.93	Table 39 (page 166 of AR)
CRT-P vs. CRT-D	1	179/617	166/595	NR	Not significant	(page 165 of AR)

Number of hospitalisations due to heart failure						
CRT-P vs. medical therapy	4			0.58	0.35 to 0.96	Figure 14 (page 168 of AR)
Worsening heart failure						
CRT-P vs. medical therapy	3	204/695	288/688	0.71	0.63 to 0.80	Figure 15 (page 170 of AR)
Participants with improvement in ≥ 1 NYHA class						
CRT-P vs. medical therapy	3	696/1109	301/799	1.68	1.52 to 1.86	Figure 16 (page 175 of AR)
CRT-D vs. medical therapy	1	283/497	76/199	2.14	2.14 to 1.53	Table 43 (page 174 of AR)
CRT-P vs. CRT-D	1	298/489	283/497	0.93	0.84 to 1.04	Table 43 (page 174 of AR)

Change in LVEF (Median change from base line)						
CRT-P vs. medical therapy	1	: +4.6,	-0.2		p<0.001	Figure 16 (page 175 of AR)
Change in 6-minute walk distance at 6 months						
CRT-P vs. medical therapy	3			Mean difference 38.14	21.74 to 54.54	Figure 17 (page 176 of AR)
CRT-D vs. medical therapy	1	46	1		<0.001	Table 44 (page 177 of AR)
CRT-P vs. CRT-D	1	40	46	MD -6.0	-19.87 to 7.87	Table 44 (page 177 of AR)

People with both conditions (population 3)

Population	No. of included trial	Event rate (n/N)		Relative effect (relative risk or hazard ratio)	95% CI	Reference
		CRT-D	ICD			
All-cause mortality						
Population 3 overall	9	302/2722	327/2342	0.84	0.73 to 0.96	Figure 19 (page 208 of AR)
Subgroup of NYHA class II	3	262/2086	291/1736	0.82	0.71 to 0.96	Figure 19 (page 208 of AR)
Subgroup of NYHA class III	5	40/638	136/591	0.95	0.60 to 1.50	Figure 19 (page 208 of AR)
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 19 (page 208 of AR)

Total cardiac deaths						
Population 3 overall	7	145/1446	177/1429	0.82	0.67 to 1.00	Figure 20 (page 209 of AR)
Subgroup of NYHA class II	2	132/979	164/1005	0.81	0.66 to 1.01	Figure 20 (page 209 of AR)
Subgroup of NYHA class III	4	13/451	13/409	0.89	0.40 to 1.96	Figure 20 (page 209 of AR)
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 20 (page 209 of AR)
Heart failure deaths						
Population 3 overall	4	6/433	10/446	0.64	0.18 to 2.22	Figure 21 (page 210 of AR)
Subgroup of NYHA class II	1	0/85	0/101	Not estimable		Figure 21 (page 210 of AR)

Subgroup of NYHA class III	2	6/332	10/330	0.64	0.18 to 2.22	Figure 21 (page 210 of AR)
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 21 (page 210 of AR)
Sudden cardiac deaths						
Population 3 overall	6	6/703	4/671	1.45	0.43 to 4.92	Figure 22 (page 211 of AR)
Subgroup of NYHA class II	1	2/85	1/101	2.38	0.22 to 25.76	Figure 22 (page 211 of AR)
Subgroup of NYHA class III	4	4/602	3/555	1.22	0.29 to 5.04	Figure 22 (page 211 of AR)
Subgroup of NYHA class IV	1	0/16	0/15	Not estimable		Figure 22 (page 211 of AR)
Arrhythmias						

Population 3 overall	4	104/553	118/564	0.90	0.71 to 1.14	Figure 24 (page 215 of AR)
Subgroup of NYHA class II	1	19/85	26/101	0.87	0.52 to 1.46	Figure 24 (page 215 of AR)
Subgroup of NYHA class III	3	85/468	92/463	0.91	0.70 to 1.18	Figure 24 (page 215 of AR)
Change in NYHA class (mean difference)						
Population 3 overall	3			Mean difference: -0.19	-0.34 to -0.05	Figure 25 (page 218 of AR)
Subgroup of NYHA class II	1	-0.18	0.01	-0.19	-0.37 to -0.01	Figure 25 (page 218 of AR)
Subgroup of NYHA class III	2			-0.20	-0.43 to 0.03	Figure 25 (page 218 of AR)
Proportion of people with improvement in NYHA class						

Population 3 overall	3	93/201	61/211	1.81	0.91 to 3.60	Figure 26 (page 218 of AR)
Subgroup of NYHA class III	2	80/185	60/196	1.44	0.87 to 2.38	Figure 26 (page 218 of AR)
Subgroup of NYHA class IV	1	13/16	1/15	12.19	1.81to 82.15	Figure 26 (page 218 of AR)
Change in LVEF (mean difference)						
Population 3 overall	8			2.15	0.45 to 3.86	Figure 27 (page 221 of AR)
Subgroup of NYHA class II	2			5.05	0.23 to 9.87	Figure 27 (page 221 of AR)
Subgroup of NYHA class III	5			0.79	-0.58 to 2.16	Figure 27 (page 221 of AR)
Subgroup of NYHA class IV	1	28	22	6.00	1.50 to 10.50	Figure 27 (page 221 of AR)

Change in peak VO₂ (mean difference)						
Population 3 overall	5			0.75	0.23 to 1.27	Figure 28 (page 222 of AR)
Subgroup of NYHA class II	1	0.5	0.2	0.30	-0.75 to 1.35	Figure 28 (page 222 of AR)
Subgroup of NYHA class III	4			0.84	-0.23 to 1.46	Figure 28 (page 222 of AR)
Change in 6-minute walk distance (mean difference)						
Population 3 overall	6			14.53	2.94 to 26.11	Figure 29 (page 222 of AR)
Subgroup of NYHA class II	1	38	33	5.00	-26.33 to 36.33	Figure 29 (page 222 of AR)
Subgroup of NYHA class III	5			16.04	3.56 to 28.51	Figure 29 (page 222 of AR)

Appendix C: Summary results of the cost-effectiveness analysis by the Assessment Group

Population 1

Table 1: Base-case result population 1

Description	ICD+OPT		OPT		ICER (£/QALY)
	Costs (£)	QALYs	Costs	QALYs	
Base-case ICD for secondary prevention of SCD Mixed gender cohort of 65-year old patients (all cause mortality from AVID trial)	31,382	6.75	15,890	5.95	19,479
Mixed age cohort (distribution of ICD implants by age used for the age distribution of patients)	31,838	6.91	16,559	6.17	24,967
ICD for primary prevention of SCD in patients with remote MI using MADIT II all-cause mortality for a cohort of 64-year old patients	31,583	6.35	14,783	5.17	14,231
ICD for primary prevention of SCD in patients with mild-moderate heart failure (60 year-old patients with mild-moderate heart failure with indication for an ICD, all-cause mortality of the placebo arm, the RR for ICD of 0.77 (95% CI 0.66, 0.89), and the distribution of patients by NYHA class from the SCD-HeF)	32,416	6.28	17,760	5.79	29,756
ICD for primary prevention of SCD in patients with cardiomyopathy 60 year-old patients with cardiomyopathy, a pooled RR of 0.74 (95% CI 0.58, 0.93) from the non-ischaemic subgroup of SCD-HeFT, AMIOVIRT, CAT, and DEFINITE. The SCD-HeFT distribution of patients by NYHA	40,218	8.42	24,845	7.83	26,028

Table 2 Univariate sensitivity analysis results for Population 1

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALY	ICER (£/QALY gained)
Base case	-	-	15,492	0.80	19,479
<i>Survival and HRs</i>					
All-cause mortality HR (ICD)	0.75	0.61	17,126	1.37	12,480
		0.93	13,772	0.18	78,268
<i>Event probabilities</i>					
Risk of surgery related death (ICD)	0.003	0	15,491	0.82	18,950
		0.055	15,507	0.48	32,605
Device lifetime ln(λ) and γ	-15.78 1.94 (~ 8 years)	-16.182 1.889 (~13 years)	13,158	0.80	16,456
		-15.385 1.996 (~5 years)	19,467	0.79	24,706

Table 3: Scenario analyses population1

Scenario	Description	ICD+OPT		OPT		ICER (£/QALY)
		Costs (£)	QALYs	Costs	QALYs	
Base-case	ICD for secondary prevention of SCD	31,382	6.75	15,890	5.95	19,479
OPT only for comparator arm	patients in the comparator arm being managed with OPT only (no upgrades to a device)	31,382	6.75	5,088	5.59	22,710
Alternative assumption for risk of hospitalisation due to arrhythmia	risk of hospitalisation due to arrhythmia was assumed to be 0.032 for both the arms	37,120	6.74	29,759	6.34	18,185
Alternative assumption about utility	a mean utility estimate of 0.75 irrespective of NYHA class and treatment arm					22,372
Alternative assumption about device related cost*	Upper limit of 95% CI					37,832
	lower limit of 95% CI					16,888
* include cost associated with implantation, perioperative complications, treatment of lead displacement, infection, and device replacement						

Population 2

Table 4. Base case and OPT only scenario analysis results for Population 2

Strategy	Cost (£)	QALYs	ICER (£/QALY gained)
Base case (vs. next best option^b)			
OPT	7,615	3.48	-
CRT-P + OPT	26,460	4.17	27,584
CRT-D + OPT	38,163	4.58	28,420
OPT only scenario (vs. next best option^b)			
OPT only	7,300	3.47	-
CRT-P + OPT	26,430	4.17	27,644
CRT-D + OPT	38,162	4.58	28,429

^b Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated;

Table 5: Population 2 subgroup, univariate, scenario and probabilistic analyses for CRT-P+ vs. OPT

CRT-P+OPT vs. OPT		Intervention		Comparator		
Description		Costs (£)	QALYs	Costs	QALYs	ICER (£/QALY)
Base-case (mixed gender cohort of 70-year old patients)		26,460	4.17	7,615	3.48	27,584
Mixed age cohort (using distribution of patients with heart failure by age group reported in literature)		28,016	4.47	8,218	3.75	28,928
Risk of hospitalisation for non-fatal arrhythmia with CRT-P (0.0075)	0.0002					15,780
	0.0148					31,978
RR of HF death with CRT-P(0.67)	0.51					23,307
	0.88					36,019
RR of HF death with CRT-D(0.73)	0.47					23,522
	1.11					34,720
RR of SCD with CRT-P (1)	0.54					19,825
	1.13					30,925
Scenario analyses						
OPT only scenario		26,430	4.17	7,300	3.47	27,644
Shorter devices' lifetime (using the device lifetime estimates in Fox and colleagues)		28,555	4.15			31,334
Alternative utility assumption (utility estimates used by Fox and colleagues)		26,460	4.21			22,892
Alternative assumption about device related cost*	Upper limit of 95% CI					48,486

	lower limit of 95% CI					20,977
Probabilistic sensitivity analysis						
PSA was performed to by 10,000 iterations		25,874	4.14	7,604	3.48	27,434***
* include cost associated with implantation, perioperative complications, treatment of lead displacement, infection, and device replacement						
** supplement of the Assessment Report						
*** Interquartile range (16,314; 47,527)						
Blank cells indicate that values have not been reported in the Assessment Report						

Table 6: Population 2 subgroup, univariate, scenario and probabilistic analyses for CRT-D+OPT vs. CRT-P+OPT

Description	CRT-D		CRT-P		ICER (£/QALY)
	Costs (£)	QALYs	Costs	QALYs	
Base-case (mixed gender cohort of 70-year old patients)	38,163	4.58	26,460	4.17	28,420
Mixed age cohort (using distribution of patients with heart failure by age group reported in literature)	39,932	4.88	28,016	4.47	30,321
Scenario analyses					
Shorter devices' lifetime (using the device lifetime estimates in Fox and colleagues)	42,627	4.56	28,555	4.15	34,416
Alternative utility assumption (utility estimates used by Fox and colleagues)	38,163	4.63	26,460	4.21	27,893
Alternative assumption about device related cost*	Upper limit of 95% CI				61,967
	lower limit of 95% CI				28,090
Probabilistic sensitivity analysis					
PSA was performed to by 10,000 iterations	38,156	4.56	25,874	4.14	27,899 ***

Univariate sensitivity analysis				
Parameter (base-case value)	Value in sensitivity analysis	ΔCosts (£)	ΔQALYs	ICER (£/QALY)
RR of HF death with CRT-D (0.72)	0.47	13,754	0.78	17,602
	1.11	9,545	0.01	793,839
RR of SCD with CRT-P (1)	0.54	10,063	0.06	169,196
	1.13	12,108	0.50	24,250
RR of SCD with CRT-D (0.44)	0.23	12,817	0.62	20,180
	0.86	9,912	0.08	129,220
Device lifetime (CRT-D), (~7y)	~13yrs	8,608	0.43	20,238
	~4yrs	17,811	0.38	46,640
RR of HF death with CRT-P(0.67)	0.51	10,966	0.25	43,231
	0.88	12,563	0.60	21,042
Risk of hospitalisation for non-fatal arrhythmia with CRT-P(0.0075)	0.0002	21,857	0.54	40,450
	0.0148	6,335	0.34	18,707
Baseline mortality due to HF, $\ln(\lambda)$, γ (-6.115, 1.223)	-6.253, 1.180	12,546	0.52	24,157
	-5.977, 1.265	10,864	0.31	35,220
Baseline mortality due to SCD, $\ln(\lambda)$, γ , (-6.069, 1.140)	-6.173, 1.107	11,460	0.33	34,318
	-5.964, 1.173	11,924	0.49	24,316

Population 3

Table 8: Population 3 Base case and OPT only scenario

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
Base case (vs. next best option^b)				
ICD + OPT	39,719	7.45	5.57	-
OPT	40,006	7.59	5.67	2,824
CRT-P + OPT	51,202	7.96	5.94	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	35,193
OPT only scenario (vs. next best option^b)				
OPT only	9,426	6.41	4.79	-

ICD + OPT	39,719	7.45	5.57	Extendedly dominated
CRT-P + OPT	51,202	7.96	5.94	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	35,010

Table 9 Population 3 univariate sensitivity analysis

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Univariate sensitivity analysis results for CRT-D + OPT vs OPT					
Base case	-	-	10,906	0.31	35,193
RR of all-cause mortality (OPT)	1.563	1.163	9,109	0.07	124,733
		2.083	12,972	0.58	22,240
Univariate sensitivity analysis results for OPT vs. ICD + OPT					
Base case	-	-	287	0.10	2,824
Device lifetime (CRT-D)	(~7y)	(~13y)	-6,129	0.12	Dominant
		(~4y)	8,653	0.07	123,385

Device lifetime (ICD)	(~ 8 years)	(~13 years)	3,505	0.10	35,868
		- (~5 years)	-5,086	0.11	Dominant
Baseline risk of hospitalisation for non-fatal arrhythmia (CRT-D)	0.0285	0.0146	-4,565	-0.09	49,987
		0.0424	2,086	0.19	10,896
RR of hospitalisation for non-fatal arrhythmia (OPT)	1	0.8	-1,978	0.04	Dominant
		1.2	1,923	0.15	13,107
RR of hospitalisation for non-fatal arrhythmia (ICD)	1.11	0.88	2,330	0.10	22,346
		1.41	-2,334	0.10	Dominant
Baseline risk of all-cause mortality (CRT-D), $\ln(\lambda), \gamma$	-6.334, 1.234	-6.467, 1.198	2,047	0.14	14,124
		-6.202, 1.270	-1,092	0.06	Dominant
Lead displacement CRT-D	0.0037	0.0004	-1,083	0.11	Dominant
		0.0071	1,600	0.09	17,916

Table 10: Population 3 scenario analysis

Scenario analyses	
Shorter devices' lifetime (using the device lifetime estimates in Fox and colleagues)	OPT dominated ICD + OPT, CRT-D + OPT extendedly dominated CRT-P + OPT ICER for CRT-D + OPT vs. ICD + OPT: £23,690 per QALY gained
Estimates of all-cause mortality reported for men in the CRT-D arm, and the respective hazard	Both CRT-P+OPT and CRT-D+OPT extendedly dominated by ICD+OPT ICER for ICD+OPT vs. OPT: £154 per QALY gained

ratio for ICD for the whole population, from the MADIT-CRT trial (1.00, 95% CI 0.69, 1.44).			
Alternative assumption about device related cost	Upper limit of 95% CI	CRT-D + OPT vs. ICD + OPT	£50,824
		CRT-D + OPT vs.CRT-P + OPT	£43,853
		CRT-D + OPT vs.OPT alone	£60,864
	lower limit of 95% CI	CRT-D + OPT vs.ICD + OPT	£22,271
		CRT-D + OPT vs.CRT-P + OPT	£13,829
		CRT-D + OPT vs.OPT alone	£28,200

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation

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Date completed 29th January 2013

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Source of funding: This report was commissioned by the NIHR HTA Programme as project number 10/109/01 and will be published in full in *Health Technology Assessment* (www.hta.ac.uk/1698).

Declared competing interests of authors

None.

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare 1) no financial support for the submitted work from anyone other than their employer; 2) no financial relationships with commercial entities that might have an interest in the submitted work; 3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and 4) no non-financial interests that may be relevant to the submitted work.

Acknowledgements

We would like to thank members of our advisory group panel who provided expert advice and comments on the protocol, map of eligible trials, clinical pathways, and/or a draft of this report: Dr R Anderson, Associate Professor of Health Economics and Evaluation & Deputy Director, Peninsula Technology Assessment Group (PenTAG), University of Exeter; Professor AJ Camm, Professor of Clinical Cardiology, St George's Hospital Medical School, London; J Fearnley, Head of Strategic Operations, Arrhythmia Alliance The Heart Rhythm Charity; Dr A Morley-Davies, Consultant Cardiologist/Electrophysiologist, University Hospital of North Staffordshire; Dr C Pepper, Consultant Cardiologist, Leeds General Infirmary; Dr D Todd, Liverpool Heart and Chest Hospital NHS Foundation Trust.

We are also grateful to Karen Welch, Information Specialist, SHTAC, University of Southampton, for generating and running the literature searches, Geoff Frampton, Research Fellow, SHTAC, University of Southampton, for contributing to the background section, Jeremy Jones, Principal Research Fellow in Health Economics, SHTAC, University of Southampton, for contributing to the development of the protocol and economic evaluation, and Jonathan Shepherd, Principal Research Fellow, SHTAC, University of Southampton, for reviewing a draft of this report.

Rider on responsibility for the report

The views and opinions expressed in this report are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. *Health Technology Assessment* 2013.

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TABLE OF CONTENTS

Executive Summary	12
1 BACKGROUND	24
1.1 Description of underlying health problem	24
1.1.1 Sudden cardiac death	24
1.1.2 Heart Failure	26
1.2 Description of the technology under assessment	28
1.3 Management of the disease	32
1.3.1 SCD	32
1.3.2 HF	34
1.4 Current service provision	37
2 DEFINITION OF THE DECISION PROBLEM	40
2.1 Decision problem	40
2.2 Overall aims and objectives of assessment	41
3 METHODS for the systematic reviewS of clinical effectiveness and cost-effectiveness	42
3.1 Identification of studies	42
3.2 Inclusion and exclusion criteria	43
3.2.1 Population	43
3.2.2 Interventions	43
3.2.3 Comparators	44
3.2.4 Outcomes	44
3.2.5 Study design	45
3.3 Screening and data extraction process	45
3.4 Critical appraisal	45
3.5 Method of data synthesis	46
4 CLINICAL EFFECTIVENESS	47
4.1 Overall quantity of evidence identified	47
4.2 People at risk of sudden cardiac death as a result of ventricular arrhythmias	51
4.2.1 Quantity and quality of research available	51
4.2.1.1 Characteristics of the included studies	54
4.2.1.2 Risk of bias	78
4.2.1.3 Methodological comments	81
4.2.2 Assessment of effectiveness	82
4.2.2.1 All-cause mortality	82
4.2.2.2 Total cardiac deaths	86
4.2.2.3 Sudden cardiac death/arrhythmic deaths	90
4.2.2.4 Cardiac non-arrhythmic deaths	94
4.2.2.5 Other causes of death: non-cardiac deaths	97
4.2.2.6 Cumulative mortality	101
4.2.2.7 Survival	102
4.2.2.8 Heart failure hospitalisations	103
4.2.2.9 Symptoms/complications related to arrhythmias	103
4.2.2.10 QoL	108
4.2.2.11 Adverse Events	122
4.2.2.12 Subgroup analyses reported by included RCTs	133
4.2.3 Other relevant trials	136
4.2.4 Summary of clinical effectiveness: people at risk of sudden cardiac death as a result of ventricular arrhythmias	138
4.3 People with heart failure as a result of LVSD and cardiac dyssynchrony	143
4.3.1 Quantity and quality of research available	143
4.3.1.1 Characteristics of the included studies	143
4.3.1.2 Risk of bias	150

4.3.1.3	Methodological comments.....	153
4.3.2	Assessment of effectiveness.....	154
4.3.2.1	All-cause mortality.....	154
4.3.2.2	Total cardiac deaths.....	157
4.3.2.3	Heart failure deaths.....	159
4.3.2.4	Sudden cardiac death.....	161
4.3.2.5	Other causes of death.....	162
4.3.2.6	Hospitalisations due to heart failure.....	165
4.3.2.7	Arrhythmias.....	170
4.3.2.8	Worsening heart failure.....	170
4.3.2.9	Change in NYHA class.....	173
4.3.2.10	Change in LVEF.....	175
4.3.2.11	Exercise capacity.....	175
4.3.2.12	QoL.....	179
4.3.2.13	Adverse events.....	182
4.3.2.14	Subgroup analyses reported by included RCTs.....	187
4.3.3	Summary of clinical effectiveness: people with heart failure as a result of LVSD and cardiac dyssynchrony.....	190
4.4	People with both conditions.....	193
4.4.1	Quantity and quality of research available.....	193
4.4.1.1	Characteristics of the included studies.....	193
4.4.1.2	Risk of bias.....	201
4.4.1.3	Methodological comments.....	204
4.4.2	Assessment of effectiveness.....	206
4.4.2.1	All-cause mortality.....	206
4.4.2.2	Total cardiac deaths.....	208
4.4.2.3	Heart failure deaths.....	210
4.4.2.4	Sudden cardiac death.....	211
4.4.2.5	Other causes of death.....	212
4.4.2.6	Survival.....	212
4.4.2.7	Hospitalisations related to heart failure.....	213
4.4.2.8	Arrhythmias.....	214
4.4.2.9	NYHA class.....	216
4.4.2.10	Worsening heart failure.....	218
4.4.2.11	Left ventricular ejection fraction.....	219
4.4.2.12	Exercise capacity.....	221
4.4.2.13	QoL.....	224
4.4.2.14	Adverse events.....	227
4.4.2.15	Subgroup analyses reported by included RCTs.....	236
4.4.3	Summary of clinical effectiveness: people with both conditions.....	243
4.5	Summary of SHTAC peer review of clinical effectiveness in the ABHI joint submission.....	245
4.5.1	Individual patient level data network meta-analysis: a critical appraisal.....	245
4.5.1.1	Methods.....	246
4.5.1.2	Results.....	249
4.5.1.3	Discussion.....	256
5	ECONOMIC ANALYSIS.....	258
5.1	Systematic review of existing cost-effectiveness evidence.....	258
5.1.1	Quantity and quality of research available.....	259
5.1.2	Economic evaluations of ICDs.....	260
5.1.2.1	Buxton and colleagues ⁴²	268
5.1.3	Economic evaluations of CRT.....	269
5.1.3.1	Fox and colleagues, ⁴³ Bond and colleagues ²⁰³	272
5.1.4	Summary of published economic evaluations.....	276
5.2	Systematic review of health-related quality of life studies.....	277
5.2.1	Summary of the health-related quality of life review.....	281

5.3	Review of the manufacturers' submission	282
5.3.1	Review of the ABHI submission to NICE	282
5.3.2	Modelling approach	283
5.3.3	Assumptions	284
5.3.4	Estimation of effectiveness	284
5.3.5	Critical appraisal of the MS model	286
5.3.6	Estimation of QALYs	287
5.3.7	Estimation of costs	288
5.3.8	Cost-effectiveness results	289
5.3.9	Summary of ABHI submission	292
5.3.10	Critique of the ABHI submission	292
5.4	Independent economic evaluation	294
5.4.1	Statement of the decision problem and perspective for the cost-effectiveness analysis	294
5.4.2	Strategies and comparators	294
5.4.3	Methods for economic analysis	295
5.4.3.1	Model type and rationale for model structure	295
5.4.3.2	Relevant patient populations	297
5.4.3.3	Treatment options to be evaluated	297
5.4.3.4	Treatment pathways	298
5.4.3.5	Discounting	304
5.4.3.6	Presentation of results for the base case analyses	304
5.4.3.7	Assessment of uncertainty	304
5.4.4	Data Sources and Parameter Estimates	305
5.4.4.1	Population 1 - patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT	305
5.4.4.2	Population 2 - Patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT	310
5.4.4.3	Population 3 - Patients with both conditions	317
5.4.4.4	Parameters common to all populations	321
5.4.5	Results of independent economic analysis	334
5.4.5.1	Population 1 - patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT	334
5.4.5.2	Population 2 - Patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT	343
5.4.5.3	Population 3 - Patients with both conditions	357
5.4.6	Summary of independent economic evaluation	373
6	ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES	376
7	DISCUSSION	377
7.1	Statement of principal findings	377
7.1.1	Clinical effectiveness	377
7.1.1.1	People at risk of sudden cardiac death: ICDs compared with OPT	377
7.1.1.2	People with heart failure as a result of LVSD and cardiac dyssynchrony: CRT-P or CRT-D compared with each other or with OPT	381
7.1.1.3	People with both conditions: CRT-D compared with OPT, CRT-P or ICD	383
7.1.1.4	Summary of industry-submitted IPD NMA	385
7.1.2	Cost effectiveness	387
7.1.2.1	Summary of previously published economic evaluations	387
7.1.2.2	Summary of systematic review of quality of life studies	387
7.1.2.3	Summary of industry-submitted economic evaluation	387
7.1.2.4	Summary of independent economic model	388
7.2	Strengths and limitations of the assessment	390
7.3	Uncertainties	395
8	CONCLUSIONS	396
8.1	Implications for service provision	396
8.2	Suggested research priorities	396

9	REFERENCES.....	397
10	APPENDICES.....	415

APPENDICES

Appendix 1: Comparison of inclusion criteria in previous and present TARs	415
Appendix 2: Review methods from the research protocol.....	415
Appendix 3: Sources of information, including databases searched and search terms.....	415
Appendix 4: Economic evaluation checklist.....	415
Appendix 5: List of excluded clinical effectiveness studies and recent abstracts.....	415
Appendix 6: Ongoing trials.....	415
Appendix 7: Hospitalisations: total, cardiac and non-cardiac.....	415
Appendix 8: Data extraction: people at risk of sudden cardiac death due to ventricular arrhythmias	415
Appendix 9: Data extraction: people with heart failure as a result of LVSD and cardiac dyssynchrony	415
Appendix 10: Data extraction: people with both conditions.....	415
Appendix 11: SHTAC peer review of manufacturers' submission	415
Appendix 12: List of excluded economic evaluations	415
Appendix 13: Data extraction: cost-effectiveness.....	415
Appendix 14: List of excluded QoL studies	415
Appendix 15 Parameters included in the probabilistic sensitivity analyses.....	415
Appendix 16 Regression analyses for deriving model parameters	415
Appendix 17 Validation of the independent economic model.....	415

TABLES

Table 1: Deaths in England and Wales due to CHD and SCD in 2010	25
Table 2: NYHA Heart Failure Classification.....	27
Table 3: Device implant rates in England during 2010 compared with national targets ⁵⁸	38
Table 4 Combinations of presenting symptoms and ECGs in resynchronisation and defibrillation device implant patients in England, 2010 (%) ⁵⁸	39
Table 5: Summary of inclusion criteria.....	43
Table 6: List of RCTs included in the systematic review of clinical effectiveness	49
Table 7: Summary of included studies.....	52
Table 8: Study characteristics: Cardiac arrest survivors / ventricular arrhythmia - Secondary prevention	56
Table 9: Study characteristics: Post-Myocardial infarction - Primary prevention.....	58
Table 10: Study characteristics: Cardiomyopathy, CABG surgery, Heart failure - Primary prevention	60
Table 11: Key participant characteristics: cardiac arrest - secondary prevention.....	65
Table 12: Key participant characteristics: myocardial infarction (MI).....	67
Table 13: Participant characteristics: cardiomyopathy; CABG surgery; heart failure.....	68
Table 14: Medication at discharge: cardiac arrest/MI.....	73
Table 15: Medication: Cardiomyopathy / CABG surgery / Heart failure.....	75
Table 16: Risk of bias	80
Table 17: All-cause mortality	84
Table 18: Total cardiac deaths	89
Table 19: Sudden cardiac deaths/arrhythmic deaths.....	92
Table 20: Non-arrhythmic cardiac deaths.....	96
Table 21: Other causes of death (non-cardiac)	99
Table 22: Cumulative mortality	104
Table 23: Survival.....	105
Table 24: Hospitalisations.....	106
Table 25: Symptoms/complications related to arrhythmia	107
Table 26: Quality of life outcomes	112
Table 27: Adverse events.....	124

Table 28: SCD-HeFTsubgroups.....	135
Table 29: Included RCTs for people with heart failure	143
Table 30: Study characteristics	145
Table 31: Key Participant characteristics.....	147
Table 32: Medication at baseline.....	149
Table 33: Risk of bias	152
Table 34: All-cause mortality	156
Table 35: Total cardiac deaths	158
Table 36: Heart failure deaths.....	160
Table 37: Sudden cardiac death	163
Table 38: Other causes of death.....	164
Table 39: Hospitalisations related to heart failure: number of people	166
Table 40: Hospitalisations related to heart failure: number of events and/or days of admission.....	169
Table 41: Arrhythmias	172
Table 42: Worsening heart failure	172
Table 43: Changes in NYHA class	174
Table 44: Change in 6-minute walk.....	177
Table 45: Change in peak oxygen consumption	178
Table 46: Quality of Life Measures	180
Table 47: Adverse events for participants with a CRT device (randomised to CRT-P on or off).....	184
Table 48: Adverse events for participants randomised to CRT-P or OPT (no device).....	185
Table 49: Changes in LVEF for ischemic or non-ischemic heart disease	188
Table 50: Effect of CRT-P on death from any cause or unplanned hospitalisation for a major cardiovascular event failure in pre-defined subgroups	189
Table 51: Included RCTs for people with both conditions	193
Table 52: Study characteristics	196
Table 53: Key Participant characteristics.....	198
Table 54: Medication at baseline	199
Table 55: Risk of bias	203
Table 56: Crossovers to alternative device	205
Table 57: All-cause mortality	207
Table 58: Total cardiac deaths	209
Table 59: Heart failure deaths.....	210
Table 60: Sudden cardiac death	211
Table 61: Other causes of death.....	212
Table 62: Survival.....	213
Table 63: Hospitalisation related to heart failure.....	214
Table 64: Arrhythmias	215
Table 65: NYHA class	217
Table 66: LVEF	220
Table 67: Exercise capacity	223
Table 68: Quality of Life	225
Table 69: Flow of participants through studies.....	229
Table 70: Adverse events reported for study population	230
Table 71: Adverse events reported by intervention	234
Table 72: MADIT-CRT ¹³² subgroups.....	238
Table 73: MADIT-CRT ¹⁵² outcomes by gender	239
Table 74: RAFT ¹⁴¹ subgroup analyses	240
Table 75: RAFT ¹⁴¹ NYHA subgroups	241
Table 76: RethinQ ¹⁴³ subgroup analyses.....	242
Table 77 Hazard ratios (95% confidence intervals) for all-cause mortality from NMA with covariables for the comparisons between the different devices and OPT.....	251
Table 78 Baseline monthly probability of hospitalisation by covariate pattern (patient receiving OPT)	252

Table 79 All cause hospitalisation treatment effects (i) derived from the NMA and (ii) used in the MS economic model (events per month).....	252
Table 80 Monthly all cause hospitalisation transition probabilities (ICD, events per month).....	253
Table 81 Monthly all cause hospitalisation transition probabilities (CRT-P, events per month).....	253
Table 82 Monthly all cause hospitalisation transition probabilities (CRT-D, events per month).....	253
Table 83 Comparison of indicative individuals with population equivalents.....	254
Table 84 Treatment specific utility increments by device and NYHA group from the IPD analysis and adjusted values for use in the MS economic model.....	255
Table 85: Summary of characteristics of economic evaluations of ICD versus OPT.....	262
Table 86: Summary of the quality of economic evaluations on ICD.....	266
Table 87: Summary of characteristics of economic evaluations of CRT versus OPT.....	270
Table 88: Summary of the quality of economic evaluations on CRT.....	274
Table 89: Characteristics of included QoL studies.....	280
Table 90: Critical appraisal checklist of economic evaluation ^a	287
Table 91: Summary of the ABHI base case deterministic results.....	290
Table 92: Treatment strategies being compared for each population group.....	297
Table 93. Weibull model parameters for all-cause mortality – Population 1.....	306
Table 94. Peri- and post-operative complications with ICD.....	308
Table 95. Distribution of the participants of AVID, MADIT II, and SCD-HeFT trials by NYHA class at baseline.....	309
Table 96: Key clinical parameters used in the model for population 1.....	309
Table 97. Weibull model parameters for SCD and HF mortality – Population 2.....	310
Table 98: Non-cardiac mortality by age and sex.....	311
Table 99: Distribution of patients by NYHA class.....	315
Table 100: Key clinical parameters used in the SHTAC model for population 2.....	316
Table 101. Weibull model parameters for all-cause mortality – Population 3.....	317
Table 102: Distribution of patients per NYHA class.....	320
Table 103: Key clinical parameters used in the SHTAC model for population 3.....	321
Table 104. Heart device implantation by age in the UK population.....	322
Table 105: Utilities for patients with heart failure.....	325
Table 106: Device costs.....	326
Table 107: Mean device lifetime.....	327
Table 108: Procedure costs.....	328
Table 109: Proportion of operative complications in included CRT trials.....	330
Table 110: Resource use and costs associated with treatment of infection.....	331
Table 111: Device-related total costs used in the model.....	332
Table 112: Proportion of drug (OPT) by NYHA class.....	333
Table 113: Drug costs (OPT) by NYHA class.....	333
Table 114: Population 1 base case results for 65-year old patients from AVID trial.....	334
Table 115. Number of events for cohorts of 1,000 patients – Population 1.....	335
Table 116. Overall distribution of health state categories over patients’ lifetime for Population 1.....	336
Table 117: Population 1 base case results by age and mixed age cohort.....	337
Table 118: MADIT II subgroup analysis results.....	337
Table 119. SCD-HeFT s subgroup analysis results.....	338
Table 120. Cardiomyopathy subgroup analysis results.....	339
Table 121: Univariate sensitivity analysis results for Population 1.....	339
Table 122. Hospitalisation due to arrhythmia scenario analysis results.....	341
Table 123. Base case summary of cost-effectiveness results for Population 2.....	343
Table 124. Overall distribution of patients’ lifetime by health state categories for Population 2.....	345
Table 125. Number of events for cohorts of 1,000 patients – Population 2.....	346
Table 126. Base case results by age and mixed age cohort for Population 2.....	348
Table 127 Univariate sensitivity analysis results for CRT-P + OPT versus OPT (Population 2).....	350
Table 128. Univariate sensitivity analysis results for CRT-D + OPT versus OPT (Population 2).....	350
Table 129. Univariate sensitivity analysis for CRT-D + OPT versus CRT-P + OPT (Population 2).....	352
Table 130. Device lifetime estimates.....	353

Table 131. Shorter devices' lifetime scenario results (Population 2)	353
Table 132. Utility values used in scenario analysis for Population 2	353
Table 133. Utilities scenario results for Population 2	354
Table 134. Base case summary of probabilistic cost-effectiveness results for Population 2	355
Table 135. Base case summary of cost-effectiveness results for Population 3	357
Table 136. Overall distribution of patients' lifetime by health state categories for Population 3	359
Table 137. Number of events for cohorts of 1,000 patients – Population 3	360
Table 138. MADIT-CRT scenario cost-effectiveness results (Population 3)	361
Table 139. Univariate sensitivity analysis results for CRT-D + OPT vs OPT	362
Table 140. Univariate sensitivity analysis results for CRT-D + OPT vs ICD + OPT	363
Table 141. Univariate sensitivity analysis results for CRT-D + OPT vs CRT-P + OPT	364
Table 142. Univariate sensitivity analysis results for OPT alone versus ICD + OPT	366
Table 143. Most cost-effective strategy according to the variation of the most influential parameters	368
Table 144. Shorter devices' lifetime scenario results (Population 3)	369
Table 145. CRT effect on HF scenario results for Population 3	370
Table 146. Utilities scenario results for Population 3	370
Table 147. Base case summary of the probabilistic cost-effectiveness results for Population 3	371

FIGURES

Figure 1: Proportions of SCD by different aetiologies ³	25
Figure 2: Key elements in the NICE Heart Failure Guideline diagnostic pathway ⁵⁵	35
Figure 3: Flowchart of identification of studies	48
Figure 4: All-cause mortality	86
Figure 5: Total cardiac deaths	88
Figure 6: Sudden cardiac deaths/arrhythmic deaths	94
Figure 7: Non-arrhythmic cardiac deaths	97
Figure 8: Other causes of death: Non-cardiac deaths	101
Figure 9: All-cause mortality, cardiomyopathy RCTs and SCD-Heart nonischemic CHF subgroup ..	136
Figure 10: All-cause mortality CRT-P vs OPT	157
Figure 11: Heart failure deaths CRT-P vs OPT	161
Figure 12: Sudden cardiac death CRT-P vs OPT	162
Figure 13: Number of people hospitalised due to heart failure, CRT-P vs OPT	167
Figure 14 Number of hospitalisations due to heart failure, CRT-P vs OPT	168
Figure 15 Worsening heart failure, CRT-P vs OPT	170
Figure 16: Participants with improvement in ≥ 1 NYHA class for CRT-P vs OPT	175
Figure 17: Change in 6-minute walk distance at 6 months	176
Figure 18: Change in MLWHF scores	182
Figure 19: All-cause mortality	208
Figure 20: Total cardiac deaths	209
Figure 21: Heart failure deaths	210
Figure 22 Sudden cardiac deaths	211
Figure 23: Heart failure hospitalisations	214
Figure 24: Arrhythmias	216
Figure 25: Change in NYHA class	218
Figure 26: Proportion of people with improvement in NYHA class	218
Figure 27: Change in LVEF	221
Figure 28: Change in peak VO ₂	222
Figure 29: Change in 6-minute walk distance	222
Figure 30: Change in MLWHF score	224
Figure 31: Flow chart of identification of studies for inclusion in the review of cost effectiveness ..	260
Figure 32: Flow chart of identification of studies for inclusion in the review of HRQoL	278
Figure 33: General schematic of the model	296
Figure 34. Cost-effectiveness plane for Population 1	334

Figure 35. Cost-effectiveness scatter plot for Population 1	342
Figure 36. Cost-effectiveness acceptability curve for Population 1	343
Figure 37. Cost-effectiveness plane for Population 2	344
Figure 38. Cost-effectiveness scatter plot for Population 2	356
Figure 39. Cost-effectiveness acceptability curve for Population 2.....	356
Figure 40. Cost-effectiveness plane for Population 3	358
Figure 41 Cost-effectiveness scatter plot for Population 3	372
Figure 42. Cost-effectiveness acceptability curve for Population 3.....	373

EXECUTIVE SUMMARY

Background

This assessment updates and expands on two previous technology assessment reports, which evaluated the clinical and cost-effectiveness of implantable cardioverter defibrillators for arrhythmias, and of cardiac resynchronisation (biventricular pacing) for heart failure. Three populations were defined by the scope for this assessment: people at increased risk of sudden cardiac death (SCD) as a result of ventricular arrhythmias despite optimal pharmacological therapy (OPT); people with heart failure as a result of left ventricular systolic dysfunction (LVSD) and cardiac dyssynchrony despite OPT; and people with both conditions. However, there is considerable overlap between these groupings. Risk factors for SCD due to ventricular arrhythmia include coronary heart disease, prior myocardial infarction, cardiomyopathy, and heart failure. Heart failure resulting from LVSD and cardiac dyssynchrony occurs when the chambers of the heart do not contract in synchrony and the left ventricle of the heart fails to pump blood efficiently round the body. Drugs may be used to suppress the development of ventricular arrhythmias that may result in SCD, but these are not able to stop an arrhythmia once it has started. An implantable cardioverter defibrillator (ICD) can restore normal heart rhythm using pacing, cardioversion or defibrillation. Cardiac resynchronisation therapy (CRT) devices resynchronise the contraction of the heart using biventricular pacing (CRT-P). Certain CRT devices combine the functionality of a CRT-P and an ICD (CRT-D).

Objectives

- To assess the clinical-effectiveness and cost-effectiveness of ICDs in addition to optimal pharmacological therapy (OPT) for the treatment of people who are at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT;
- To assess the clinical-effectiveness and cost-effectiveness of CRT-P or CRT-D in addition to OPT for the treatment of people with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT;
- To assess the clinical-effectiveness and cost-effectiveness of CRT-D in addition to OPT for the treatment of people who have both an increased risk of SCD as a result of ventricular arrhythmias and heart failure as a result of LVSD and cardiac dyssynchrony despite OPT.

Methods

Data sources: Electronic bibliographic databases, including MEDLINE, EMBASE, and The Cochrane Library, were searched from inception to November 2012 for English language articles.

Bibliographies of included articles and manufacturers' submissions (MS) to NICE were also searched. Experts in the field were asked to identify additional published and unpublished references.

Study Selection: Titles and, where available, abstracts were screened for eligibility by two reviewers independently. The inclusion criteria specified in the protocol were applied to the full text of retrieved papers by one reviewer and checked independently by a second reviewer. The inclusion criteria were as follows:

- People at increased risk of SCD as a result of ventricular arrhythmias despite optimal pharmacological treatment: studies comparing ICD with OPT.
- People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment: studies comparing CRT-P or CRT-D compared each other or with OPT.
- People with both conditions described above: studies comparing CRT-D with ICD, CRT-P or OPT.
- Studies must have included one or more of the following outcome measures: Mortality, adverse effects of treatment, health related quality of life (HRQoL), symptoms and complications related to tachyarrhythmias and/or heart failure, heart failure hospitalisations, change in NYHA class, change in left ventricular ejection fraction (LVEF).
- For the systematic review of clinical effectiveness only RCTs were eligible, and for the systematic review of cost-effectiveness, only full economic evaluations were eligible.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved through discussion at each stage. The manufacturers' submission to NICE was reviewed.

Data synthesis

Studies were synthesised through a narrative review with full tabulation of the results of all included studies. Where appropriate studies were combined in a meta-analysis.

Economic Model

The model previously developed for the technology assessment of CRT for heart failure was adapted to estimate the cost-effectiveness of ICDs, CRT-P and CRT-D in the scoped populations. The Markov state transition model simulated disease progression in a cohort of patients, who moved between distinct health states over their lifetime. Disease progression varied according to the characteristics of the population group and the care pathway they follow. The key events modelled were hospitalisation due to HF or arrhythmia, transplant, surgical failure, death, peri-operative complications of implant procedure, routine device replacements, lead displacement, infections, and device upgrades. Utility values for the several health states modelled were used to estimate the benefit of each intervention in terms of quality-adjusted life years (QALYs). Resource use and cost estimation aimed at costing all relevant resources consumed in the care of patients in the three populations. As in the previous model for CRT devices, the resources considered in the current model included medication, resources

involved in device implantation, device-related complications and maintenance, hospitalisation due to heart failure or severe arrhythmia, and heart transplantation. Costs and benefits were discounted at 3.5% per annum. The perspective of the cost-effectiveness analysis was that of the NHS and Personal Social Services. Uncertainty was explored through deterministic and probabilistic sensitivity analysis.

Results

Clinical effectiveness

Twenty six RCTs were included. Thirteen RCTs compared ICDs with medical therapy in people at risk of SCD as a result of ventricular arrhythmias, four RCTs compared CRT-P (and CRT-D in one RCT) with OPT in people at risk of heart failure due to LVSD and cardiac dyssynchrony, and nine RCTs compared CRT-D with ICD in people with both conditions. No RCTs comparing CRT-D with OPT or with CRT-P were identified for people with both conditions.

People at risk of SCD as a result of ventricular arrhythmias

People with previous ventricular arrhythmia/cardiac arrest (secondary prevention):

- Compared with AAD, ICDs reduced the risk of all-cause mortality (4 RCTs, RR 0.75, 95% CI, 0.61 to 0.93; $p=0.01$), sudden cardiac/arrhythmic deaths (4 RCTs, RR 0.49, 95% CI, 0.34 to 0.69; $p<0.0001$) and total cardiac deaths (2 RCTs, RR 0.74, 95% CI, 0.61 to 0.91; $p=0.004$). No differences were found for non-arrhythmic cardiac deaths (2 RCTs, RR 0.97, 95% CI, 0.72 to 1.31; $p=0.83$) or other non-cardiac causes of death (2 RCTs, RR 0.79, 95% CI, 0.45 to 1.37; $p=0.40$).
- Using different measures of QoL, one RCT found no significant differences between groups, whilst a second RCT found improvements in QoL with ICD but not the control.
- Pre-specified subgroups for age, LVEF, cause of arrhythmia and qualifying arrhythmia did not differ significantly from each other or the overall population for all-cause mortality.

People with a recent myocardial infarction (within 6 to 41 days, or 31 days or less):

- Meta-analysis found no difference in all-cause mortality (2 RCTs, RR 1.04, 95% CI, 0.86 to 1.25; $p=0.69$), total cardiac deaths (RR 0.97, 95% CI, 0.79 to 1.20; $p=0.8$) or non-cardiac deaths (RR 1.39, 95% CI, 0.86 to 2.27; $p=0.18$). People with ICD had a lower risk of SCD (RR 0.45, 95% CI, 0.31 to 0.64; $p<0.0001$), but a higher risk of non-arrhythmic cardiac death (RR 1.77, 95% CI, 1.30 to 2.40; $p=0.0002$). One trial reporting cumulative mortality found no statistically significant difference. QoL was not reported.
- No significant differences in all-cause mortality were found for 13 pre-specified subgroups (age, gender, congestive heart failure on admission, criterion of inclusion, ST-elevation MI, early

reperfusion for ST-elevation MI, number of vessels, smoking and NYHA class at discharge, diabetes, hypertension, lipid abnormalities, number of risk factors) reported by one trial.

People with remote myocardial infarction (more than three weeks or one month previously):

- Meta-analysis found a reduction in all-cause mortality (2 RCTs, RR 0.57, 95% CI, 0.33 to 0.97; $p=0.04$), total cardiac deaths (RR 0.59, 95% CI, 0.42 to 0.83; $p=0.003$) and SCD (RR 0.36, 95% CI, 0.23 to 0.55; $p<0.00001$) with ICD. There was no difference in non-arrhythmic cardiac death (RR 0.95, 95% CI, 0.41 to 2.18; $p=0.9$) or non-cardiac death (RR 1.06, 95% CI, 0.58 to 1.95; $p=0.84$). One trial reporting hospitalisations found higher rates per 1000 months follow-up among people with ICDs (11.3 vs 9.4, $p=0.09$), with higher heart failure hospitalisations (19.9% vs 14.9%).
- Differences in QoL measured by HU13 were not statistically significant between groups at follow-up.
- All-cause mortality for 12 pre-specified subgroups (age, gender, ejection fraction, NYHA class or QRS interval, hypertension, diabetes, left bundle-branch block, atrial fibrillation, the interval since the most recent MI, type of ICD, and blood urea nitrogen) was similar, with no statistically significant interactions.

People with non-ischemic or idiopathic dilated cardiomyopathy:

- Meta-analysis of three RCTs found no significant difference in all-cause mortality (RR 0.77, 95% CI, 0.52 to 1.15; $p=0.20$), total cardiac deaths (RR 2.03, 95% CI, 0.17 to 23.62; $p=0.57$), non-arrhythmic cardiac death (RR 1.13, 95% CI, 0.42 to 3.03; $p=0.81$) or non-cardiac death (RR 0.65, 95% CI, 0.13 to 3.29; $p=0.60$). However a reduction was found in SCD (RR 0.26, 95% CI, 0.09 to 0.77; $p=0.02$) with ICD.
- Two trials reported no significant differences in QoL.
- One trial reported six pre-specified subgroup analyses for all-cause mortality (age, sex, LVEF, QRS interval, NYHA class and history of atrial fibrillation), none of the differences between subgroups were statistically significant.
- Meta-analysis of the three cardiomyopathy trials and the non-ischaemic congestive heart failure subgroup of SCD-HeFT found a statistically significant reduction in all-cause mortality (RR 0.74, 95% CI 0.58 to 0.93, $p=0.01$) with ICD.

People scheduled for CABG surgery:

- One RCT found no difference in all-cause mortality (RR 1.08, 95% CI, 0.85 to 1.38; $p=0.53$), total cardiac deaths (HR 0.97, 95% CI, 0.71 to 1.33, $p=0.84$), non-arrhythmic (HR 1.24, 95% CI, 0.84 to 1.84; $p=0.28$), non-cardiac death (RR 1.50, 95% CI, 0.82 to 2.73; $p=0.19$). Rates of SCD

were lower with ICD, but this did not reach statistical significance (HR 0.55, 95% CI, 0.29 to 1.03; p=0.06).

- HRQoL was higher among people with OPT for all measures, and this was statistically significant for some.
- Hazard ratios for ICD compared with control for all-cause mortality were found to be similar among ten pre-specified subgroups (age, gender, heart failure, NYHA class, LVEF, diabetes mellitus, QRS complex duration, use of ACE inhibitors, use of class I or class III antiarrhythmic drugs, and use of beta-adrenergic-blocking drugs).

A broad population with mild to moderate heart failure:

- One three-arm trial compared ICD, amiodarone and placebo. Compared with placebo, ICDs reduced the risk of all-cause mortality (HR 0.77 (97.5% CI, 0.62, 0.96; p=0.007), total cardiac death (HR 0.76, 95% CI, 0.60 to 0.95; p=0.018) and SCD (compared with placebo and amiodarone groups combined, RR 0.44, 95% CI, 0.31 to 0.61; p<0.00001). There was no difference in non-arrhythmic cardiac death (RR 1.14, 95% CI, 0.88 to 1.48; p=0.32) or deaths from non-cardiac causes (RR 0.92, 95% CI, 0.66 to 1.27; p=0.60) compared with placebo and amiodarone groups combined.
- No significant difference was found in QoL. A significant decrease in perceptions of QoL was found using the SF-36 among people who had received an ICD shock within the previous month compared with those who had not received a shock.
- There was no interaction of ICD therapy with the cause of congestive heart failure (ischaemic or non-ischaemic) for all-cause mortality or other modes of death. Compared with placebo, ICDs reduced the risk of all-cause mortality, cardiac mortality and sudden death presumed to be ventricular tachyarrhythmic in people with NYHA class II, but not in those with NYHA class III. The interaction between ICD therapy and NYHA class was not statistically significant for heart failure (p=0.29) or noncardiac (p=0.11) deaths.

Adverse events:

- Adverse events were reported by all four RCTs of people with previous ventricular arrhythmias. Up to 30% of the ICDs groups reported adverse events, with most related to the placement and operation of the device. Rates for OPT appeared lower.
- The nine RCTS of people who had not suffered a life threatening arrhythmia reported adverse event rates between 5% and 61% of people with an ICD, depending on the definition of adverse event and length of follow-up. Three trials reporting adverse event rates for the comparator treatment found rates between 12% to 55%. Lead, electrode or defibrillator generator related problems affected 1.8 to 14% of people in five trials reporting this.

People with heart failure as a result of LVSD and cardiac dyssynchrony

- Compared with OPT, CRT-P reduced the risk of all-cause mortality (4 RCTs, RR 0.75, 95% CI 0.58 to 0.96; $p=0.02$), heart failure deaths (2 RCTs, RR 0.67, 95% CI 0.51 to 0.88; $p=0.004$) and heart failure hospitalisations (4 RCTs, RR 0.61, 95% CI 0.44 to 0.83), but not SCD (3 RCTs, RR 0.97, 95% CI 0.44 to 2.14; $p=0.94$), total cardiac deaths (1 RCT, $p=0.334$) or non-cardiac deaths (1 RCT, $p=0.122$).
- An improvement in NYHA class (3 RCTs, RR 1.68, 95% CI 1.52 to 1.86; $p<0.00001$), LVEF (1 RCT, $p<0.001$) exercise capacity (3 RCTs) and QoL (4 RCTs, MLWHFQ score MD -10.33, 95% CI -13.31 to -7.36; $p<0.00001$) was also found for CRT-P compared with OPT.
- Pre-specified subgroup analysis found people with non-ischaemic heart disease had a greater change in LVEF, but there was little difference in the effect of CRT-P on the composite outcome (death from any cause or unplanned hospitalisation for a major cardiovascular event) for 16 subgroups.
- One RCT found that, compared with OPT, CRT-D reduced the risk of all-cause mortality (HR 0.64, 95% CI 0.48 to 0.86, $p=0.003$), total cardiac deaths (RR 0.68, 95% CI 0.50 to 0.93, $p=0.02$), SCD (HR 0.44, 95% CI 0.23 to 0.86, $p=0.02$) and heart failure hospitalisations (RR 0.77, 95% CI 0.63 to 0.93, $p=0.008$), but not heart failure deaths (HR 0.73, 95% CI 0.47 to 1.11; $p=0.143$) or non-cardiac deaths (CRT-D 2.3% vs OPT 3.6%, $p=0.717$).
- Improvement in NYHA class (57% vs 38%, $p<0.001$), exercise capacity (6 MWT 46 m vs 1m), and QoL (MLWHFQ score (-26 vs -12 , $p<0.001$) were also found for CRT-D compared with OPT at 6 months.
- Total cardiac deaths (RR 1.38, 95% CI 1.06 to 1.81, $p=0.02$) and SCD (RR 2.72, 95% CI 1.58 to 4.68, $p=0.0003$) were higher with CRT-P than CRT-D. All-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, $p=0.12$), heart failure deaths (RR 0.98, 95% CI 0.68 to 1.42, $p=0.93$), and heart failure hospitalisations (28% vs 29%) were similar for those with CRT-P and those with CRT-D.
- Changes in NYHA class, exercise capacity and QoL were similar for CRT-P and CRT-D.
- Adverse events: two trials randomised people with successful implantation only. The other two trials reported device-related deaths between 0.2% and 0.8% for those with CRT-P and 0.5% for those with CRT-D. Moderate or severe adverse events related to implantation procedure were reported as 10% for those with CRT-P and 8% for those with CRT-D by one trial, with 13% and 9% of CRT-P and CRT-D implantations unsuccessful. Moderate or severe adverse events from any cause were more common among those with CRT-D than OPT (CRT-D 69%, CRT-P 66%, OPT 61%, CRT-D vs OPT $p=0.03$, CRT-P vs OPT, $p=0.15$). Reported complications included lead displacements, infections and coronary-sinus dissections.

People with both conditions

- Compared with ICD, CRT-D reduced the risk of all-cause mortality (8 RCTs, RR 0.84, 95% CI 0.73 to 0.96, $p=0.01$) and total cardiac deaths (6 RCTs, RR 0.82, 95% CI 0.67 to 1.00, $p=0.05$). No difference in SCD was found (3 RCTs, RR 1.45, 95% CI 0.43 to 4.92, $p=0.55$).
- CRT-D reduced the risk of heart failure hospitalisation compared with ICD (3 RCTs, RR 0.75, 95% CI 0.64 to 0.88, $p=0.0005$).
- No difference in the proportion of people experiencing at least one episode of ventricular tachycardia or ventricular fibrillation was found (4 RCTs, RR 0.90, 95% CI 0.71 to 1.14, $p=0.38$).
- An improvement in mean NYHA class (2 RCTs, MD -0.19, 95% CI -0.34 to -0.05, $p=0.008$), but not in the proportion of people improved by one or more NYHA class; (3 RCTs RR 1.81, 95% CI 0.91 to 3.60, $p=0.09$) was found with CRT-D.
- Improvement in LVEF (8 RCTs, MD 2.15, 95% CI 0.45 to 3.86, $p=0.01$), exercise capacity, and QoL (MLWHFQ score, 6 RCTs, MD -6.9, 95% CI -10.4 to -3.4, $p=0.0001$) were found with CRT-D compared with ICD.
- Pre-specified subgroup analyses found greater benefit with CRT-D for a composite outcome in people with QRS duration ≥ 150 versus < 150 ms (2 RCTs) and for the proportion of people with an improvement in peak oxygen uptake in those with QRS ≥ 120 ms versus < 120 ms (1 RCT). CRT-D was associated with greater benefit in women than in men (1 RCT) and in people with LBBB than in those with nonspecific intraventricular conduction delay (1 RCT). Distance walked in 6 minutes for was improved with CRT-D in non-ischemic cardiomyopathy but not in ischemic cardiomyopathy (1 RCT). Other evaluated subgroups showed no statistically significant effects.
- One large RCT trial found that device or implantation related complications within 30 days of implantation were significantly higher in the CRT-D group than the ICD group (13.3% vs 6.8%, $p<0.001$), as was device-related hospitalisation (20% vs 12.2%, HR 1.68, 95% CI 1.32 to 2.13, $p<0.001$).

Cost-effectiveness

The systematic review of published economic evaluations identified 51 studies (36 studies of ICDs and 17 of CRT). ICDs were reported to be cost effective in almost half of the ICD studies. One relevant UK study reported a mean ICER for an average UK secondary prevention patient of £76,139 per QALY gained. Almost all CRT studies reported that CRT was cost effective. One relevant UK study estimated an ICER of £16,735 per QALY gained for CRT-P compared with OPT, and an ICER of £40,160 per QALY gained for CRT-D compared with CRT-P.

The systematic review of HRQoL found six relevant studies. Two studies were conducted in patients who had received an ICD; one found that mean EQ-5D score did not change with time after implant

and the other reported no difference between EQ-5D score of primary and secondary prevention patients, and that quality of life for ICD patients was similar to the general population. Four cohort studies reported EQ-5D scores in heart failure and overall results show decreased EQ-5D scores compared with the general population particularly in NYHA Class III and IV.

One industry submission was received from ABHI. The general approach taken in the MS seems reasonable although it is not clear if uncertainty is properly assessed. Subgroups specified by ABHI do not directly address those scoped by NICE. Overall, ABHI's results show that for most subgroups there is at least 1 device with an ICER below £30,000 per QALY gained, and in some cases a different device might be below £20,000 per QALY gained.

People at risk of SCD as a result of ventricular arrhythmias

- The addition of ICD to OPT for secondary prevention of SCD has an ICER of £19,479 per QALY gained compared with OPT alone. Its probability of being cost-effective at a WTP of £20,000 and £30,000 per QALY gained is 51% and 82%, respectively.
- The ICER for the mixed-age cohort is slightly higher (£24,967/QALY), as it increased with age and 52% of these patients are expected to be over 65 years old.
- Subgroup analysis with MADIT II trial data shows that ICD + OPT is cost-effective (ICER = £14,231/QALY) for primary prevention of SCD in patients with remote myocardial infarction.
- For the SCD-HeFT trial (patients with mild to moderate heart failure), the estimated ICER for ICD + OPT is £29,756 per QALY gained compared with OPT alone.
- For patients with non-ischaemic cardiomyopathy the ICER was £26,028 per QALY gained.
- The parameters with greater impact on the ICER were the time horizon, the HR for all-cause mortality associated with the ICD + OPT arm, the risk of surgical death during ICD implantation, and the lifetime of the device.

People with heart failure as a result of LVSD and cardiac dyssynchrony

- The addition of CRT-P to OPT (in the initial stage of management of heart failure) presented an estimated ICER of £27,584 per QALY gained compared with initial management with OPT alone (allowing for the subsequent implants). Similarly, the initial implant of CRT-D alongside OPT showed an ICER of £27,899 per QALY gained compared with OPT alone. When comparing CRT-D + OPT with CRT-P + OPT, a slightly higher ICER was estimated (£28,420 per QALY gained).
- At a WTP of £20,000 per QALY gained, the initial management with OPT alone followed by the clinically necessary device implants is the strategy with highest probability of being cost-

effective (81%). Above a WTP of £28,000 per QALY, the strategy with highest probability of being cost effective is CRT-D + OPT (38%).

- The incremental cost-effectiveness results for the comparisons relevant for Population 2 seem to be sensitive mainly to device-related costs and to parameters that determine the incremental benefit of the devices on patients' survival, such as the RRs of SCD and HF death for CRT-P. CRT-D device's lifetime also showed to be particularly influential due to the incremental costs incurred when it became shorter.
- In a scenario assuming the upper limit estimates of device-related costs or lower estimates for the longevity of all devices, both CRT-P + OPT and CRT-D + OPT became non-cost-effective compared with initial management with OPT alone (followed by the subsequent upgrades).

People with both conditions

- The base case found that the most cost-effective strategy for people with both conditions at a WTP range of £20,000 to £30,000 per QALY is the initial management with OPT alone (followed by device implantation and subsequent upgrades as necessary). Both strategies with the initial implantation of CRT devices present ICERs over the WTP range of £20,000 to £30,000 per QALY compared with OPT alone (CRT-D £35,193/QALY; CRT-P £41,414/QALY). Costs and QALYs for CRT-D and CRT-P are similar.
- CRT-D + OPT is cost-effective compared with ICD + OPT at a WTP of £30,000 (£27,195/QALY).
- At a WTP of £30,000 per QALY, OPT alone, ICD + OPT, CRT-D + OPT, and CRT-P + OPT have 44%, 31%, 15%, and 10% probability of being cost-effective, respectively. Above the WTP of £42,000 per QALY, the intervention with highest probability of being cost effective is CRT-D + OPT (31%).
- In an alternative scenario using MADIT CRT data, CRT-P and CRT-D are extendedly dominated by ICD + OPT, which is the most cost effective strategy (ICER £154/QALY gained versus OPT).
- The cost-effectiveness results for the comparison of CRT-D + OPT versus ICD + OPT were quite robust to the variation of input parameters. The most influential parameters were RR of all-cause mortality with ICD and lifetime of CRT-D and ICD devices.

Discussion

A *de novo* economic model was developed for the current appraisal following recognised guidelines and systematic searches were conducted to identify the data inputs for the model. The main results have been summarised and presented. To address the decision problem specified in the NICE scope for the current appraisal, the independent model is based on the adaptation of a model structure used in the previous appraisal of cardiac resynchronisation for heart failure (TA120) developed by Fox and colleagues, providing a consistent approach and comparability. Despite following recognised guidance on developing economic models, the evaluation has some limitations, including structural assumptions about disease progression and treatment provision, the extrapolation of trial survival estimates over time, and assumptions around parameter values where evidence was not available for specific patient groups. Where limitations have arisen in the evaluation, these have been identified in the report. Assumptions made or data identified from alternative sources has been checked through clinical advice and the effects of parameters thought to be influential to the results have been assessed through sensitivity analyses.

Conclusions

The addition of ICD to OPT was cost-effective at a WTP threshold of £30,000 for all of the scenarios modelled: previous ventricular arrhythmias/cardiac arrest, myocardial infarction more than 3 weeks previously, non-ischaemic cardiomyopathy, and ischaemic or non-ischaemic congestive heart failure and LVEF 35% or less; and in some cases at a WTP threshold of £20,000. Both CRT-P and CRT-D presented an ICER below £30,000 per QALY gained compared with OPT, as did the comparison of CRT-D with CRT-P in people with heart failure as a result of LVSD and cardiac dyssnchrony. In people with both conditions, the ICER for the comparison of CRT-D + OPT with ICD + OPT was below £30,000 per QALY (unless no difference in all-cause mortality was assumed) but not for the comparison with initial management with OPT alone. The costs and QALYs for CRT-D and CRT-P were similar.

An RCT comparing CRT-D and CRT-P in people with heart failure due to LVSD and cardiac dyssynchrony is required, for both those with and without an ICD indication. A trial is needed into the benefits of ICD in non-ischaemic cardiomyopathy in the the absence of dyssynchrony.

LIST OF ABBREVIATIONS

AAD	Antiarrhythmic drugs
ABHI	Association of British healthcare industries
ACC	American college of cardiology
ACE	Angiotensin-converting enzyme
AHA	American heart association
AMIOVIRT	Amiodarone versus implantable cardioverter-defibrillator randomized trial
ARVD	Arrhythmogenic right ventricular dysplasia
ARR	Absolute risk reduction
AVID	Antiarrhythmics versus implantable defibrillators trial
BNP	B-type natriuretic peptide
CABG Patch	Coronary artery bypass graft patch trial
CARE-HF	Cardiac resynchronization-heart failure trial
CASH	The cardiac arrest study Hamburg
CAT	Cardiomyopathy trial
CI	Confidence interval
CIDS	Canadian implantable defibrillator study
CVD	cardiovascular death
CHD	Coronary heart disease
CHF	Congestive heart failure
COMPANION	Comparison of medical therapy, pacing, and defibrillation in patients with left ventricular systolic dysfunction trial
CONTAK-CD	RCT of the CONTAK-CD device
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronisation therapy
DASI	Duke activity status index
DEBUTE	Defibrillators in non-ischemic cardiomyopathy treatment evaluation trial
DEFINITE	Defibrillators in nonischemic cardiomyopathy treatment evaluation trial
DINAMIT	Defibrillator in acute myocardial infarction trial
ECG	Electrocardiogram/echocardiography
ECHOES	Echocardiographic heart of England screening study
EHRA	European heart rhythm association
EP	Electrophysiological
ESC	European society of cardiology
GPRD	General practice research database
HF	Heart failure
HR	Hazard ratio
HRS	Heart rhythm society
HU13	Health utilities index 13
ICD	Implantable cardiac defibrillator
IPD	Individual patient data
IQR	Inter-quartile range
IRIS	Immediate risk stratification improves survival trial
ITT	Intention-to-treat analysis
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MADIT	Multicenter automatic defibrillator implantation trial
MADIT-CRT	Multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy trial
MAVERICK	The midlands trial of empirical amiodarone versus electrophysiology-guided

	interventions and implantable cardioverter-defibrillators
MCS	Mental component summaries
MWD	Minute walk distance
MHI-5	Mental health inventory 5
MI	Myocardial infarction
MIRACLE	Multicenter InSync randomized clinical evaluation trial
MIRACLE ICD	Multicenter InSync ICD randomized clinical evaluation trial
MS	Manufacturer's submission
MUSTIC	Multisite stimulation in cardiomyopathies trial
MUSTT	Multicenter unsustained tachycardia trial
NICE	The national institute of health and clinical excellence
NMA	Network meta-analysis
NSVT	Nonsustained ventricular tachycardia
NTproBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart association
OPT	Optimal pharmacological therapy
PCS	Physical component summaries
PES	Programmed electrical stimulation
PNS	Phrenic nerve stimulation
PSS	Personal social services
PVC	Premature ventricular complexes
RAFT	Recurrent atrial fibrillation trial
RCT	Randomised controlled trial
RethinQ	Cardiac resynchronization therapy in patients with heart failure and narrow QRS
RHYTHM ICD	The Resynchronization for the HemodyNamic treatment for heart failure management implantable cardioverter defibrillator study
RR	Risk ratio
RRR	Risk ratio reduction
SCD	Sudden cardiac death
SCD-Heft	Sudden cardiac death in heart failure trial
SNPs	Serum natriuretic peptides
STAI	State trait anxiety inventory
TAR	Technology assessment report
VF	Ventricular fibrillation
VT	Ventricular tachycardia
QALY	Quality-adjusted life year
QoL	Quality of life
QRS interval	An Electrocardiogram (ECG) trace pattern (comprising three ECG waves: Q, R and S) corresponding to the depolarisation of the right and left ventricles of the heart. The duration or 'width' of the QRS interval is an indicator of ventricular dyssynchrony.
QT	Q and T wave on ECG
QWBS	Quality of well being schedule
WTP	Willingness to pay

1 BACKGROUND

This technology assessment has been undertaken on the request of the NIHR HTA programme to inform the National Institute of Health and Clinical Excellence (NICE) appraisal of ‘Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)’.

1.1 Description of underlying health problem

This assessment encompasses people at risk of sudden cardiac death (SCD) as a result of ventricular arrhythmias (abnormal heart rhythms) and people with heart failure (HF) as a result of left ventricular systolic dysfunction (LVSD) and cardiac dyssynchrony. For the purposes of this assessment and in line with the NICE scope,¹ three populations are considered:

1. People at increased risk of SCD as a result of ventricular arrhythmias despite receiving optimal pharmacological therapy (OPT).
2. People with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT.
3. People with both conditions described above.

In practice, however, these are not distinct populations and there is considerable overlap between the groups, such that people with HF due to LVSD are at risk of SCD from ventricular arrhythmia.

1.1.1 Sudden cardiac death

The widely accepted definition of SCD is a sudden and unexpected death from cardiac causes within an hour of the onset of symptoms.² Coronary heart disease (CHD) (narrowing or blocking of the coronary arteries) is the most common clinical finding associated with SCD, with about 80% of such deaths linked to this condition (Figure 1). CHD causes SCD mainly because it can lead to ventricular tachycardia (VT) which is an abnormally fast heart rhythm originating in one of the ventricles, and ventricular fibrillation (VF), which is an uncoordinated and erratic contraction of the heart muscle of the ventricles. Patients with cardiomyopathies (diseases of heart muscle) account for a further 10% to 15% of SCD and there is likely to be significant overlap between this group and those with CHD (i.e. some patients will have both conditions). The remaining 5-10% of SCD cases are associated with other disorders, either structurally abnormal congenital cardiac conditions or structurally normal but electrically abnormal hearts.³

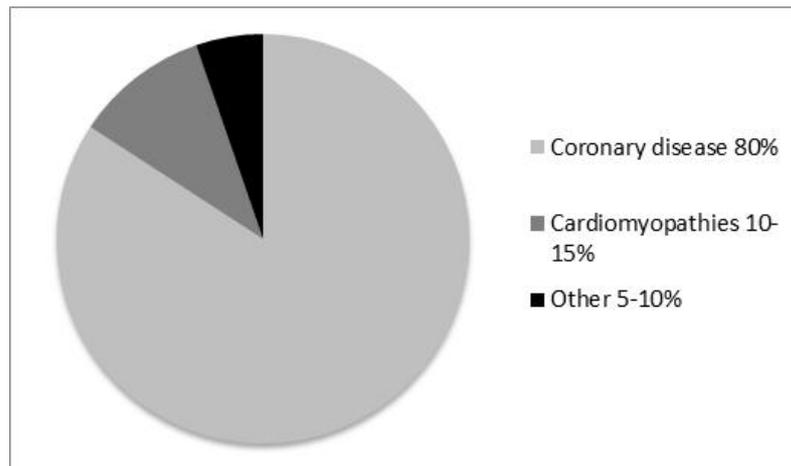


Figure 1: Proportions of SCD by different aetiologies³

Deaths in England and Wales due to CHD in 2010 numbered 140,301 (Table 1). It is thought that approximately 50% of all CHD-related deaths are SCDs.⁴ The cause of SCD is frequently VT or VF, but may also be due to asystole (cessation of electrical activity in the heart), or causes other than arrhythmias (e.g. ischaemia)^{5;6} Commonly, VT develops initially, followed by degeneration to VF which then leads to the development of asystole.⁷ According to guidelines of the American College of Cardiology, American Heart Association and European Society of Cardiology for management of patients with ventricular arrhythmias and the prevention of SCD,⁸ VF is the rhythm recorded at the time of sudden cardiac arrest in 75%-80% of cases. There is evidence that the incidence of VT/VF events has declined over time, perhaps reflecting an impact of treatment strategies targeted at coronary artery disease.⁹⁻¹²

Table 1: Deaths in England and Wales due to CHD and SCD in 2010

	Total	Males	Females
Coronary heart disease ^{a13}	140,301	81,405	58,896
Sudden cardiac death ^b	70,151	40,703	29,448
Ventricular fibrillation ^c	52,613-56,121	30,527-32,562	22,086-23,558

^a Deaths from coronary heart disease defined as ICD codes I20 to I25 inclusive.¹⁴ ^b Estimated as 50% of deaths from CHD.⁴ ^c Estimated as 75-80% of SCD.⁸

People known to be at risk of SCD include patients who have already experienced a prior event which they survived such as life-threatening arrhythmia (accounting for 5-10% of SCD), hemodynamic abnormalities including HF (7-15% of SCD) and acute coronary syndromes such as myocardial infarction (MI) and angina pectoris ($\leq 20\%$ of SCD).⁴ However, in 30% or more of SCDs, CHD had not been previously diagnosed in the patient and in the final third of SCDs, the patients were known to have cardiac disease but were considered to be at low risk for SCD.⁴

A recent systematic review of 67 studies world-wide¹⁵ estimated that the average survival rate for adults following an out of hospital cardiac arrest was 7%. Depending upon the clinical scenario, a small proportion of people who do survive a first life-threatening cardiac episode may remain at a high risk of further episodes (e.g. if VF is due to left ventricular dysfunction). Secondary prevention (prevention of an additional life-threatening event) may therefore be required. When appropriate treatment and secondary preventive strategies are implemented, recent studies have reported 5 year survival ranging from 69 to 100%,^{16;17} although these may over-estimate survival. It is important to recognise the multiple causes of the electrical process of VF, since not all patients with VF will be amenable to ICD therapy. For example, VF or VT occurring as a primary electrical process in Brugada syndrome would be expected to respond well to ICD therapy, whereas VF due to massive heart damage in a major acute MI may not. Deciding on the rational use of ICD therapy can be complex, as the risk of arrhythmic death and therefore the potential benefit from ICD therapy varies between pathologies (e.g. ischaemic heart disease, non-ischaemic cardiomyopathy, or electrical disease) and also with the progression of the disease (e.g. the impact of ICD may vary depending upon the time after an MI that the therapy is started).

Preventing a first life-threatening event (primary prevention of SCD) is challenging because it requires identifying people with a sufficient level of risk for primary prevention to be appropriate. There are multiple risk factors for SCD which include increasing age, hereditary factors, being in the top 10% of risk for coronary atherogenesis, inflammatory markers (e.g. C-reactive protein), hypertension, left ventricular hypertrophy, intraventricular conduction abnormalities (e.g. left bundle-branch block), obesity, diabetes and lifestyle factors (e.g. smoking, excessive alcohol consumption, lack of physical activity, social and economic stressors).⁸ Currently no optimal strategy for risk stratification exists.¹⁸

1.1.2 Heart Failure

HF is a clinical syndrome characterised by symptoms (breathlessness and fatigue) and signs (fluid retention) caused by failure of the heart to pump adequately. It is usually a chronic condition predominantly affecting people over the age of 50 years and has a poor prognosis.¹⁹ Coronary artery disease (ischaemic heart disease) has been identified as the most common cause of HF in two UK studies.^{20;21} Other causes of HF are LVSD, hypertension, valve disease, atrial fibrillation or flutter, cardiomyopathy (either hypertrophic or restrictive) or cor pulmonale (pulmonary heart disease). The cause of HF was unknown in approximately a third of cases.^{20;21} The NICE scope for this appraisal¹ focusses on HF that is a result of LVSD. LVSD is an impairment in the ability of the left ventricle to pump blood into the circulation during contraction (systole).¹⁹

The prognosis for HF patients is poor with deterioration in quality of life (QoL) and reduced life expectancy.¹⁹ In addition, HF patients may also be at risk from SCD. Patients with HF and LVSD from the Echocardiographic Heart of England Screening Study (ECHOES) cohort had a 5- year survival rate of 53%²² and 3.8% of the deaths that occurred among those with HF and LVSD were sudden deaths,²² although SCD may be underestimated in this study. The 10-year survival in ECHOES for those with HF and LVSD was 27.4%.²³ The severity of HF graded according to the New York Heart Association (NYHA) classification is an indicator of prognosis.²⁴⁻²⁷ This system has four classes to which patients can be assigned with severity increasing with class number from I to IV (Table 2), however it is worth noting that clinicians may differ in the way they interpret and assign these classes.²⁸

Table 2: NYHA Heart Failure Classification

Class	Comfort at rest?	Limitation to physical activity?	Effect of physical activity
I	Yes	None	No undue fatigue, palpitation, dyspnoea or angina pain.
II	Yes	Slight	Ordinary physical activity can result in fatigue, palpitation, dyspnoea or angina pain
III	Yes	Marked	Less than ordinary activity causes fatigue, palpitation, dyspnoea, or angina pain.
IV	May have HF or angina symptoms even at rest	Always	Unable to carry our any physical activity without new or increasing discomfort

The most recent estimates for the incidence of HF in the UK come from the General Practice Research Database (GPRD).²⁹ In 2009 these data indicated that HF incidence (per 100,000 person years) was higher in Wales (men 44.6/100,000 and women 24.9/100,000) than in England (men 37.5/100,000 and women 23.0/100,000). Incidence of HF increased with age, being highest in those over age 75 years (e.g. in England, men 326.0/100,000 and women 256.2/100,000) and incidence rates are higher in men compared with women for all ages. From these data and those for Scotland and Northern Ireland, it has been estimated that there are over 27,000 new cases of HF in the UK each year.²⁹

The corresponding estimates for the prevalence of HF in the UK derived from the GPRD²⁹ are similar in England and Wales (for all ages in men 0.9% in England and 1.0% in Wales, for all ages in women

0.7% in England and Wales). In total this corresponds to almost 160,000 cases in England and Wales in 2009. Data from the ECHOES cohort have indicated that from the total HF cases identified, approximately 50% have HF with LVSD.²² Applying this proportion to the prevalence data for England and Wales from the GRPD would suggest approximately 80,000 cases of HF with LVSD in 2009.

1.2 Description of the technology under assessment

The current technology assessment concerns specific types of cardiac implantable electronic devices for the prophylaxis and/or treatment of conduction system disease that use one or more of the following approaches to restore normal heart rhythm:

- ‘pacing’ - a series of low-voltage electrical impulses delivered at a fast rate to correct the heart rhythm;
- cardioversion’ - one or more small electric shocks delivered to the heart to restore a normal rhythm; or
- ‘defibrillation’ - one or more large electric shocks delivered to the heart to restore a normal rhythm

Cardiac resynchronisation therapy (CRT) devices are a specific type of cardiac pacemaker that have three conducting leads (connected to the right atrium and both ventricles) and are used to correct inconsistency of the heartbeat between the right and left sides of the heart (dyssynchrony), referred to as biventricular pacing. These devices are known as CRT-pacers (CRT-P) (or biventricular pacers).

Implantable cardioverter defibrillators (ICDs) are used to provide cardioversion and/or defibrillation shocks to correct more serious dysfunction of the heart rhythm, including VT, VF and asystole, any one of which may be associated with SCD. ‘Single chamber’ ICDs have a single conducting lead connected only to the right ventricle; ‘dual chamber’ ICDs have two leads, connected to the right atrium and right ventricle. In addition to their cardioversion and defibrillation ability, modern ICDs provide the functionality of a standard pacemaker to treat slow heart rhythms (if necessary) by pacing the right-hand chamber(s) of the heart.

Modern types of CRT device may combine both the functionality of a CRT-P and that of an ICD, and these are referred to as CRT-defibrillators (CRT-D).

CRT is aimed at a specific subset of the heart failure population with evidence of delayed left ventricular activation (as manifest by prolongation of the QRS complex). Because this population is *a priori* at risk of arrhythmic death, CRT can be combined with an ICD. ICDs and CRT-D are appropriate for patients with a high risk of SCD, whilst CRT-P are appropriate in patients with less serious cardiac arrhythmias. However, as noted above heart disease is a complex and progressive condition, and patients who are initially implanted with a CRT-P may subsequently develop heart disease and risk of SCD, and an upgrade from a CRT-P to a CRT-D or ICD may be appropriate.³⁰

Although they may differ in function, CRT and ICD devices are similar in size and structure, about the size of a pocket watch (capacity 30-40 cc, weight around 70g, thickness approximately 13mm) and consist of a battery-powered pulse generator controlled by a microcomputer. They are implanted under the skin, typically just below the collar bone on the left or right side of the chest, and (depending on the device type), have one or more leads (tiny wires) which are routed through veins to the heart's chambers for sensing electrical activity and for providing the corrective pacing, cardioversion and/or defibrillation impulses. Modern CRT and ICD devices store a record of the heart's electrical activity and contain a wireless transmitter/receiver to enable the device to be programmed and interrogated from an external computer using wireless telemetry. Readings from a device may be transmitted by telephone, enabling the cardiologist to remotely check the performance of the device while the patient is at home.

Early devices were implanted by the trans-thoracic method, but current CRT and ICD devices are placed under the skin in the pectoral region with trans-venous insertion of the leads into the heart under local anaesthesia, using high-resolution X-ray angiography to guide the placing of the leads. The procedure for primary prevention typically requires a maximum of one night's stay in hospital. For secondary prevention the length of stay will depend upon any underlying health problems. The longevity of CRT and ICD devices is limited by their battery life, which is in the range 4 to 7 years, depending on a number of factors including the pacing mode, pacing percentage, and capacitor recharge interval.³¹⁻³³ Replacement of batteries alone is not feasible, so when the battery is due for renewal the pulse generator unit has to be replaced, in a minor surgical procedure. Where possible the connecting leads are left in situ and only the generator unit itself replaced, although eventually one or more of the connecting leads may also require replacement.

Modern devices can be specifically programmed to deliver resynchronisation shocks independently to the atria and ventricles of the heart to correct a wide range of arrhythmias. The devices can also be programmed according to which of the heart's chambers they monitor (sense) to detect existing electrical activity. The ability of CRT and ICD devices to recognise different types of arrhythmia may

enable them to deliver more appropriate therapy, in particular lessening the incidence of inappropriate shocks. Several coding systems (typically comprising three to five letters) have been developed to indicate the programmed pacing/sensing modes. A widely-used code developed by The Heart Rhythm Society and the British Pacing and Electrophysiology Group (BPEG) consists of three letters to describe the pacing chamber, (atrium, A; ventricle, V; or dual (i.e. both), D), the sensed chamber (A, V, or D), and whether pacing is inhibited (I) or activated in response to the sensed beat, or, if dual pacing and sensing are programmed, whether dual (D) inhibition and activation (for the different chambers) occurs. As an example, the code “VVI” would indicate ventricular pacing (shocks are delivered to the ventricle), ventricular sensing (electrical activity is monitored in the ventricle), and that pacing is inhibited if an electrical beat is sensed in the ventricle. To illustrate a more complex example, the code “DDD” would indicate a device programmed for dual-chamber pacing and sensing. In this case the atrium would be stimulated if sinus bradycardia is detected. Both atrium and ventricle would be stimulated if bradycardia exists independently in both chambers. If heart block exists with normal sinus function the ventricle would be paced in synchrony with the atrium, and if sinus rhythm exists pacing would be totally inhibited.

The most recent development in cardiac implantable electronic devices is the ‘subcutaneous ICD’ (S-ICD), which was approved by the US Food and Drug Administration in April 2012. The S-ICD is positioned just under the skin, outside the rib cage, and can be implanted under local anaesthesia. The electronics and batteries of the S-ICD enable it to deliver enough energy to defibrillate the heart without the need for a connecting lead to the heart, which avoids lead-related complications including the risk of dangerous infections (other potential procedural complications are considered below). A disadvantage of the S-ICD, however, is that it cannot provide long-term pacing. An RCT comparing S-ICD with tranvenous ICD (NCT01296022)³⁴ is currently underway and due to complete in March 2015, and a registry study of S-ICD (NCT01085435)³⁵ is due to complete in December 2016.

Potential procedural complications

The most challenging technical aspect of a CRT device implantation is the optimal placement of the third lead in the coronary sinus vein. The final position of the LV pacing lead depends on the anatomy of the cardiac venous system, as well as the performance and stability of the pacing lead and the need to avoid phrenic nerve stimulation (PNS).³⁶ The left phrenic nerve (which sends signals between the brain and the diaphragm) may be stimulated by the LV pacing lead, causing uncomfortable diaphragmatic twitch, which could prevent optimal LV lead placement and can hinder LV stimulation. PNS occurs in around 20% of patients with bipolar leads.³⁷ A recent systematic review of implantation-related complications in 11 ICD and 7 CRT trials suggests that the most common complications include coronary vein dissection (1.3%) and coronary vein perforation (1.3%), with coronary vein-related complications occurring in only 2.0% of patients.³⁸ This low rate is attributed to

the growing experience of physicians combined with technical progress.³⁸ Overall incidence of lead dislodgement for non-thoracotomy ICDs was 1.8%, with higher rates of lead dislodgement in the CRT trials, which varied from 2.9% to 10.6%.³⁸ The reported rate of overall leads dislodged during and after 3,095 successful implantations was 5.9%.³⁸ A recent study in the USA,³⁹ which was based on the National Cardiovascular Data Registry, found that, after adjusting for diagnostic test results and comorbidities, dual-chamber ICDs were associated with a 40% greater odds of procedural complications and 45% greater odds of mortality than single-chamber ICDs, illustrating a greater risk of procedural complications with the more complex types of ICD device. Another recent study in the USA⁴⁰ examined 16-year trends from 1993 to 2008 in the incidence of infections related to cardiac implantable electronic devices, based on data from the National Inpatient Sample (NIS). There has been a marked increase in infection incidence, notably since 2004, and this has been associated with an increase in in-hospital mortality and increased treatment costs. Reasons for the increased incidence of device-related infections are unclear, but could be related to the increased use of ICD and CRT devices relative to traditional pacemakers. Due to the demands placed on the battery, the longevity of ICD and CRT devices is lower than that of traditional pacemakers, and the need for more frequent surgical replacement of ICDs and CRT devices might at least in part explain why the number of device-related infections has increased.⁴⁰

Setting, cost and equipment

CRT and ICD device implants are carried out in local hospital or cardiac centres and can take from one to three hours depending on the type of device. Implantation of bi-ventricular or resynchronisation devices are more complicated and take longer than other ICDs. Implantation procedures are usually performed by senior cardiologists with specialist training in the technique, supported by cardiac technicians and nurses. Follow-up visits for patients can be as often as every 3 to 12 months, requiring support from senior cardiologists, cardiac nurses and technicians. According to the HRS/EHRA Expert Consensus, while neither direct nor remote monitoring follow-up visits should be longer than 12 months, six monthly follow-up for ICD and CRT-D devices are recommended.⁴¹ The increasing complexity of devices could impact on the time needed for follow-up visits.

The costs of implantable resynchronisation and defibrillation devices based on NHS Purchasing and Supply Agency estimates including leads (but excluding VAT) were reported by Buxton and colleagues (ICDs)⁴² and Fox and colleagues (CRT-P and CRT-D devices).⁴³ At 2012 prices (based on an adjustment for inflation⁴⁴) the costs would be around £4,091 for a CRT-P device, £17,184 for a CRT-D device, and £18,303 for an ICD, although the costs may vary in different settings due to negotiated procurement discounts.⁴³ In addition to the cost of the device itself, high quality digital X-ray equipment is necessary for coronary sinus angiography and positioning of the LV pacing lead, as well as an external ICD programmer (a telemetry computer commercially produced and marketed for

use with the device⁴¹) to enable the cardiologist to adjust the settings of the ICD after surgery or at follow-up visits as required.

1.3 Management of the disease

Existing guidelines for SCD and HF include NICE guidance on ICDs for arrhythmias⁴⁵ and CRT for HF,⁴⁶ and NICE clinical guideline on management of chronic HF.⁴⁷ Guidelines on the use of CRT have also been published by the European Society of Cardiology,⁴⁸ the Heart Failure Society of America⁴⁹ and jointly by the American College of Cardiology Foundation and the American Heart Association.⁵⁰ A 10-year National Service Framework for Coronary Heart Disease was published by the UK Department of Health in 2000,⁵¹ but this did not make specific recommendations on the use of CRT or ICD devices and is now out of date. Given the absence of a national framework, Heart Rhythm UK has recently developed standards for the implantation and follow-up of CRT devices.⁵²

1.3.1 SCD

Diagnosis of SCD

Since SCD can happen without warning, it is important for general practitioners and secondary care providers to be aware of risk factors so that patients at high risk of SCD can be identified and referred for cardiac evaluation. A range of diagnostic tests may be used to identify risk of SCD. An ECG can detect abnormalities in the heart's electrical activity and may reveal evidence of heart damage due to coronary heart disease, or signs of a previous or current heart attack. Electrophysiological (EP) testing is sometimes used to identify the origins of an arrhythmia and programmed electrical stimulation (PES) of the heart may be used in stimulating the heart to induce the arrhythmia. An EP or PES study may be used prior to implantation of an ICD in order to confirm the need for an ICD or diagnostic work-up. Other tests that may be used to identify SCD risk include ultrasound echocardiography and cardiac MRI (to image or film different parts or the whole of the heart), blood tests (to check concentrations of chemicals involved in heart function, e.g. potassium and magnesium), and cardiac catheterisation (e.g. if blood samples from within the heart are required, or to inject dye for angiographic studies).

Implantable devices for SCD

Ventricular arrhythmia, particularly sustained VT and VF are life-threatening events. For patients who meet specified treatment criteria, the NICE guidance issued in 2006 (TA95)⁴⁵ recommends that ICD (or CRT-D) therapy is recommended as a prophylactic intervention to reduce the risk of SCD (primary prevention) and also to prevent any further episodes (secondary prevention) in patients who meet specified treatment criteria. Patients with sustained ventricular arrhythmias associated with

haemodynamic compromise in the presence of LVSD should be considered for ICD therapy after reversible factors are addressed. Patients with LVSD and who have recently had a myocardial infarction (MI) or patients who have a cardiac condition that is associated with a high risk of sudden death should also be considered for ICD therapy in addition to optimal pharmacological therapy (OPT). OPT (as described below) is used as an adjunct or provided for those patients for whom an ICD would not be appropriate (e.g. those with a severely limited prognosis).

Specific recommendations of the NICE guidance⁴⁵ (which does not cover non-ischaemic dilated cardiomyopathy) are that ICDs may be used as primary prevention if patients have a history of previous (≥ 4 weeks) MI and either have left ventricular (LV) dysfunction with an LVEF $<35\%$ (no worse than NYHA class III) and non-sustained VT on Holter [24-hour electrocardiogram (ECG)] monitoring, and inducible VT on electrophysiological (EP) testing; or left ventricular dysfunction with an LVEF of $<30\%$ (no worse than NYHA class III) and QRS duration of ≥ 120 milliseconds; individuals with a familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia (ARVD), or have undergone surgical repair of congenital heart disease.⁴⁵

ICDs as secondary prevention for arrhythmias are recommended for individuals who present, in the absence of a treatable cause, with one of the following: survived a cardiac arrest due to either VT or VF; spontaneous sustained VT causing syncope or significant haemodynamic compromise; sustained VT without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF $<35\%$) (no worse than NYHA class III).⁴⁵

Optimal pharmacological therapy for SCD

Chronic prophylactic anti-arrhythmic drug therapy is aimed at suppressing the development of arrhythmias in patients at high risk of SCD. The class III drugs, such as amiodarone, have been shown to have the best efficacy profile and are very commonly used. These drugs may enhance the maintenance of sinus rhythm, but cannot terminate an arrhythmia once it is initiated. A meta-analysis based on 8522 patients from 15 trials found that amiodarone reduced the risk of SCD by 29% and cardiovascular death (CVD) by 18% in patients at risk of SCD.⁵³ However, amiodarone therapy was neutral with respect to all-cause mortality and was associated with a high discontinuation rate and significant end-organ adverse reactions including hepatic, pulmonary, and thyroid toxicity, with a two- and five-fold increased risk of pulmonary and thyroid toxicity respectively.⁵³ Other drugs that may be included in the optimal pharmacological therapy of SCD are ACE inhibitors (recommended for all patients with LV systolic dysfunction to improve ventricular geometry and function), aldosterone receptor antagonists (for people resistant to other drug therapy) and beta blockers (to reverse ventricular remodelling) amongst others.⁵⁴

1.3.2 HF

Diagnosis of HF

The NICE clinical guideline CG108, “Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care”⁴⁷ provides a diagnostic pathway for HF, the key elements of which are shown in Figure 2. Serum natriuretic peptides (protein substances secreted by the wall of the heart when it is stretched or under increased pressure) should be measured in people with suspected heart failure without MI, although the guideline cautions that levels of serum natriuretic peptides (SNPs) can be reduced by certain conditions (e.g. obesity) or treatments [e.g. diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers]. Conversely other conditions [e.g. left ventricular hypertrophy, renal dysfunction, chronic obstructive pulmonary disease (COPD)] can cause high levels of SNPs. Therefore an electrocardiogram (ECG) and other tests (e.g. chest X-ray, blood tests, urinalysis, spirometry) may be required to evaluate other possible diagnoses. Transthoracic Doppler 2D echocardiography is used to assess the function (systolic and diastolic) of the left ventricle, to detect intracardiac shunts, and to exclude important valve disease. If a poor image is obtained, other imaging methods (e.g. radionuclide angiography, cardiac magnetic resonance imaging, or transoesophageal Doppler 2D echocardiography) can be considered.

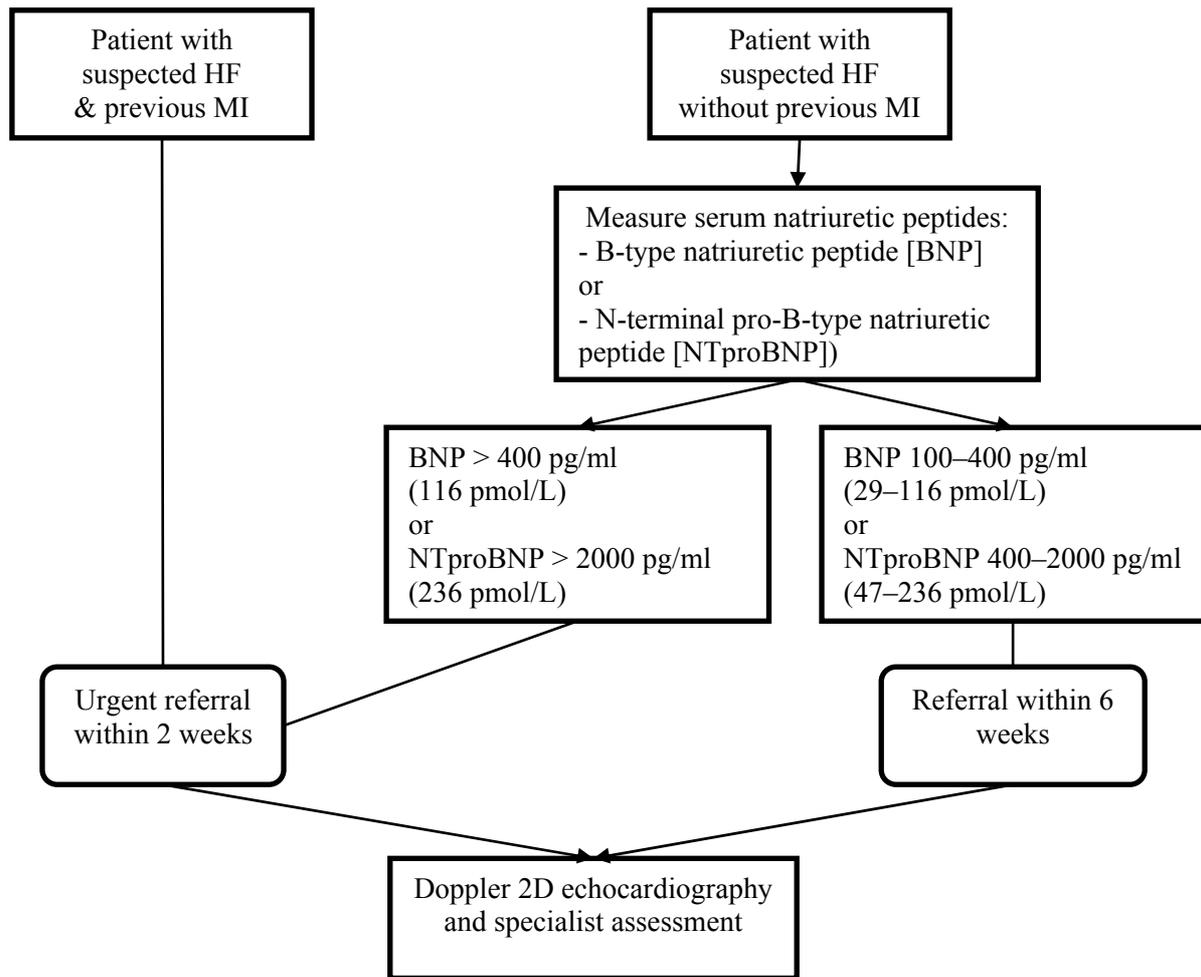


Figure 2: Key elements in the NICE Heart Failure Guideline diagnostic pathway⁵⁵

Management of HF

A patient presenting with the typical signs and symptoms of heart failure should receive specialist assessment including echocardiography.⁴⁷ If heart failure is diagnosed the goals of treatment are to reduce mortality and improve the health outcome of patients. In clinical practice, pharmacological agents are routinely used as the first-line therapy in managing heart failure⁴⁷ (details of OPT for HF are given below).

In addition to drug therapy, according to the NICE clinical guideline, individuals should be encouraged to participate in exercise-based cardiac rehabilitation (including a psychological and educational component), to give up smoking if applicable or be referred to a smoking cessation service, and to abstain from alcohol consumption if they have alcohol-related HF.⁴⁷ Similarly, the European Society of Cardiology recommends that individuals with HF should be enrolled in a multidisciplinary-care management programme.⁵⁶

Implantable devices for HF

As the severity of heart failure symptoms increases, a patient's symptoms may no longer be controlled by OPT or lifestyle changes. There are multiple syndromes associated with heart failure that could predispose patients to the need for further intervention. In patients with heart failure, the existence of a modifiable risk factor such as arrhythmias may constitute a rationale for the use of multiple interventions. The NICE pathway for chronic heart failure⁵⁵ indicates that when symptoms are not controlled by optimal pharmacological therapy, treatment with a CRT-P or a CRT-D can be considered for patients meeting specific criteria.

Current NICE guidance issued in 2007 (TA120)⁴⁶ recommends CRT-P as a treatment option for individuals with HF who fulfil all the following criteria: are currently experiencing or have recently experienced NYHA class III–IV symptoms; are in sinus rhythm - either with a QRS duration of 150 ms or longer estimated by standard ECG or with a QRS duration of 120–149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography; have a LVEF of $\leq 35\%$; are receiving OPT. CRT-D may be considered for individuals who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD device (see above).

Comments received from a clinical expert indicate that CRT is increasingly being considered for people without symptoms with the aim of improving prognosis by modifying the natural history of heart failure. Another interventional procedure that may be considered for patients with severe refractory symptoms is cardiac transplant. For those awaiting a donor heart, short-term circulatory support with a left ventricular assist device (LVAD) may be indicated.⁵⁷

Optimal pharmacological therapy for HF

Optimal medical drug therapy for HF can include ACE inhibitors, diuretics (for the relief of congestive symptoms and fluid retention), beta-blockers, aldosterone antagonists, digoxin (if symptoms continue despite ACE inhibitors), amiodarone, anticoagulants (to reduce the risk of stroke), aspirin (to reduce the risk of vascular events), statins (to reduce the risk of MI and stroke), inotropic agents (to stimulate the heart muscle) and calcium channel blockers (for co-morbid hypertension and angina).

The NICE 2010 clinical guideline suggests that medical drug therapy for HF has two aims – firstly to improve patients' morbidity (by reducing symptoms, improving exercise tolerance, reducing hospital admissions and improving QoL) and, secondly, to improve patients' prognosis (by reducing all-cause mortality or HF-related mortality). According to the guideline, first-line treatment should include both ACE inhibitors and beta-blockers licensed for HF for all individuals with HF due to LVSD.⁴⁷

If an individual remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker, second-line treatment recommendations are to add one of the following: an aldosterone antagonist licensed for HF [especially if the patient has moderate to severe HF (NYHA class III–IV) or has had an MI within the past month] or an angiotensin II receptor antagonist (ARB) licensed for HF [especially if the patient has mild to moderate HF (NYHA class II–III)] or hydralazine in combination with nitrate [especially if the patient is of African or Caribbean origin and has moderate to severe HF (NYHA class III–IV)].⁴⁷

Pharmacological recommendations for all types of HF include diuretics, calcium channel blockers, amiodarone, anticoagulants, aspirin and inotropic agents (such as dobutamine, milrinone or enoximone). ACE inhibitor therapy should not be initiated in individuals with a clinical suspicion of haemodynamically significant valve disease.⁴⁷

1.4 Current service provision

Current service provision is difficult to ascertain since the most recent audits of the use of CRT devices and ICDs in England and Wales^{58;59} suggest there is considerable regional variation in implant rates. There is also a lack of information on patient referral patterns for the receipt of resynchronisation and defibrillation devices in the NHS.⁶⁰

The National Heart Failure Audit April 2010-March 2011⁶¹ did not capture any information on the use of CRT devices or ICDs, but recommended that such data should be collected in future audits.

The most recent study to have reported the use of CRT devices and ICDs was the “Cardiac Rhythm Management: UK National Clinical Audit 2010”⁵⁸ which compared the rates of implantation of bradycardia pacemakers, ICDs and CRT devices during 2000-2010 in comparison with national targets (a recent update of the audit provides additional data for January to December 2011, but is an interim version pending final publication⁵⁹). The audit collected data from 28 cardiac networks (regional groups of hospitals providing implants of pacemakers, CRT devices and ICDs) in England. There is clearly wide regional variation in the rates of implantation, with some cardiovascular networks having achieved or exceeded national target implant rates during 2010 whilst other networks have not (Table 3). However, there is some debate about what the national targets should be. For example, a target of 100 ICD implants per million patients per annum has been proposed⁵⁸ but other estimates that assume adherence to published guidelines suggest the annual implant rate for ICDs should be higher, between 105 and 504 per million patients.⁶⁰ The wide regional variation in implant rates appears to suggest underuse in regions with low implant rates.⁶⁰ The audit⁵⁸ noted that the ratio of CRT-P implants to CRT-D implants and the ratio of ICD to CRT-D implants were highly variable among the cardiac networks in England, but it is not possible to determine the extent to which this

variation reflects differences in local clinical practice and/or differences between patient populations. A study of ICD referral patterns in a single cardiac network in southern England⁶⁰ found that implant rates were higher in areas whose local hospital was a regional cardiac centre compared to district general hospitals (with or without a device specialist), suggesting that some of the observed regional variation may reflect the structure of cardiac networks (the number and type of hospitals they include) and their patient referral pathways.⁶⁰ The discrepancy observed within the study of cardiac network was greatest with respect to the use of ICDs for coronary artery disease primary prevention indications, and the authors suggested that this most likely reflects underuse of the therapy in the district hospitals rather than overuse in the regional cardiac centre.⁶⁰ A related study in the same cardiac network retrospectively investigated the management of ICD-implanted patients who developed heart failure.⁶² Such patients may potentially benefit by being upgraded from an ICD to a CRT device. However, only a low proportion of these patients was found to have received an upgrade, raising the question of whether a CRT device might have been a more appropriate initial choice than an ICD for this patient subgroup.⁶²

Table 3: Device implant rates in England during 2010 compared with national targets⁵⁸

Device type	Average^a (range) number of implants per million patients, adjusted for age and sex	National target (number of implants per million patients, adjusted for age and sex)
ICD	72 (34-131)	100
All CRT devices (CRT-P + CRT-D)	114 (68-182)	130
All defibrillator devices (ICD + CRT-D)	131 (81-197)	Not reported

^a not explicitly stated whether mean or median

The audit⁵⁸ reported data on the types of physiological pacing that were employed and also some data on the presenting symptoms and electrocardiogram patterns in patients with implants. Since there is substantial overlap in the indications for resynchronisation and defibrillation devices,⁶² clinicians' choice between ICD, CRT-D and CRT-P devices may in some cases have been arbitrary,⁵⁸ and the audit did not discriminate between all the possible pacing and defibrillation modes that can be programmed in modern implantable devices. Overall, in England during 2010, ICDs were the device type employed most frequently for syncope/cardiac arrest with VT/VF; CRT-D devices were the most frequent type implanted for heart failure with VT/VF; and CRT-P devices were the most frequent type employed in patients who had heart failure without VT/VF. Both CRT-D and ICD, but rarely CRT-P, were used for prophylaxis (Table 4). All device types were implanted more often in males than

females (80.1% of ICDs, 83.4% of CRT-D and 68.4% of CRT-P devices were in males). In 2011, a much higher proportion of CRT-D devices was implanted for primary prevention than for secondary prevention (78.3% vs 21.7% respectively), although the proportions of ICDs for primary and secondary prevention were similar (48.3% and 51.4% respectively).⁵⁸

Table 4 Combinations of presenting symptoms and ECGs in resynchronisation and defibrillation device implant patients in England, 2010 (%)⁵⁸

Presenting symptom and ECG	ICD	CRT-D	CRT-P	Total (rounded)
Syncope/cardiac arrest and VT/VF	79.3	20.4	0.2	100
Heart failure and VT/VF	29.8	68.2	1.9	100
Heart failure and any rhythm except VT/VF	3.9	20.6	75.5	100
Prophylactic (no symptoms) – all presenting ECGs	48.5	48.8	2.7	100

The demand for device implants will increase due to a growing ageing population. In addition, there are increasing demands to expand the use of CRT devices, i.e. to include individuals with NYHA class I-II symptoms, ejection fraction of less than 30% and QRS wider than 130 milliseconds. This will increase the burden on existing services within cardiology, as well as raising the importance of device costs. The UK National Clinical Audit⁵⁸ confirms that there has been a substantial increase in the number of CRT and ICD devices implanted in England and Wales during 2000-2010. The interim update of the audit⁵⁹ suggests, however, that although more ICDs per million patients were implanted in England in 2011 than in 2010, the rate of increase has slowed, and, overall, the total number of CRT implants per million patients was similar during 2010 and 2011.

In addition to the variation within the UK (Table 3), there is considerable variation in the utilisation of implantable defibrillators across Europe⁵⁸ and ICD/CRT-D implant rates are considerably higher in the USA than in Europe.⁶³ The UK has approximately 0.7 ICD implant centres per million population, which is lower than in France, Germany, Italy and the USA.⁶³ It has been suggested that lower utilisation rates may reflect three main factors: a shortage of implant centres and electrophysiologists; poorly developed referral strategies/care pathways; and problems with specialist health care investment.⁶³ The recently-collected data^{58;63} suggest that systematic planning of ICD services is lacking in the UK, with under-utilisation of CRT and ICD devices, although it is unclear if this impacts on the equality of service provision.

2 DEFINITION OF THE DECISION PROBLEM

This section states the key factors that will be addressed by this assessment, and defines the scope of the assessment in terms of these key factors in line with the definitions provided in the NICE scope.⁶⁴

This assessment updates and expands on two previous technology assessment reports: ‘The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review’⁶⁵ (which itself was an update of a TAR published in 2000⁶⁶) and ‘The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model’.⁴³ The key differences between the present assessment and the previous assessments are outlined below and summarised in Appendix 1.

2.1 Decision problem

The interventions included within the scope of this assessment are ICD, CRT-P and CRT-D, each in addition to OPT.

Three populations are defined by the NICE scope:⁶⁴

1. People at increased risk of SCD as a result of ventricular arrhythmias despite OPT;
2. People with HF as a result of LVSD and cardiac dyssynchrony despite OPT;
3. People with both conditions described above.

The first group, people at risk of SCD as a result of ventricular arrhythmias, includes and expands on the population considered in the previous ICDs TAR.⁶⁵ For the present assessment this population is not restricted by NYHA classification and there is no specified cut-off for LVEF. The second group, people with HF as a result of LVSD and cardiac dyssynchrony, includes and expands on the population considered in the previous CRT TAR.⁴³ As in the previous TAR, this population is not restricted by NYHA classification in the present assessment, but unlike the previous TAR there is no specified cut-off for LVEF. The third group, people with both conditions, were not considered in the previous TARs.^{43;65} People with cardiomyopathy are not excluded from consideration in this assessment.

Whilst the three populations are considered separately within the report for the purposes of this assessment, it is acknowledged that in practice these are not distinct groupings and that there is considerable overlap between the groups; people with HF due to LVSD are at risk of SCD from ventricular arrhythmia.

The NICE scope⁶⁴ did not indicate whether any subgroups of patients were of interest. No subgroups were predefined in the earlier guidance TA95, but subgroup analyses were reported in some included studies by left ventricular ejection fraction (LVEF), QRS duration, and history of HF requiring treatment. Subgroups that were thought to be of interest in TA120 and were therefore predefined were age, atrial fibrillation, NYHA class, degree of LVSD, degree of dyssynchrony, ischaemic and non-ischaemic heart failure. Relevant subgroups for the current assessment may also include renal failure. If sufficient evidence is available consideration will be given to these subgroups.

The relevant comparisons for this assessment are as follows:

- For people at increased risk of SCD as a result of ventricular arrhythmias despite OPT, ICD will be compared with standard care (OPT without ICD);
- For people with HF as a result of LVSD and cardiac dyssynchrony despite OPT, CRT-P and CRT-D will be compared with each other or with standard care (OPT without CRT);
- For people with both conditions described above, CRT-D will be compared with ICD, CRT-P or standard care (OPT alone).

The clinical outcomes of interest include mortality (including progressive HF mortality, non-HF mortality, all-cause mortality and SCD), health-related quality of life (HRQoL), symptoms and complications related to tachyarrhythmias and/or HF, HF hospitalisations, change in NYHA class, change in left ventricular ejection fraction, and adverse effects of treatment. Outcomes for the assessment of cost-effectiveness will include direct costs based on estimates of health care resources associated with the interventions as well as consequences of the interventions, such as treatment of adverse events.

2.2 Overall aims and objectives of assessment

The aims of this health technology assessment are threefold:

- to assess the clinical-effectiveness and cost-effectiveness of ICDs in addition to OPT for the treatment of people who are at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT;
- to assess the clinical-effectiveness and cost-effectiveness of CRT-P or CRT-D in addition to OPT for the treatment of people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT;
- to assess the clinical-effectiveness and cost-effectiveness of CRT-D in addition to OPT for the treatment of people who have both an increased risk of sudden cardiac death as a result of ventricular arrhythmias and heart failure as a result of LVSD and cardiac dyssynchrony despite OPT.

3 METHODS FOR THE SYSTEMATIC REVIEWS OF CLINICAL EFFECTIVENESS AND COST-EFFECTIVENESS

The *a priori* methods for systematically reviewing the evidence of clinical effectiveness and cost-effectiveness were described in the research protocol (Appendix 2), which was sent to experts and to NICE for comment. Although helpful comments were received relating to the general content of the research protocol, there were none that identified specific problems with the methodology of the review. The methods outlined in the protocol are briefly summarised below.

3.1 Identification of studies

A search strategy was developed, tested and refined by an experienced information scientist. The strategy identified clinical-effectiveness studies of ICDs for arrhythmias and CRT for the treatment of heart failure. Additional search strategies identified studies reporting on the cost-effectiveness of ICDs and CRT, and studies reporting on the epidemiology and natural history of arrhythmias and heart failure. Searches to inform cost-effectiveness modeling were also conducted. Sources of information and search terms are provided in Appendix 3. The most recent search was carried out in November 2012.

The following electronic databases were searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); Medline In-Process and Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); Zetoc (Mimas); NIHR-Clinical Research Network Portfolio; Clinical Trials.gov and Current Controlled Trials. Searches were carried out from database inception to the present for studies in the English language. Searches were limited to randomised controlled trials (RCTs) for the assessment of clinical effectiveness and to full economic evaluations for the assessment of cost effectiveness. Bibliographies of retrieved papers and the manufacturers' submission to NICE were assessed for relevant studies that met the inclusion criteria, and the expert advisory group were contacted to identify additional published and unpublished evidence.

3.2 Inclusion and exclusion criteria

The inclusion criteria for population, interventions and comparators are summarised in Table 5.

Table 5: Summary of inclusion criteria

Population	People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT	People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite OPT	People with both conditions described to the left
Interventions	ICD in addition to OPT	CRT-P or CRT-D in addition to OPT	CRT-D in addition to OPT
Comparators	Standard care (OPT without ICD)	CRT-P vs CRT-D Standard care (OPT without CRT)	ICD CRT-P Standard care (OPT alone)

3.2.1 Population

- People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment.
- People with heart failure as a result of LVSD and cardiac dyssynchrony despite optimal pharmacological treatment.
- People with both conditions described above.

LVSD was defined as reduced LVEF using the cut-off provided by the publications (an arbitrary cut-off was not imposed by this review). Similarly, cardiac dyssynchrony was as defined by the publications; usually a prolonged QRS interval. Trials clearly stating that participants had reduced LVEF, cardiac dyssynchrony and an indication for an ICD were considered as having both conditions.

3.2.2 Interventions

The interventions under consideration for each patient group are:

- For people at increased risk of sudden cardiac death:
 - ICDs in addition to OPT.
- For people with heart failure:
 - CRT-P or CRT-D in addition to OPT.
- For people with both conditions:
 - CRT-D in addition to OPT.

3.2.3 Comparators

The comparators under consideration for each patient group are:

- For people at increased risk of sudden cardiac death:
 - Standard care (OPT without ICD).
- For people with heart failure:
 - CRT-P or CRT-D were compared with each other;
 - Standard care (OPT without CRT).
- For people with both conditions:
 - ICD;
 - CRT-P;
 - Standard care (OPT alone).

When screening studies for inclusion it became apparent that the pharmacological therapy in some of the older studies may not be considered optimal by current standards. After consultation with NICE and clinical experts, it was decided that trials in which the pharmacological therapy in either the intervention or comparator arm was not optimal (i.e. current best practice based on clinical opinion) would be included in the systematic review.

3.2.4 Outcomes

Studies must have included one or more of the following outcome measures to have been eligible for inclusion in this review:

- Mortality (including progressive heart failure mortality, non-heart failure mortality, all-cause mortality and sudden cardiac death)
- Adverse effects of treatment
- Health related quality of life
- Symptoms and complications related to tachyarrhythmias and/or heart failure
- Heart failure hospitalisations
- Change in NYHA class
- Change in left ventricular ejection fraction

3.2.5 Study design

- For the systematic review of clinical effectiveness, only RCTs were eligible.
- Studies published as abstracts or conference presentations from 2010 onwards were only included if sufficient details were presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- Systematic reviews of the clinical-effectiveness of ICDs and CRT were used as a source of references.
- For the systematic review of cost-effectiveness, studies were only included if they reported the results of full economic evaluations [cost-effectiveness analyses (reporting cost per life year gained), cost-utility analyses or cost-benefit analyses].
- For the systematic review of quality of life, primary studies or QoL collected as part of a trial using EQ-5D (not VAS), specified by NYHA class for people with heart failure, were included
- Non-English language studies were excluded.

3.3 Screening and data extraction process

Studies were selected for inclusion in the systematic review of clinical effectiveness through a two-stage process using the criteria defined above. The titles and abstracts of studies identified by the search strategy were screened by two reviewers to identify all citations that potentially met the inclusion criteria. Full papers of relevant studies were retrieved and assessed by two independent reviewers using a standardised eligibility form. Full papers or abstracts describing the same study were linked together, with the article reporting key outcomes designated as the primary publication. Data from included studies were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. At each stage, any disagreements were resolved by discussion, with the involvement of a third reviewer where necessary.

Titles and abstracts identified by the search strategies for the systematic reviews of cost-effectiveness and quality of life were assessed for potential eligibility by two health economists using predetermined inclusion criteria. Full papers were assessed for inclusion two reviewers.

3.4 Critical appraisal

The risk of bias of the clinical-effectiveness studies was assessed according to criteria devised by the Cochrane Collaboration.⁶⁷ Criteria were applied by one reviewer and checked by a second reviewer, with differences in opinion resolved by consensus and by consultation with a third reviewer if

necessary. Economic evaluations were appraised using criteria based on those recommended by Drummond and colleagues,⁶⁸ the requirements of the NICE reference case⁶⁹ and the suggested guideline for good practice in decision analytic modelling by Philips and colleagues⁷⁰ (Appendix 4). Published studies carried out from the UK NHS and Personal Social Services (PSS) perspective were examined in more detail.

3.5 Method of data synthesis

Clinical-effectiveness data were synthesised through a narrative review with tabulation of the results of included studies. Where data were of sufficient quality and homogeneity, meta-analysis of the clinical-effectiveness studies was performed to estimate the risk ratio and 95% confidence intervals for relevant outcomes. The random effects method was used. Meta-analysis was performed by using Cochrane Review Manager 5 (RevMan). Statistical heterogeneity was assessed using Chi² and degrees of freedom (df), and I² statistic. Where standard deviations were not presented in the published papers, these were calculated from the available statistics (confidence intervals, standard errors or p values).⁶⁷ A minority of papers reported median values with 95% confidence intervals; in these cases rather than omitting the trial from a meta-analysis, it was assumed that the data were symmetrical (and so the median would be similar to the mean value) and the median was used directly in the meta-analysis.

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

4 CLINICAL EFFECTIVENESS

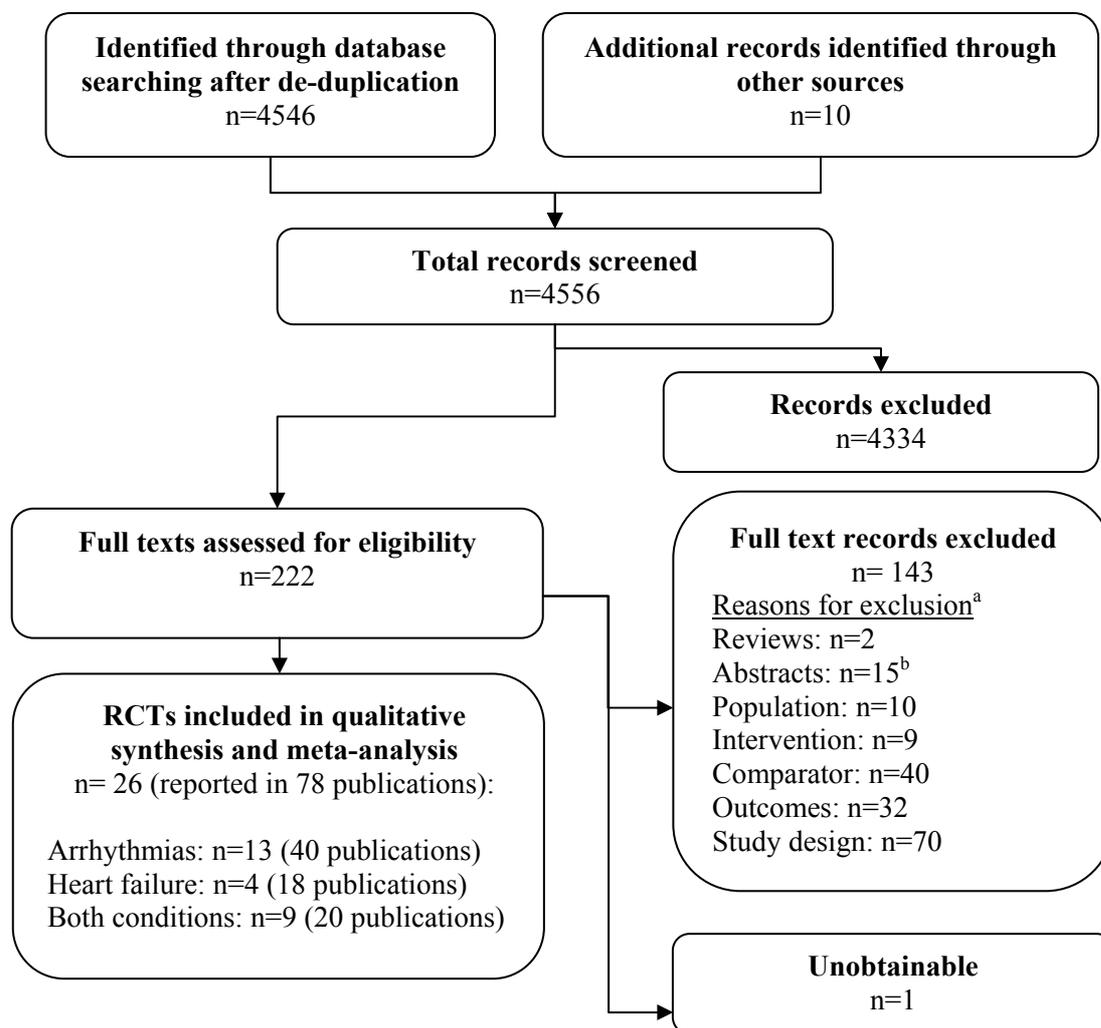
4.1 Overall quantity of evidence identified

Searches identified a total of 4556 references after de-duplication, and full texts of 222 references were retrieved after screening titles and abstracts. The number of references excluded at each stage of the systematic review is shown in Figure 3. Selected references which were retrieved but later excluded are listed in Appendix 5 with reasons for exclusion. Papers were often excluded for more than one reason; the most common reason being study design (70 papers), followed by comparator (40 papers) and outcomes (32 papers). Although not formally assessed, the level of agreement between reviewers for screening was considered good.

Searches identified five relevant trials in progress, a summary of which can be seen in Appendix 6.

Twenty six eligible RCTs were identified (references listed in Table 6), many of these trials were reported in several publications (a total of 78 papers). Thirteen RCTs were considered to involve people at increased risk of sudden cardiac death as a result of ventricular arrhythmias (Section 4.2), four trials were considered to involve people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony (Section 4.3) and nine RCTs were considered to involve people with both of these conditions (Section 4.4). Further details on the quantity and quality of research for each of these populations are described in the following sections.

Figure 3: Flowchart of identification of studies



^a Studies could be excluded for more than one reason; ^b 16 of the abstracts/conference presentations were published from 2010 onwards (Appendix 5) and were excluded as there was insufficient details to allow an appraisal of the methodology and the assessment of results as per the protocol.

Table 6: List of RCTs included in the systematic review of clinical effectiveness

Trial name	Publication (bold text indicated primary or key publication)
<i>People at increased risk of sudden cardiac death as a result of ventricular arrhythmias</i>	
AMIOVIRT	Strickberger et al., 2003; ⁷¹ Wijetunga and Strickberger, 2003 ⁷²
AVID	AVID investigators, 1997 ⁷³ and 1999; ⁷⁴ Hallstrom 1995; ⁷⁵ Schron et al., 2002 ⁷⁶
CABG Patch	Bigger et al., 1997; ⁷⁷ and 1993; ⁷⁸ 1998; ⁷⁹ 1999; ⁸⁰ Spotnitz et al., 1998; ⁸¹ Namerow et al., 1999 ⁸²
CASH	Kuck et al., 2000 ⁸³
CAT	Bänsch et al., 2002; ⁸⁴ The German dilated cardiomyopathy study investigators, 1992 ⁸⁵
CIDS	Connolly et al., 2000; ⁸⁶ Connolly et al., 1993; ⁸⁷ Sheldon et al., 2000; ⁸⁸ Irvine et al., 2002; ⁸⁹ Bokhari et al., 2004 ⁹⁰
DEBUT	Nademanee et al., 2003 ⁹¹
DEFINITE	Kadish et al., 2004; ⁹² Kadish et al., 2000; ⁹³ Schaechter et al., 2003; ⁹⁴ Ellenbogen et al., 2006; ⁹⁵ Passman et al., 2007 ⁹⁶
DINAMIT	Hohnloser et al., 2004; ⁹⁷ Hohnloser et al., 2000 ⁹⁸
IRIS	Steinbeck et al., 2009; ⁹⁹ Steinbeck, 2004 ¹⁰⁰
MADIT I	Moss et al., 1996; ¹⁰¹ MADIT executive Committee, 1991 ¹⁰²
MADIT II	Moss et al., 2002; ¹⁰³ and 1999; ¹⁰⁴ Greenberg et al., 2004; ¹⁰⁵ Noyles et al., 2007; ¹⁰⁶
SCD-Heft	Bardy et al., 2005; ¹⁰⁷ Mitchell et al., 2008; ¹⁰⁸ Mark et al., 2008; ¹⁰⁹ Packer et al., 2009 ¹¹⁰
<i>People with heart failure as a result of LVSD and cardiac dyssynchrony</i>	
CARE-HF	Cleland et al., 2005; ¹¹¹ and 2001; ¹¹² 2006; ¹¹³ 2007; ¹¹⁴ 2009; ¹¹⁵ Gras et al., 2007; ³⁶ Gervais et al., 2009; ¹¹⁶ Ghio et al., 2009 ¹¹⁷
COMPANION	Bristow et al., 2004; ¹¹⁸ and 2000; ¹¹⁹ FDA report, 2004; ¹²⁰ Carson et al., 2005; ¹²¹ Anand et al., 2009 ¹²²
MIRACLE	Abraham et al., 2002; ¹²³ and 2000; ¹²⁴ FDA report, 2001; ¹²⁵ Sutton et al., 2003 ¹²⁶
MUSTIC	Cazeau et al., 2001 ¹²⁷
<i>People with both conditions described above</i>	
CONTAK-CD	Higgins et al., 2003; ¹²⁸ Saxon et al., 1999; ¹²⁹ Lozano et al., 2000; ¹³⁰ FDA report, 2002 ¹³¹
MADIT-CRT	Moss et al., 2009; ¹³² and 2005; ¹³³ Solomon et al., 2010; ¹³⁴ Goldenberg et al., 2011; ¹³⁵ and 2011; ¹³⁶ Arshad et al., 2011 ¹³⁵
MIRACLE ICD	Young et al., 2003 ¹³⁷

MIRACLE ICD II	Abraham <i>et al.</i>, 2004¹³⁸
Piccirillo 2006	Piccirillo <i>et al.</i>, 2006¹³⁹
Pinter 2009	Pinter <i>et al.</i>, 2009¹⁴⁰
RAFT	Tang <i>et al.</i>, 2010;¹⁴¹ Tang <i>et al.</i>, 2009¹⁴²
RethinQ	Beshai <i>et al.</i>, 2007;¹⁴³ Beshai & Grimm, 2007¹⁴⁴
RHYTHM ICD	Summary of Safety and Effectiveness, 2004¹⁴⁵ and 2005¹⁴⁶

4.2 People at risk of sudden cardiac death as a result of ventricular arrhythmias

4.2.1 Quantity and quality of research available

Eleven of the 13 RCTs included reported their findings in more than one paper; a summary of the included papers for each trial can be seen in Table 7. Seven of these RCTs plus one additional RCT (MUSTT¹⁴⁷) were included in the 2005 TAR,⁶⁵ as can be seen in Table 7. One further RCT (MAVERIC¹⁴⁸) was noted in the 2005 TAR⁶⁵ as in progress at that time. The interventions in the MUSTT¹⁴⁷ and MAVERIC¹⁴⁸ trials did not meet the scope of the present review, however as these were included in the previous TARs^{65;66} they are discussed in section 4.2.2.12. A list of other excluded studies can be seen in Appendix 5.

The RCTs used different criteria to identify groups at ‘high risk’ of sudden cardiac death from ventricular arrhythmia. AVID,⁷³ CASH,⁸³ CIDS⁸⁶ and DEBUT⁹¹ included people who had previous ventricular arrhythmia or had been resuscitated from cardiac arrest. Four studies included people with either a recent MI (DINAMIT⁹⁷ and IRIS⁹⁹) or MI more than 3 to 4 weeks prior to study entry (MADIT I,¹⁰¹ MADIT II¹⁰³). AMIOVIRT,⁷¹ CAT⁸⁴ and DEFINITE⁹² included people with cardiomyopathy. CABG Patch⁷⁷ recruited patients scheduled for CABG surgery and at high risk for sudden death, and SCD-Heft recruited a broad population of patients with mild to moderate heart failure. The results will be discussed according to the ‘high risk’ group of the participants.

Table 7: Summary of included studies

Trial	2005 TAR⁶⁵ (reason for exclusion)	Present TAR (participants)	Publication (bold text indicated primary or key publication)
<i>Secondary prevention</i>			
AVID	Included	Included (cardiac arrest)	AVID investigators, 1997⁷³ and 1999; ⁷⁴ Hallstrom 1995; ⁷⁵ Schron <i>et al.</i> , 2002 ⁷⁶
CASH	Included	Included (cardiac arrest)	Kuck <i>et al.</i>, 2000⁸³
CIDS	Included	Included (cardiac arrest)	Connolly <i>et al.</i>, 2000;⁸⁶ Connolly <i>et al.</i> , 1993; ⁸⁷ Sheldon <i>et al.</i> , 2000; ⁸⁸ Irvine <i>et al.</i> , 2002; ⁸⁹ Bokhari <i>et al.</i> , 2004 ⁹⁰
DEBUT	Excluded (participants)	Included (SUDES)	Nademanee <i>et al.</i>, 2003⁹¹
<i>Primary prevention</i>			
MADIT I	Included	Included (remote from MI)	Moss <i>et al.</i>, 1996;¹⁰¹ MADIT executive Committee, 1991 ¹⁰²
MADIT II	Included	Included (remote from MI)	Moss <i>et al.</i>, 2002;¹⁰³ and 1999; ¹⁰⁴ Greenberg <i>et al.</i> , 2004; ¹⁰⁵ Noyles <i>et al.</i> , 2007; ¹⁰⁶
DINAMIT	In progress	Included (early post MI)	Hohnloser <i>et al.</i>, 2004;⁹⁷ Hohnloser <i>et al.</i> , 2000 ⁹⁸
IRIS	New	Included (early post MI)	Steinbeck <i>et al.</i>, 2009;⁹⁹ Steinbeck, 2004 ¹⁰⁰
AMIOVIRT	Excluded (participants)	Included (cardiomyopathy)	Strickberger <i>et al.</i>, 2003;⁷¹ Wijetunga and Strickberger, 2003 ⁷²
CAT	Included	Included (cardiomyopathy)	Bänsch <i>et al.</i>, 2002;⁸⁴ The German dilated cardiomyopathy study investigators, 1992 ⁸⁵
DEFINITE	Excluded (participants)	Included (cardiomyopathy)	Kadish <i>et al.</i>, 2004;⁹² Kadish <i>et al.</i> , 2000; ⁹³ Schaechter <i>et al.</i> , 2003; ⁹⁴ Ellenbogen <i>et al.</i> , 2006; ⁹⁵ Passman <i>et al.</i> , 2007 ⁹⁶
CABG Patch	Included	Included (need for CABG)	Bigger <i>et al.</i>, 1997;⁷⁷ and 1993; ⁷⁸ 1998; ⁷⁹ 1999; ⁸⁰ Spotnitz <i>et al.</i> , 1998; ⁸¹ Namerow <i>et al.</i> , 1999 ⁸²

MUSTT	Included	Excluded due to intervention	Buxton <i>et al.</i>, 1999; ¹⁴⁷ Lee <i>et al.</i> , 2002 ¹⁴⁹
SCD-Heft	In progress, in NICE TA	Included (heart failure)	Bardy <i>et al.</i>, 2005; ¹⁰⁷ Mitchell <i>et al.</i> , 2008; ¹⁰⁸ Mark <i>et al.</i> , 2008; ¹⁰⁹ Packer <i>et al.</i> , 2009 ¹¹⁰

SUDS, Sudden unexpected death syndrome.

4.2.1.1 Characteristics of the included studies

Study characteristics are summarised in Table 8, Table 9 and Table 10, and participant characteristics are summarised in Table 11, Table 12 and Table 13. Additional detail can be found in Appendix 8.

Intervention and comparators

The NICE scope and systematic review protocol defined the intervention for this group of people as ‘ICDs in addition to OPT’ and the comparator as ‘standard care (OPT without ICD)’. Concepts of OPT have changed over time and OPT varies depending on the population (e.g. previous VF, post MI, heart failure), making a standard definition of OPT difficult. Standards of reporting have also changed, making it difficult in some instances to be clear what participants have received. As a consequence it was decided and agreed with NICE, to include studies that compared ICDs (with or without OPT) with the different types of medical therapy, reporting the details of the pharmacological therapy used. The studies included were eligible on all other selection criteria.

The trials of people with previous VF or cardiac arrest compared ICD with antiarrhythmic drugs (AADs), including either amiodarone or beta blocker (sotalol) (AVID⁷³), amiodarone or beta-blocker (metoprolol) in separate groups (CASH⁸³) or amiodarone (CIDS⁸⁶), or with beta-blockers (propranolol, DEBUT⁹¹). Use of other medication was permitted in these trials. AVID⁷³ permitted use of aspirin, beta-blockers and ACE inhibitors where clinically appropriate in both groups. CASH⁸³ reported concurrent therapies at discharge (see below). CIDS⁸⁶ stated that antiarrhythmic drugs could be used in both groups to control supraventricular or nonsustained ventricular tachycardias that were symptomatic or might cause discharge of the ICD. DEBUT⁹¹ permitted other beta-blocking agents or amiodarone if intolerable side-effects developed from propranolol or if frequent shocks from recurrent ventricular fibrillation occurred, but did not provide additional data. Pharmacological therapy received by the participants is discussed in further detail below.

Trials of people with recent (IRIS,⁹⁹ DINAMIT⁹⁷) or remote (MADIT I,¹⁰¹ MADIT II)¹⁰³ MI compared ICD plus OPT versus OPT, although the pharmacological therapy in MADIT may not be considered optimal by current standards. Pharmacological therapy received by the participants is discussed in further detail below.

The trials of people with cardiomyopathy compared ICD plus OPT versus amiodarone plus OPT (AMIOVIRT⁷¹), or ICD plus OPT versus OPT (CAT,⁸⁴ DEFINITE⁹²). Pharmacological therapy received by the participants is discussed in further detail below.

CABG Patch⁷⁷ included people scheduled for CABG surgery and compared ICD plus OPT vs OPT (trial protocol prohibited use of AADs for asymptomatic ventricular arrhythmias), although the pharmacological therapy may not be considered optimal by current standards. Pharmacological therapy received by the participants is discussed in further detail below. The ICDs used in this trial were epicardial defibrillators, mostly committed devices (i.e. they deliver a shock even if the arrhythmia stops before the end of charging) that were not capable of storing electrograms.

SCD-HEFT¹⁰⁷ was a three arm trial comparing ICD, amiodarone and placebo in a broad population of patients with mild-to moderate heart failure. All participants received OPT.

Table 8: Study characteristics: Cardiac arrest survivors / ventricular arrhythmia - Secondary prevention

Parameter	Study name			
	AVID 1997 ⁷³	CASH 2000 ⁸³	CIDS 2000 ⁸⁶	DEBUT 2003 ⁹¹
Study design	RCT	RCT	RCT	RCT (pilot & main study)
Target population	Resuscitated from near-fatal VF; or symptomatic sustained VT with hemodynamic compromise.	Resuscitated from cardiac arrest secondary to documented sustained VA.	Previous sustained VA.	Sudden Unexplained Death Syndrome (SUDS) survivors or probable survivors.
Intervention	ICD + medical therapy	ICD + medical therapy	ICD +AAD for symptomatic VT	ICD + β -blocker or amiodarone if frequent shocks
Comparator	AAD + medical therapy	AAD: amiodarone or metoprolol + medical therapy	Amiodarone +AAD for symptomatic VT	Beta-blocker: long-acting propranolol. Other B-blockers if intolerable side effects.
Country (no. of centres)	USA (52), Canada (3), New Mexico (1)	Germany (multicentre, number unclear)	Canada (19), Australia (3), USA (2)	Thailand (unclear)
Sample size (randomised)	1016	288	659	Pilot 20; Main 66.
Length of follow-up	Mean 18.2 (SD 12.2) months	Mean 57 (SD 34) months	Mean years: 3 years.	Maximum 3 years
Key inclusion criteria	VF, VT with syncope or VT without syncope but with ejection fraction ≤ 0.40 and systolic blood pressure < 80 mm Hg; chest pain, or near	Not reported. Rate was the only criterion selected for detection of a sustained ventricular arrhythmia.	Any of following in absence of either recent acute MI (≤ 72 hrs) or electrolyte imbalance: documented VF; out-of-hospital cardiac arrest requiring	SUDS survivor: a healthy subject without structural heart disease who had survived unexpected VF or cardiac arrest after successful resuscitation.

Parameter	Study name			
	AVID 1997 ⁷³	CASH 2000 ⁸³	CIDS 2000 ⁸⁶	DEBUT 2003 ⁹¹
	syncope. ⁷⁵ If patients underwent revascularisation their ejection fraction had to be ≤ 0.40 .		defibrillation or cardioversion; documented, sustained VT causing syncope; other documented, sustained VT at a rate ≥ 150 bpm causing presyncope or angina in a patient with a LVEF $\leq 35\%$; or unmonitored syncope with subsequent documentation of either spontaneous VT ≥ 10 s or sustained (≥ 30 s) monomorphic VT induced by programmed ventricular stimulation.	Probable SUDS survivor: a subject without structural heart disease who experienced symptoms indicative of the clinical presentation of SUDs, especially during sleep. ECG abnormalities showing RBBB-like pattern with ST elevation in right precordial leads and inducible VT/VF in electrophysiology testing.

AAD, Antiarrhythmic drugs. VA, Ventricular arrhythmias.

Table 9: Study characteristics: Post-Myocardial infarction - Primary prevention

Parameter	Study name			
	DINAMIT 2004 ⁹⁷	IRIS 2009 ⁹⁹	MADIT I 1996 ¹⁰¹	MADIT II 2002 ¹⁰³
Target population	Recent MI (6 to 40 days); reduced LVEF and impaired cardiac autonomic function.	Recent MI (≤ 31 days) and predefined markers of elevated risk.	Previous MI and LV dysfunction.	High risk cardiac patients with prior MI and advanced LV dysfunction.
Study design	RCT	RCT	RCT	RCT
Intervention	ICD + OPT	ICD + OPT	ICD + conventional medical therapy	ICD + conventional medical therapy
Comparator	OPT	OPT	Conventional medical therapy	Conventional medical therapy
Country (no. of centres)	Canada (25), Germany (21), France, (8), UK (4), Poland (4), Slovakia (2), Austria (2), Sweden (2), USA (2), Czech Republic (1), Switzerland (1), Italy (1)	Austria, Czech Republic, Germany, Hungary, Poland, Russia, Slovak Republic, (92)	USA (30), Europe (2)	USA (71), Europe (5)
Sample size	674	898	196	1232
Length of follow-up	Mean (SD) 30 (13) months	Average (range) 37 (0 to 106) months	Average (range) 27 (<1 to 60) months	Average (range) 20 months (6 days to 53 months)
Key inclusion criteria	Recent MI (6 to 40 days previously); LVEF ≤ 0.35 ; SD of normal-to-normal RR intervals of ≤ 70 msec or a mean RR	Predefined markers of elevated risk; at least one of: heart rate ≥ 90 bpm on first available ECG (within 48 hrs	NYHA class: I, II or III; LVEF: ≤ 0.35 ; Q-wave or enzyme-positive MI >3 weeks prior entry; a documented episode of	LVEF: ≤ 0.30 last 3 months; MI >1 month prior study entry.

Parameter	Study name			
	DINAMIT 2004 ⁹⁷	IRIS 2009 ⁹⁹	MADIT I 1996 ¹⁰¹	MADIT II 2002 ¹⁰³
	interval of ≤ 750 msec (HR ≥ 80 beats per min) over a 24-hour period as assessed by 24-hour Holter monitoring performed at least 3 days after the infarction.	of MI) and LVEF $\leq 40\%$ (on one of days 5-31 after MI); nonsustained VT of ≥ 3 consecutive ventricular premature beats during Holter ECG monitoring, with a 150 bpm or more (on days 5 to 31).	asymptomatic, unsustained VT unrelated to an acute MI; no indications for coronary artery bypass grafting or coronary angioplasty within past 3 months; sustained VT or fibrillation reproducibly induced and not suppressed after the intravenous administration of procainamide (or equivalent).	

Table 10: Study characteristics: Cardiomyopathy, CABG surgery, Heart failure - Primary prevention

Parameter	Study name				
	AMIOVIRT 2003 ⁷¹	CAT 2002 ⁸⁴	DEFINITE 2004 ⁹²	CABG Patch 1997 ⁷⁷	SCD-Heft2005 ¹⁰⁷
Target population	Non-ischemic (DCM) and asymptomatic NSVT	Recent onset idiopathic DCM and impaired LVEF and without documented symptomatic VT.	Nonischaemic cardiomyopathy and moderate-to-severe LV dysfunction.	Patients scheduled for CABG surgery and at risk for sudden death (LVEF < 0.36 and abnormalities on an ECG).	Broad population of patients with mild-to-moderate heart failure.
Study design	RCT	RCT (pilot)	RCT	RCT	RCT
Intervention	ICD + OPT	ICD + OPT	ICD + OPT	ICD + OPT	ICD + OPT
Comparator	Amiodarone + OPT	OPT	OPT ^a	OPT No specific therapy for VA.	Amiodarone or Placebo (2 groups) + OPT
Country/no. of centres	USA (10)	Germany (15)	USA (44), Israel (4)	USA (35), Germany (2)	USA (99%), Canada, New Zealand (total 148)
Sample size	103	104	458	900	2521
Length of follow-up	Mean (SD) 2 (1.3) years	2-years	Mean (SD) 29 (14.4) months	Mean 32 months	Median (range) 45.5 (24 to 72.6) months
Key	NIDCM (LVdysfunction	NYHA class II or III;	LVEF < 36%; presence of	Scheduled for CABG	NYHA class II or III

Parameter	Study name				
	AMIOVIRT 2003 ⁷¹	CAT 2002 ⁸⁴	DEFINITE 2004 ⁹²	CABG Patch 1997 ⁷⁷	SCD-Heft2005 ¹⁰⁷
inclusion criteria	in the absence of, or disproportionate to the severity of CAD); LVEF \leq 0.35; asymptomatic NSVT; NYHA class I to III.	LVEF \leq 30%; aged 18-70 years; symptomatic DCM \leq 9 months.	ambient arrhythmias; history of symptomatic heart failure; presence of nonischaemic dilated cardiomyopathy.	surgery; LVEF $<$ 0.36, marker of arrhythmia: abnormalities on an ECG.	chronic, stable CHF due to ischaemic or non-ischaemic causes; LVEF \leq 35%; ischaemic CHF defined as LVSD associated with marked stenosis or a documented history of MI; nonischaemic CHF defined as LVSD without marked stenosis.

^a Antiarrhythmic drugs discouraged but allowed for symptomatic atrial fibrillation or supraventricular arrhythmias.

Participants

Cardiac arrest

The DEBUT trial⁹¹ differed notably from the other three trials (AVID,⁷³ CASH⁸³ and CIDS⁸⁶) of people resuscitated from cardiac arrest, as participants in DEBUT⁹¹ were survivors or probable survivors (symptoms indicative of the clinical presentation) of sudden unexplained death syndrome (SUDS) in otherwise normal hearts. All participants in the DEBUT study⁹¹ were of Thai origin and were similar to people with Brugada syndrome (a genetic disorder characterised by abnormal ECG findings and increased risk of cardiac death); as such the trial findings should also apply to this group of people.

The majority of participants in AVID,⁷³ CASH⁸³ and CIDS⁸⁶ had ischaemic heart disease (70 to 83%). A small proportion of those in CASH⁸³ and CIDS⁸⁶ had dilated cardiomyopathy. Two thirds of participants in AVID⁷³ and around three quarters of those in CIDS⁸⁶ had a previous MI.

All participants in CASH⁸³ and DEBUT,⁹¹ 90% in CIDS⁸⁶ and 60% in AVID⁷³ had congestive heart failure. The majority (approximately 87%) of people in CASH⁸³ had NYHA Class I or Class II heart failure, whereas about half those in AVID⁷³ and CIDS⁸⁶ fell into these categories. Almost 40% of participants in CIDS⁸⁶ had moderate to severe heart failure (NYHA Class III and IV), compared with 10% of people in AVID⁷³ and 16% (all NYHA Class III) of people in CASH.⁸³ Mean LVEF was higher in CASH⁸³ (46%) than in AVID⁷³ (32%) or CIDS⁸⁶ (34%), suggesting there may have been disproportionate representation of relatively healthy participants in CASH.⁸³ Mean QT interval ranged from 387 msec (DEBUT⁹¹) to 445 msec (AVID).⁷³

The people in DEBUT⁹¹ were younger (mean age 40 to 48 years) than in the other three trials (mean age 56 to 65 years), and all had NYHA class I heart failure. LVEF was higher in DEBUT⁹¹ (mean LVEF 66-69%) than in AVID,⁷³ CASH⁸³ and CIDS,⁸⁶ and QT interval slightly lower.

Myocardial infarction (MI)

MADIT I¹⁰¹ and MADIT II¹⁰³ included people with MI more than three weeks or one month previously. Participants in MADIT I¹⁰¹ were also required to have a LVEF of 35% or less, whereas MADIT II¹⁰³ required advanced left ventricular dysfunction (LVEF \leq 30%). DINAMIT⁹⁷ and IRIS⁹⁹ recruited people with recent MI (within 6 to 40 days and 5 to 31 days, respectively). DINAMIT⁹⁷ required participants to have a LVEF of 35% or less and standard deviation of normal-to normal RR intervals of \leq 70 msec or a mean RR interval of \leq 750 msec (heart rate \geq 80 beats per minute) over 24 hours. IRIS⁹⁹ included people with at least one of the following markers of risk: heart rate 90 beats per minute or more on first available ECG and LVEF 40% or less; or nonsustained ventricular tachycardia

of three or more consecutive ventricular premature beats during Holter ECG monitoring with a heart rate of 150 beats per minute or greater.

DINAMIT⁹⁷ had the greatest majority of participants in NYHA class I or II (around 70%), compared with 88% of participants in IRIS⁹⁹ and 63 to 67% of participants in MADIT I,¹⁰¹ and around 70% of participants in MADIT II.¹⁰³ The trials had either no or very few participants in NYHA class IV. Mean LVEF ranged from 23% (MADIT II¹⁰³) to 35% (IRIS⁹⁹), reflecting the different inclusion criteria of the studies.

The mean age of the participants in these trials was similar, ranging from 61.5 (DINAMIT⁹⁷) to 65 (MADIT II¹⁰³) years. The majority of participants (76% DINAMIT⁹⁷ to 92% MADIT I¹⁰¹) were men.

Cardiomyopathy

AMIOVIRT⁷¹ and DEFINITE⁹² recruited people with non-ischaemic dilated cardiomyopathy, non-sustained ventricular tachycardia, and LVEF of 35% or less. CAT⁸⁴ enrolled people with recent onset (less than 9 months) idiopathic dilated cardiomyopathy and LVEF of 30% or less, but without documented symptomatic ventricular arrhythmias. Note that despite participants not having suffered ventricular arrhythmias, the low LVEF indicates risk of ventricular arrhythmias and sudden cardiac death, and was therefore judged eligible for inclusion in this review. Also, non-sustained ventricular tachycardia was identified with Holter ECG in over half of participants at baseline.

The majority of participants in these trials were in NYHA class II or III, with none in NYHA class IV. AMIOVIRT⁷¹ (13-18%) and DEFINITE⁹² (18-25%) had more people with NYHA class I than CAT,⁸⁴ as this was an exclusion criteria of CAT.⁸⁴ Despite the lower cut-off for LVEF for inclusion in CAT,⁸⁴ mean LVEF at baseline was similar or slightly higher than the other two trials (CAT⁸⁴ 24-25%, AMIOVIRT⁷¹ 22-23%, DEFINITE⁹² 21-22%). Mean QRS interval was similar between CAT⁸⁴ (ICD: 102 (SD 29), OPT 114 (SD 29) msec) and DEFINITE⁹² (115, range 78-196), although the measures of variance suggest that some participants had cardiac dyssynchrony.

Participants in CAT⁸⁴ had a median duration of symptoms of just 3 months, compared to around 3 years in AMIOVIRT⁷¹ and DEFINITE.⁹² The participants in CAT⁸⁴ were also slightly younger (mean age 52 years) than in AMIOVIRT⁷¹ (mean age 59 years) or DEFINITE⁹² (mean age 58 years). The majority of participants (approximately 71% AMIOVIRT⁷¹ and DEFINITE⁹² to 80% CAT⁸⁴) were men.

CABG surgery

Participants in CABG Patch⁷⁷ were scheduled for CABG surgery and at risk for sudden cardiac death (LVEF less than 36%) with abnormalities on an ECG. People with a history of sustained ventricular tachycardia or fibrillation were excluded. The majority of participants (71-74%) were in NYHA class II or III, and mean LVEF was 27%. Most participants (83%) had previous myocardial infarction (Appendix 8). Mean age was about 64 years and 82-87% were men.

Mild to moderate heart failure

SCD-HeFT¹⁰⁷ included a broad population of people with mild to moderate heart failure due to ischaemic or non-ischaemic causes and a LVEF of 35% or less. Ischaemic congestive heart failure was defined as LV systolic dysfunction associated with $\geq 75\%$ narrowing of at least 1 of 3 major coronary arteries (marked stenosis) or a documented history of myocardial infarction. Nonischaemic congestive heart failure was defined as LV systolic dysfunction without marked stenosis. Overall 70% of participants were in NYHA class II and 30% were in class III. Median LVEF was 24%-25%, and less than a quarter had non-sustained ventricular tachycardia. Median age was 60 years and most (77%) were men.

Table 11: Key participant characteristics: cardiac arrest - secondary prevention

Parameter	AVID ⁷³		CASH ⁸³			CIDS ⁸⁶		DEBUT – pilot ⁹¹		DEBUT – main ⁹¹	
	ICD	AAD	ICD	AAD		ICD	Amio	ICD	β-blocker	ICD	β-blocker
				Amio	Met						
Sample size, n	507	509	99	92	97	328	331	10	10	37	29
Age, mean (SD) or [SEM]	65 (11)	65 (10)	58 (11)	59 (10)	56 (11)	63.3 (9.2)	63.8 (9.9)	44 [11]	48 [15]	40 [11]	40 [14]
Gender, % male	78	81	79	82	79	85.4	83.7	100	100	95	100
Index arrhythmia VF, %	44.6	45.0	84 ^a			45.1 ^b	50.1 ^b	70	60	24.3	37.9
Index arrhythmia VT, %	55.4	55.0	16 ^a			39.7 ^b	37.5 ^b	0	0	5.4	6.9
Ischemic heart disease, %	81	81	73	77	70	82.9	82.2	nr	nr	nr	nr
Dilated cardiomyopathy, %	nr	nr	12	10	14	8.5	10.6	nr	nr	nr	nr
Previous MI	67	67	nr	nr	nr	77.1	75.8	nr	nr	nr	nr
No congestive heart failure	45	40	0	0	0	11.0	10.6	0	0	0	0
NYHA I, %	48	48	23	25	32	51.2	49.5	100	100	100	100
NYHA II, %			59	57	55			0	0	0	0
NYHA III, %	7	12	18	18	13	37.8	39.9	0	0	0	0
NYHA IV, %			0	0	0			0	0	0	0
LVEF, mean (SD) or [SEM]	0.32 (0.13)	0.31 (0.13)	0.46 (0.19)	0.44 (0.17)	0.47 (0.17)	34.3 (14.5)	33.3 (14.1)	67 [12]	69 [6]	66[10]	67 [7]
Heart rate, bpm	77 (18)	78 (17)	81 (17)	80 (17)	76 (16)	nr	nr	67 [12]	64 [7]	64 [11]	66 [12]
QT interval, msec, mean (SD) or [SEM]	441 (40)	445 (39)	437 (42)	430 (51)	430 (48)	nr	nr	396 [51]	387 [31]	404 [43]	394 [31]
QRS interval, msec, mean	116 (26)	117 (26)	nr	nr	nr	nr	nr	98 [29]	92 [12]	99 [30]	95 [16]

Parameter	AVID ⁷³		CASH ⁸³			CIDS ⁸⁶		DEBUT – pilot ⁹¹		DEBUT – main ⁹¹	
	ICD	AAD	ICD	AAD		ICD	Amio	ICD	β-blocker	ICD	β-blocker
				Amio	Met						
(SD) or [SEM]											
BBB (unspecified), %	23	25	17	23	19	nr	nr	nr	nr	nr	nr

Amio, Amiodarone. Met, Metoprolol. ^a Proportion with VF or VT comes from whole study population (i.e. including the discontinued arm). ^b Additional category unmonitored syncope, ICD 15.2%, Amiodarone 12.4%.

Table 12: Key participant characteristics: myocardial infarction (MI)

Parameter	DINAMIT ⁹⁷		IRIS ⁹⁹		MADIT I ¹⁰¹		MADIT II ¹⁰³	
	ICD	OPT	ICD	OPT	ICD	OPT	ICD	OPT
Sample size, n	332	342	445	453	95	101	742	490
Age, mean (SD)	61.5 (10.9)	62.1 (10.6)	62.8 (10.5)	62.4 (10.6)	62 (9)	64 (9)	64 (10)	65 (10)
Sex, % male	75.9	76.6	77.5	75.9	92	92	84	85
Arrhythmia, %	nr	nr	NSVT 22.2	NSVT 24.1	VT 100	VT 100	nr	nr
NYHA I, %	13.5	12.0	28 ^a		37	33	35	39
NYHA II, %	60.9	58.7	60 ^a		63	67	35	34
NYHA III, %	25.6	29.3	12 ^a				25	23
NYHA IV, %	0	0	0.1 ^a		0	0	5	4
LVEF %, mean (SD)	28 (5)	28 (5)	34.6 (9.3)	34.5 (9.4)	27 (7)	25 (7)	23 (5)	23 (6)
QRS interval msec, mean (SD)	107 (24)	105 (23)	nr	nr	nr	nr	50% ≥12 sec	51 % ≥12 sec
LBBB/RBBB, %	nr	nr	10.1/nr	6.4/nr	7/nr	8/nr	19/9	18/7

^a At discharge for 885 surviving patients.

Table 13: Participant characteristics: cardiomyopathy; CABG surgery; heart failure

Parameter	Cardiomyopathy						CABG surgery		Heart failure		
	AMIOVIRT ⁷¹		CAT ⁸⁴		DEFINITE ⁹²		CABG Patch ⁷⁷		SCD-Heft ¹⁰⁷		
	ICD	Amio	ICD	Control	ICD + OPT	OPT	ICD	Control	ICD	Amio	Placebo
Sample size, n	51	52	50	54	229	229	446	454	829	845	847
Age, mean (SD) or [range]	58 (11)	60 (12)	52 (12)	52 (10)	58.4 [20.3-83.9]	58.1 [21.8-78.7]	64 (9)	63 (9)	60.1 ^c [51.9-69.2]	60.4 ^c [51.7-68.3]	59.7 ^c [51.2-67.8]
Sex, % male	67	74	86	74	72.5	69.9	86.5	82.2	77	76	77
Index arrhythmia, %	NSVT 100	NSVT 100	NSVT 53.1	NSVT 58.0	NSVT 22.3 PVCs 9.2 Both 68.6	NSVT 22.7 PVCs 9.6 Both 67.7	nr	nr	NSVT 25	NSVT 23	NSVT 21
Ischemic heart disease ^a , %	4.9	11	nr	nr	nr	nr	nr	nr	nr	nr	nr
Duration of cardiomyopathy, mean (SD) or [median, range]	2.9 (4.0) yrs	3.5 (3.9) yrs	[3.0 months]	[2.5 months]	[2.39, 0.00-21.33] yrs ^b	[3.27, 0.0-38.5] yrs ^b					
NYHA I	18	13	0	0	25.3	17.9	nr	nr	0		
NYHA II	64	63	66.7	64.1	54.2	60.7	71	74	70		
NYHA III	16	24	33.3	35.8	20.5	21.4			30		
NYHA IV	0	0	0	0	0	0	nr	nr	0		

Parameter	Cardiomyopathy						CABG surgery		Heart failure		
	AMIOVIRT ⁷¹		CAT ⁸⁴		DEFINITE ⁹²		CABG Patch ⁷⁷		SCD-Heft ¹⁰⁷		
	ICD	Amio	ICD	Control	ICD + OPT	OPT	ICD	Control	ICD	Amio	Placebo
Sample size, n	51	52	50	54	229	229	446	454	829	845	847
LVEF, mean (SD) or [range]	22 (10)	23 (8)	24 (6)	25 (8)	20.9 [7-35]	21.8 [10-35]	27 (6)	27 (6)	24.0 ^c [19.0-30.0]	25.0 ^c [20.0-30.0]	25.0 ^c [20.0-30.0]
QRS interval msec, mean (SD) or [range]	nr	nr	102 (29)	114 (29)	114.7 [78-196]	115.5 [79-192]	71%	74%	nr	nr	nr
LBBB/RBBB, %	16/42	8/53	84.6/7.7	81.8/0	19.7/3.5	19.7/3.1	10/nr	12/nr	nr	nr	nr

^a1 major epicardial coronary artery with a 70% or greater stenosis. ^bDuration of heart failure, p=0.04. PVCs = premature ventricular complexes. ^cMedian plus inter-quartile range.

Pharmacological therapy

Table 14 and Table 15 displays medication at hospital discharge.

Cardiac arrest

Two thirds of participants in AVID⁷³ were receiving ACE inhibitors. Only 6% of the ICD group received antiarrhythmic drugs at discharge. Beta-blockers were more common among the ICD group (42.3%) than the AAD group (16.5%), $p < 0.001$, which may have resulted in some bias towards ICD. Aspirin was received by around 60% of participants in AVID⁷³ and warfarin was received by a greater proportion of participants in the AAD arm (35%) than in the ICD arm (22%). Half of the participants in AVID⁷³ received diuretics, around 37% received nitrates and 12% (AAD) to 18% (ICD) received calcium-channel blockers. Digitalis was received by 41% (AAD) versus 47% (ICD) of participants, $p = 0.04$. The pharmacological therapy provided in AVID⁷³ would have been considered optimal at the time the trial was conducted, although current standards would include less digitalis and more ACE inhibitors and beta-blocker therapy.

Less than half of participants in CASH⁸³ received ACE inhibitors at hospital discharge. The ICD and metoprolol groups did not receive any antiarrhythmic drugs, and the ICD and amiodarone groups did not receive any beta-blockers. Aspirin was received by around 60% of participants in the ICD group, but by fewer participants in the Amiodarone (45%) and Metoprolol (41%) arms. Less than 10% of participants in CASH⁸³ received warfarin. Less than a third of participants received diuretics, around 30% received nitrates, and 12% (Metoprolol arm) to 26% (ICD) received calcium-channel blockers. Digitalis was received by 15% (Metoprolol arm) to 26% (ICD) of participants. The pharmacological therapy provided in CASH⁸³ would have been considered optimal at the time the trial was conducted. However, beta-blocker treatment was an active comparator in this trial and was not used with ICDs, which may have resulted in bias against the ICD. ACE inhibitor use is low in this trial, but the patients did not have indications for these at the time the trial was undertaken.

None of the participants in CIDS⁸⁶ received ACE inhibitors at hospital discharge. Class I antiarrhythmic were received by just 2.4% (amiodarone arm) and 5.5% (ICD arm) of participants. A greater proportion of the ICD group than the amiodarone group received the beta-blocker sotalol (19.8% vs 1.5%), beta-blockers other than sotalol (33.5% vs 21.4%), and digoxin (29.6% vs 22.7%). No other drugs were reported. The pharmacological therapy provided in CIDS⁸⁶ would not be considered optimal by current standards, and the higher use of beta-blockers in the ICD group may bias the trial in favour of ICDs.

Medication at hospital discharge is not reported by DEBUT,⁹¹ however use of beta-blockers was low in the ICD group (8/47 in main trial and pilot study combined).

Myocardial infarction (MI)

Both groups in DINAMIT⁹⁷ were given 'best conventional medical therapy'. ACE inhibitors were taken by around 95% of participants at baseline, antiplatelet agents by 92%, beta-blockers by 87% and lipid lowering agents by 78% of participants. IRIS⁹⁹ had a similarly high usage of ACE inhibitors (91%), antiplatelet agents (96%), beta-blockers (96%) and statins (92%). Antiarrhythmics (mainly amiodarone) were taken by a small proportion of participants (ICD 13.4% vs 17.4%, p=0.11). Pharmacological therapy is considered optimal by current standards in DINAMIT⁹⁷ and IRIS.⁹⁹

MADIT¹⁰¹ presents data at one month (Table 14) and last contact (Appendix 8). Usage of ACE inhibitors (ICD 60%, medical therapy 55%) and beta-blockers (beta-blockers or sotalol: ICD 27%, medical therapy 15%) were low in this trial at one month, and beta-blocker use was not balanced between the groups. Three quarters of the medical therapy group received amiodarone at one month compared with 2% of the ICD group, but use of Class I antiarrhythmics was similar (ICD 12% vs medical therapy 10%). At one month, 56% of ICD patients and 8% of medical therapy patients had no antiarrhythmic medication. Approximately half of participants were receiving diuretics. Digitalis use was high by current standards (ICD 58%, medical therapy 38%). The pharmacological therapy provided in MADIT¹⁰¹ would not be considered optimal by current standards.

MADIT II¹⁰³ did not report medication at discharge, but presented medication at last contact, which was mean 18 months (ICD) and 17 months (OPT) from enrolment. About 70% of participants received ACE inhibitors, about 10 to 13% received amiodarone and 2 to 3% received Class I antiarrhythmic drugs. Beta-blockers were taken by 70% of participants, diuretics by 72% of the ICD group and 81% of the OPT group, digitalis by 57% of participants, and statins by about two thirds of participants. Pharmacological therapy provided in MADIT II¹⁰³ would be considered optimal by current standards.

Cardiomyopathy

AMIOVIRT⁷¹ reports that OPT was encouraged in both ICD and amiodarone groups. Therapy at discharge was not reported, but concomitant drug therapy was presented (Table 15), with no statistically significant difference between the groups. A high proportion (81 to 90%) of participants received ACE inhibitors, and approximately half received beta-blockers. Over two-thirds received diuretics and/or digoxin and a fifth received spironolactone. The beta-blocker use is slightly low in this trial compared with current standards, but the pharmacological therapy is close to optimal.

ACE inhibitors were taken by about 96% of participants at baseline in CAT,⁸⁴ but beta-blocker use was low (4% of participants). Diuretics were taken by the majority of participants (85 to 88%),

warfarin was received by 24 to 35% of participants, nitrates by 26 to 32% and calcium channel blockers by 7.4 to 16%. Observed differences between the groups were not statistically significant. Although acceptable at the time, the pharmacological therapy in CAT would not be considered optimal by current standards due to low beta-blocker use.

OPT was described for both groups in DEFINITE.⁹² A high proportion (about 86%) of participants received ACE inhibitors and a small proportion (8.7 to 13.5%) received angiotensin II-receptor blockers. Beta-blockers were taken by 85%, diuretics by 87%, and digoxin by 42%. A small proportion of each group received amiodarone (ICD 3.9%, OPT 6.6%) and nitrates (ICD 9.2%, OPT 13.1%). Pharmacological therapy in DEFINITE⁹² would be considered optimal by current standards.

CABG surgery

ACE inhibitors were taken by over half of the participants in CABG Patch.⁷⁷ 63.3% of the ICD group and 65.2% of the control group received no oral antiarrhythmic drugs. Class I antiarrhythmics were taken by 16.7% and 12%, amiodarone by 3.7% and 3.2%, and beta-blockers (other than sotalol) by 17.9% and 24% of the ICD group and control group, respectively. There is an excess of antiarrhythmic drug use in the ICD arm, which may paradoxically offset some of the ICD benefit. The majority of participants received antiplatelet drugs (84%), two thirds received digitalis and around half received diuretics (47-57%). The pharmacological therapy provided in CABG Patch⁷⁷ would have been considered optimal at the time the trial was conducted, but is low by current standards.

Mild to moderate heart failure

A high proportion (94 to 98%) of participants in SCD-HeFT¹⁰⁷ were taking ACE inhibitors or angiotensin II receptor blocker at enrolment. Beta-blockers were taken by 69% of participants, digoxin by about 70%, aspirin by about 56%, warfarin by about one third, and statin by about 40% of participants. Most (82%) received loop diuretics and 20% received potassium sparing diuretics and a minority received thiazide (7%). SCD-HeFT¹⁰⁷ also reported medication at last follow-up, where there was a statistically significant ($p < 0.001$) difference in beta-blocker use between groups (ICD 82%, amiodarone 72%, placebo 79%) (Appendix 8). Pharmacological therapy in SCD-HeFT¹⁰⁷ would be considered optimal by current standards.

Table 14: Medication at discharge: cardiac arrest/MI

Medication, %	Cardiac arrest (secondary prevention)					Recent MI				Remote MI					
	AVID ⁷³		CASH ⁸³			CIDS ⁸⁶		DINAMIT ⁹⁷		IRIS ⁹⁹		MADIT I ^{101b}		MADIT II ^{103c}	
	ICD	AAD	ICD	Amio	Met	ICD	Amio	ICD	OPT	ICD	OPT	ICD	PT	ICD	OPT
Sample size	497	496	99	92	97	328	331	332	342	445	453	93	93	742	490
ACE inhibitor	68.8	68.2	45.5	43.5	41.2			94.9	94.4	90.9	91.1	60	55	68	72
Antiarrhythmic										13.4	17.4				
-Amiodarone	1.8	95.8	0	97.8	0							2	74	13	10
- Other anti-arrhythmia drug	4.2	1.2													
- Class I antiarrhythmic						5.5	2.4					12	10	3	2
Anti-coagulants and anti-platelets								92.2	92.1	96.1	95.8				
-Acetylsalicylic acid (Aspirin)	60.7	59.2	57.6	44.6	41.2										
- Warfarin	21.9	34.8	9.1	6.5	9.3										
Beta-blocker	42.3	16.5				33.5 ^a	21.4 ^a	87.0	86.5	97.1	95.3	26	8	70	70
- Metoprolol			0	0	99.0										
- Sotalol	0.2	2.8				19.8	1.5					1	7		
- Beta-blockers or sotalol												27	15		
Calcium-channel blocker	18.4	12.1	26.3	16.3	12.4									9	9
Diuretic	48.2	50.7	33.3	27.2	30.9							53	52	72	81
Nitrates	36.4	37.0	29.3	29.3	24.7										
Other antihypertensive agent	7.6	8.8													
Digitalis	46.8	40.6	26.3	25.0	15.5							58	38	57	57

Medication, %	Cardiac arrest (secondary prevention)						Recent MI				Remote MI				
	AVID ⁷³		CASH ⁸³			CIDS ⁸⁶		DINAMIT ⁹⁷		IRIS ⁹⁹		MADIT I ^{101b}		MADIT II ^{103c}	
	ICD	AAD	ICD	Amio	Met	ICD	Amio	ICD	OPT	ICD	OPT	ICD	PT	ICD	OPT
Sample size	497	496	99	92	97	328	331	332	342	445	453	93	93	742	490
Digoxin						29.6	22.7								
Lipid lowering agent	13.2	11.5						76.8	79.5						
Statin										91.6	91.5			67	64

^a Other than solatol. ^b Medication at one month. Data missing for 2 ICD patients and 8 PT (pharmacological therapy) patients. No antiarrhythmic medication: ICD 56%, PT 8%. ^c Medication at discharge not reported by MADIT II,¹⁰³ medication at 'last contact' displayed here; mean 18 months (ICD) and 17 months (OPT) from enrolment.

Table 15: Medication: Cardiomyopathy / CABG surgery / Heart failure

Medication, %	Cardiomyopathy						CABG surgery		Heart failure		
	AMIOVIRT ^{71a}		CAT ⁸⁴		DEFINITE ⁹²		CABG Patch ⁷⁷		SDC HeFT ^{107b}		
	ICD	Amio	ICD	OPT	ICD	OPT	ICD	OPT	ICD	Amio	Plac
Sample size	51	52	50	54	229	229	430	442	829	845	847
ACE inhibitor	90	81	94.0	98.1	83.8	87.3	54.7	53.8	83	87	85
ACE inhibitor/ARB									94	97	98
Angiotensin-receptor blocker					13.5	8.7			14	14	16
Amiodarone					3.9	6.6	3.7	3.2			
Class I antiarrhythmic							16.7	12.0			
Anti-coagulants							15.3	14.7			
Anti-platelets							82.8	85.1			
- Aspirin									58	55	56
- Warfarin			24.0	35.2					32	37	33
Beta-blocker	53	50	4.0	3.7	85.6	84.3			69	69	69
- Carvedilol					56.3	58.5					
- Metoprolol					25.8	18.8					
- Sotalol							0.5	0.2			
- other					3.5	7.0	17.9	24.0			
Calcium-channel blocker			16.0	7.4			10.5	7.0			
Diuretic	71	67	88.0	85.2	87.3	86.0	57.2	47.1			
- Loop									82	82	82

Medication, %	Cardiomyopathy						CABG surgery		Heart failure		
	AMIOVIRT ^{71a}		CAT ⁸⁴		DEFINITE ⁹²		CABG Patch ⁷⁷		SDC HeFT ^{107b}		
	ICD	Amio	ICD	OPT	ICD	OPT	ICD	OPT	ICD	Amio	Plac
Sample size	51	52	50	54	229	229	430	442	829	845	847
- Potassium sparing									20	21	19
- Thiazide									8	6	7
- Spironolactone	20	19									
Nitrates			32.0	25.9	9.2	13.1	8.1	8.1			
Digitalis							68.6	64.5			
Digoxin	71	67			41.5	42.4			67	73	70
Lipid lowering agent							9.5	8.4			
Statin									38	40	38

Amio, Amiodarone. Plac, placebo. ^a Concomitant drug therapy at last follow-up. ^b At enrolment.

Outcomes

All-cause mortality was the primary outcome in all 13 trials in people at risk of sudden cardiac death due to ventricular arrhythmias.^{71;73;80;83;84;86;91;92;97;99;101;103;107} Secondary outcomes tended to focus on other measures of mortality or survival. Ten RCTs assessed total cardiac deaths,^{71;74;80;84;86;97;99;101;105;110} 13 RCTs assessed sudden cardiac and arrhythmic deaths,^{71;74;80;83;84;86;91;92;97;99;101;105;110} 11 RCTs assessed cardiac non-arrhythmic deaths,^{71;74;80;84;86;92;97;99;101;105;110} 10 RCTs assessed other non-cardiac causes of death,^{71;74;80;84;86;97;99;101;105;110} five RCTs assessed cumulative mortality,^{77;86;92;99;107} and four RCTs assessed survival.^{71;73;74;83;84} Other secondary outcome measures included heart hospitalisations (two RCTs),^{73;103} symptoms and complications related to arrhythmias (three RCTs),^{71;84;105} quality of life (seven RCTs)^{71;76;82;89;96;106;109} and adverse events (13 RCTs).^{71;73;77;83;84;86;91;92;97;99;101;103;107}

Setting

AVID⁷³ CASH⁸³ and CIDS⁸⁶ were multicentre studies; with the majority of centres in USA (AVID⁷³) or Canada (CIDS⁸⁶) or in Germany only (CASH⁸³). DEBUT⁹¹ was conducted in Thailand but the number of centres was not reported. The number of participants ranged from 66 (DEBUT main study⁹¹) to 1016 (AVID⁷³). DEBUT⁹¹ also reported a pilot study in which 20 participants were randomised. Length of follow-up ranged from mean 18.2 months (SD 12.2) in AVID⁷³ to 57 months (SD 34) in CASH.⁸³

DINAMIT,⁹⁷ IRIS,⁹⁹ MADIT I¹⁰¹ and MADIT II¹⁰³ were multicentre studies. The majority of centres for DINAMIT⁹⁷ were in Canada, Germany and Europe (4 UK centres) and IRIS⁹⁹ was conducted in Europe (not UK) and Russia. The majority of centres for MADIT I¹⁰¹ and MADIT II¹⁰³ were in the USA. Sample size ranged from 196 (MADIT I¹⁰¹) to 1232 (MADIT II).¹⁰³ Mean follow-up ranged from 20 months in MADIT II¹⁰³ to 37 months in IRIS.⁹⁹

AMIOVIRT⁷¹ and DEFINITE⁹² were multi-centre studies with the majority of centres in USA, whereas CAT⁸⁴ was a multi-centre study conducted in Germany. Sample size was relatively small in AMIOVIRT⁷¹ and CAT⁸⁴ (103 and 104 participants randomised, respectively); CAT⁸⁴ was designed as a pilot study. DEFINITE⁹² randomised 458 participants. The trials had similar lengths of follow-up; mean follow-up was 2 years in AMIOVIRT⁷¹ and CAT,⁸⁴ and 2.4 years in DEFINITE.⁹²

CABG Patch⁷⁷ was a multicentre study conducted primarily in USA, with 900 participants randomised. Mean follow-up was 32 months.

SCD-HeFT¹⁰⁷ was a multicentre study conducted mainly in USA, with 2521 participants randomised. Median follow-up was 45.5 months.

4.2.1.2 Risk of bias

The risk of bias in the included trials is summarised in Table 16 and further details for each trial can be found in the data extraction tables in Appendix 8. All 13 trials were unclear on risk of bias associated with randomisation. In fact eight trials did not report details of either randomisation or allocation concealment, therefore the risk of selection bias (differences between known and unknown baseline characteristics of the groups) is unclear. Five trials (CIDS,⁸⁶ MADIT I,¹⁰¹ IRIS,⁹⁹ DINAMIT,⁹⁷ CABG Patch⁷⁷) did not report the randomisation method, although sufficient details were reported to establish that the allocation sequence was adequately concealed and judged to have a low risk of selection bias.

It was not possible to blind participants and personnel (health care providers) in these trials, as one group received surgery. This could bias the results due to differences in behaviours across intervention groups or differences in the care provided, such as administration of co-interventions. The trials were therefore judged to have a high risk of performance bias. Cause of death was determined or reviewed by a committee blinded to treatment group in AVID,⁷³ DEFINITE,⁹² DINAMIT,⁹⁷ AMIOVIRT,⁷¹ IRIS,⁹⁹ and SCD-HeFT.¹⁰⁷ Outcome assessors were not blinded in other trials, but mortality was judged unlikely to be influenced by lack of blinding and so the trials were considered to have a low risk of detection bias for this outcome. Unblinded trials reporting QoL were judged to have a high risk of detection bias for this outcome (AVID,⁷³ AMIOVIRT,⁷¹ CIDS,⁸⁶ DEFINITE,⁹² MADIT II,¹⁰³ CABG Patch,⁷⁷ SCD-Heft).¹⁰⁷

Risk of attrition bias (differences between groups in withdrawals from the study) was low in seven of the trials (CASH,⁸³ AMIOVIRT,⁷¹ DEFINITE,⁹² MADIT I,¹⁰¹ MADIT II,¹⁰³ DINAMIT,⁹⁷ IRIS⁹⁹), and unclear in three trials (CIDS,⁸⁶ DEBUT,⁹¹ CAT⁸⁴). In AVID,⁷³ CABG Patch⁷⁷ and SCD-HeFT,¹⁰⁷ risk of attrition bias was judged to be low for mortality but high or unclear for QoL outcomes.

Risk of selective reporting bias (differences between reported and unreported findings) was considered to be low in six studies (AVID,⁷³ CASH,⁸³ DEBUT,⁹¹ AMIOVIRT,⁷¹ MADIT I,¹⁰¹ SCD-HeFT¹⁰⁷). Five studies listed outcomes in a protocol or methods section that were not reported (CIDS,⁸⁶ CAT,⁸⁴ DEFINITE,⁹² DINAMIT,⁹⁷ IRIS⁹⁹). Risk of selective reporting bias was unclear in two studies (MADIT II,¹⁰³ CABG Patch⁷⁷).

Risk of other sources of bias was judged to be high in DINAMIT,⁹⁷ as block randomisation in an unblinded trial can lead to prediction of allocation. The authors of CASH⁸³ note that centres were reluctant to enrol patients for potential ICD therapy in the early phase of the study and to deny ICD

therapy in the late phase of the study. The effect of this is unclear. Seven of the trials were stopped early (AVID,⁷³ DEBUT,⁹¹ CAT,⁸⁴ AMIOVIRT,⁷¹ MADIT I,¹⁰¹ MADIT II,¹⁰³ CABG Patch⁷⁷), however, simulation evidence suggests that inclusion of stopped early trials in meta-analyses does not lead to substantial bias.⁶⁷

Table 16: Risk of bias

Judgement^a	AVID⁷³	CASH⁸³	CIDS⁸⁶	DEBUT⁹¹	IRIS⁹⁹	DINAMIT⁹⁷	MADIT I¹⁰¹	MADIT II¹⁰³	CAT⁸⁴	AMIOVIRT⁷¹	DEFINITE⁹²	CABG Patch⁷⁷	SCD-Heft¹⁰⁷
Selection bias													
Random sequence generation	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Allocation concealment	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Performance bias													
Blinding of participants, personnel	High	High	High	High	High	High	High	High	High	High	High	High	High
Detection bias													
Blinding of outcome assessment	Low ^b High ^c	Low	Low ^b High ^c	Low	Low	Low	Low	Low ^b High ^c	Low	Low ^b High ^c	Low ^b High ^c	Low ^b High ^c	Low ^b High ^c
Attrition bias													
Incomplete outcome data addressed	Low ^b High ^c	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low ^b High ^c	Low ^b Unclear ^c
Reporting bias													
Selective reporting	Low	Low	High	Low	High	High	Low	Unclear	High	Low	High	Unclear	Low
Other bias													
Other sources	Low	Unclear	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low

^a ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias. ^b mortality. ^c QoL

4.2.1.3 Methodological comments

Similarity of groups at baseline

Although it was evident that there were differences between the 13 trials in the types of participants included (see earlier section on *Participants*), within the trials these appeared generally to be well balanced at baseline. Some differences were evident. In the IRIS⁹⁹ trial the ICD group had a higher proportion of people with left-bundle-branch block (10.1% vs 6.4%, $p=0.05$) and diabetes mellitus (37.2% vs 30.2, $p=0.03$) than the OPT group. The CAT⁸⁴ trial found a higher occurrence of bradycardias among the OPT group (18.8%) than the ICD group (2.1%, $p=0.015$). The DEFINITE⁹² trial noted that the OPT group (3.27 years) had a significantly ($p=0.04$) longer mean duration of heart failure than the ICD plus OPT group (2.39 years).

Sample size

All 13 trials included a calculation of sample size or statistical power based on the primary outcome measure of all-cause mortality.^{71;73;77;83;84;86;91;92;97;99;101;103;107} The CIDs (n=659),⁸⁶ DINAMIT (n=674),⁹⁷ DEFINITE (n=458),⁹² CABG-Patch (n=900)⁷⁷ and SCD-Heft (n=2521)¹⁰⁷ trials appeared to be adequately powered to detect a difference in all-cause mortality. In contrast, the CASH (n=288),⁸³ DEBUT (n=66),⁹¹ MADIT II (n=1232),¹⁰³ and CAT (n=104)⁸⁴ trials were thought to be underpowered based on reported sample size calculations. Five trials were stopped early due to having achieved an *a priori* stopping rule concerning crossing of efficacy boundaries (AVID (n=1016)⁷³, MADIT I (n=196)¹⁰¹, MADIT II (n=1232)¹⁰³) or due to interim analysis showing low event rates that meant that further recruitment would not achieve adequate statistical power (AMIOVIRT (n=103),⁷¹ CAT (n=104)⁸⁴).

Other issues

CASH⁸³ was designed as a 4 arm trial (ICD, amiodarone, metoprolol, propafenone), however the propafenone arm was terminated early due to interim analysis. DEBUT⁹¹ reports the results of a pilot study and main trial, although both were small.

During the course of MADIT I,¹⁰¹ a change was made from transthoracic to transvenous leads. The authors of MADIT I¹⁰¹ note that this altered the type of patient referred for entry to the trial.

Funding

AVID⁷³ and CIDS⁸⁶ received funding from National Heart, Lung, and Blood Institute and the Medical Research Council of Canada respectively. All 11 other RCTs received some or all of their funding from the ICD manufacturers, which may represent a potential conflict of interests.

^{71;77;83;84;91;92;97;99;101;103;107}

4.2.2 Assessment of effectiveness

4.2.2.1 All-cause mortality

All thirteen trials comparing the use of ICDs with antiarrhythmic drugs (AAD) in people at increased risk of sudden cardiac death due to ventricular arrhythmias reported measures of all-cause mortality as their primary outcome measure.^{71;73;77;83;84;86;91;92;97;99;101;103;107} Four trials assessed the use of ICDs compared with antiarrhythmic drugs (AAD) in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias.^{73;83;86;91} All four trials showed beneficial effects on crude mortality rates for those receiving an ICD, although only the AVID⁷³ (ICDs 15.8%, AAD 24.0%, $p < 0.012$, follow-up 18.2 months) and the main DEBUT⁹¹ (ICDs 0%, AAD 14.0%, $p < 0.02$, follow-up 3 years) trials found statistically significant differences. A separate pilot study for the DEBUT trial⁹¹ had previously shown no significant difference between ICDs and AAD groups (ICDs 0%, AAD 30.0%, $p = 0.07$, follow-up maximum 3 years). In the other two studies differences were either not statistically significant or were not assessed. The CASH trial⁸³ reported all-cause mortality rates of 36.4% for the ICDs group compared with 44.4% for the AAD group ($p = \text{not stated}$, follow-up 57 months). The CIDS trial⁸⁶ reported crude mortality rates of 25.3% for the ICDs group and 29.6% for the AAD group over the 3 years follow-up, equating to annual crude mortality rates of 8.3% for the ICDs group compared with 10.2% for the AAD group, a relative risk reduction of 19.7% (95% CI, -7.7 to 40.0; $p = 0.142$) (see Table 17). A meta-analysis of the four studies (including the DEBUT pilot study⁹¹) using a random effects model showed a statistically significant benefit for ICDs compared with AAD with a risk ratio of 0.75 (95% CI, 0.61 to 0.93; $p = 0.010$), with limited heterogeneity ($\text{Chi}^2 = 5.89$, $\text{df} = 4$, $\text{I}^2 = 32\%$) (see Figure 4).

Of the nine trials in people who had not suffered a life-threatening arrhythmia but were at increased risk, three showed statistically significant benefit on all-cause mortality for the ICDs plus OPT group compared with the different comparators (see Table 17). The three trials were the MADIT I¹⁰¹ and MADIT II¹⁰³ on people remote from their MI and the SCD-HeFT¹⁰⁷ on people with heart failure. In the MADIT I trial¹⁰¹ 15.8% of people receiving an ICD plus OPT died compared with 38.6% of people on OPT (mean follow-up 27 months), equating to a hazard ratio of 0.46 (95% CI, 0.26 to 0.82; $p = 0.009$) (see Table 17). The MADIT II trial¹⁰³ also found significant benefit with 14.2% of those with an ICD plus OPT dying compared with 19.8% who received OPT only (mean follow-up 20 months), a hazard ratio of 0.69 (95% CI, 0.51 to 0.93; $p = 0.016$). Post-trial follow-up of MADIT II¹⁰³ found continued benefit with ICDs at 8 years (HR 0.66, 95% CI 0.56 to 0.78, $p = 0.001$); analysis was undertaken on an efficacy basis by including data on crossovers, and validated in an ITT analysis.¹⁵⁰ The SCD-Heft trial,¹⁰⁷ which had a longer period of follow-up (mean 45.5 months), reported that

22% of people who received an ICD plus OPT died compared with 28.4% of those receiving amiodarone plus OPT and 28.8% of those receiving placebo plus OPT. Hazard ratios showed that the difference between the ICD plus OPT and the placebo plus OPT groups were statistically significant (HR 0.77 (97.5% CI 0.62 to 0.96; p=0.007), whereas that between the amiodarone plus OPT and the placebo plus OPT showed no statistically significant difference (HR 1.06 (97.5% CI, 0.86 to 1.30; p=0.53)).¹⁰⁷ A meta-analysis of the two MADIT trials^{101;103} using a random effects model showed a statistically significant benefit for those receiving ICDs plus OPT compared with OPT alone with a risk ratio of 0.57 (95% CI, 0.33 to 0.97; p=0.04), although there was some apparent heterogeneity (Chi²=3.54, df =1, I²=72%) which may reflect differences in disease severity (see Figure 4).

The other six trials, which included people with either cardiomyopathy,^{71;84;92} or in the early period post MI^{97;99} or were scheduled for a CABG,⁸⁰ found no statistically significant difference on all-cause mortality. The AMIOVIRT trial⁷¹ reported all-cause mortality after a mean follow-up of 2 years, finding 11.8% of those with an ICD plus OPT dying compared with 13.5% of those receiving amiodarone plus OPT (p=0.8). The CAT trial⁸⁴ reported all-cause mortality at 1 year, showing no significant difference (p=0.3672) with 8% of those with an ICD plus OPT dying compared with 3.7% of those receiving OPT. Longer mean follow-up to 5.5 years showed limited difference with 26% of the ICD plus OPT group and 31.5% of OPT group dying (p not stated). The DEFINITE trial⁹² found that 12.2% of people with an ICD plus OPT and 17.5% of those with OPT had died at a mean follow-up of 29 months, a hazard rate of 0.65 (95% CI, 0.40 to 1.06; p=0.08) (see Table 17). When these three cardiomyopathy trials were combined through a random effects meta-analysis it confirmed that there was no significant difference between the treatments with a risk ratio 0.77 (95% CI, 0.52 to 1.15; p=0.20) with no heterogeneity (Chi²=1.73, df =2, I²=0%) (see Figure 4). The effect of combining the three cardiomyopathy trials with the non-ischaeic congestive heart failure subgroup of SCD-Heft¹⁰⁷ was assessed in section 4.2.2.12. The DINAMIT⁹⁷ and IRIS⁹⁹ trials assessed the effects of ICDs plus OPT compared with OPT in people who were in the early period post MI. The DINAMIT trial⁹⁷ reported that 18.7% of people with an ICD plus OPT and 17% of those with OPT died by 30 months follow-up, resulting in a hazard ratio of 1.08 (95% CI, 0.76 to 1.55; p=0.66). Similarly the IRIS trial⁹⁹ found no significant difference on all-cause mortality between ICD plus OPT (26.1%) and OPT (25.8%) reflected in a hazard ratio of 1.04 (95% CI, 0.81 to 1.35; p=0.15). Meta-analysis of the DINAMIT⁹⁷ and IRIS⁹⁹ trials confirmed that there was no significant difference between the treatments with a risk ratio of 1.04 (95% CI, 0.86 to 1.25; p=0.69), with no heterogeneity (Chi²=0.19, df =1, I²=0%) (see Figure 4). The CABG Patch trial,⁸⁰ which included people who were scheduled for a CABG, reported mortality of 22.9% for those with an ICD plus OPT compared with 21.2% for those on OPT (p not stated), a risk ratio of 1.08 (95% CI, 0.85 to 1.38; p=0.53) (see Figure 4).

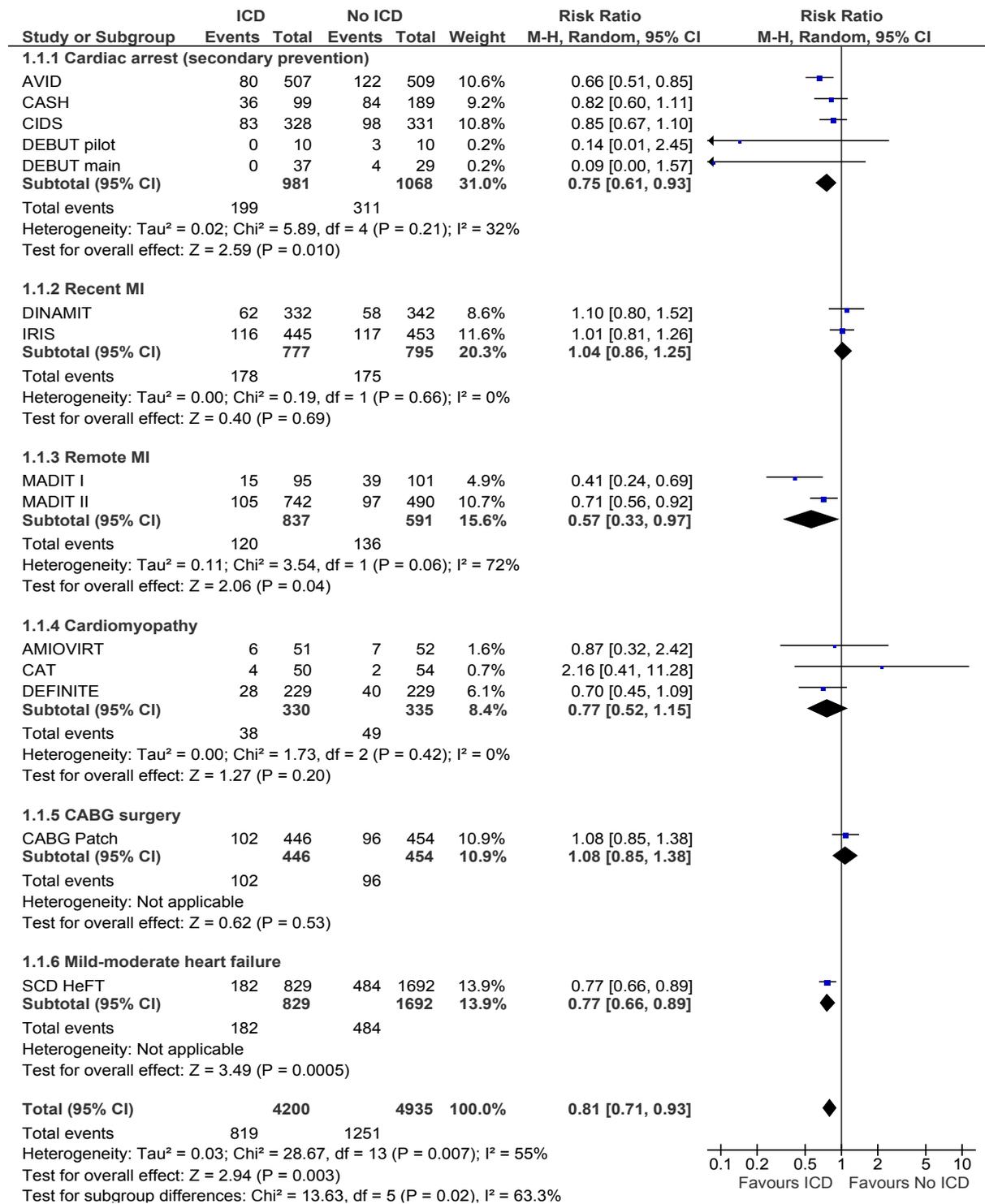
Table 17: All-cause mortality

Study	Follow-up	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI , p value
<i>Cardiac arrest</i>					
AVID ⁷³	Mean 18.2 months (SD 12.2)	80/507 (15.8%, ±95 CI 3.2)	AAD: 122/509 (24.0%, ± 95% CI 3.7)		<0.012
CASH ⁸³	57 months (SD 34)	36/99 (36.4%, CI 26.9 to 46.6) ^a	Amiodarone: 40/92 (43.5%, CI 33.2 to 54.2) ^a Metoprolol: 44/97 (45.4%, CI 35.2 to 55.8) ^a Both ^b : 84/189 (44.4%, CI 37.2 to 51.8) ^a		
CIDS ^{86c}	Mean 3 years	83/328 (25.3) [8.3]	Amiodarone: 98/331 (29.6) [10.2]	RRR 19.7	-7.7 to 40.0, 0.142
DEBUT ⁹¹ pilot study	Max 3 years after randomisation	0/10 (0)	Propranolol: 3/10 (30)		0.07
DEBUT ⁹¹ main study	3 years	0/37 (0)	Propranolol: 4/29 (14.0)		0.02
<i>Early post MI</i>					
DINAMIT ⁹⁷	average 30 months (SD 13)	62/332 (18.7) [7.5]	58/342 (17.0) [6.9]	HR 1.08	0.76 to 1.55, 0.66
IRIS ⁹⁹	average 37 months	116/445 (26.1)	117/453 (25.8)	HR 1.04	0.81 to 1.35, 0.15
<i>Remote from MI</i>					
MADIT I ¹⁰¹	average 27 months	15/95 (15.8)	39/101 (38.6)	HR 0.46	0.26-0.82, 0.009
MADIT II ¹⁰³	average 20 months	105/742 (14.2)	97/490 (19.8)	HR 0.69	0.51-0.93, 0.016
<i>Cardiomyopathy</i>					
AMIOVIRT ⁷¹	mean 2.0 years (SD 1.3)	6/51 (11.8)	Amiodarone plus OPT: 7/52 (13.5)		0.8
CAT ⁸⁴	1-year (primary end	4/50 (8.0)	2/54 (3.7)		0.3672

Study	Follow-up	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI, p value
	point)				
	mean 5.5 years (SD 2.2)	13/50 (26.0)	17/54 (31.5)		
DEFINITE ⁹²	Mean 29.0 months (SD 14.4)	28/229 (12.2)	40/229 (17.5)	HR 0.65	0.40 to 1.06, 0.08
<i>Scheduled for CABG</i>					
CABG Patch ⁸⁰	mean 32 months (SD 16)	102/446 (22.9)	96/454 (21.2)		
<i>Heart Failure</i>					
SCD-Heft ¹⁰⁷	Median for surviving patients 45.5 months (range 24 - 72.6)	182/829 (22)	Amiodarone plus OPT ^b 240/845 (28.4) Placebo plus OPT ^b 244/847 (28.8)	HR 0.77	^d 0.62 to 0.96, ^e 0.007

^a Probability level for CI around crude death rate not reported in CASH.⁸³ ^b CASH⁸³ and SCD-Heft¹⁰⁷ trials are three arm trials, however the two control arms have been combined to provide a single-pairwise comparison for the meta-analysis (Cochrane Handbook section 16.5.4⁶⁷) (see Figure 4). ^c Longer term (5.6 years) follow-up from one centre of the CIDS study has been excluded from the meta-analysis to avoid double counting of participants. ^d HRs for amiodarone versus placebo are not presented in the summary tables – see Appendix 8. ^e 97.5% CI.

Figure 4: All-cause mortality



4.2.2.2 Total cardiac deaths

Only two trials in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias, specifically the AVID⁷⁴ and CIDS⁸⁶ trials, assessed the effects of ICDs compared with AAD on total cardiac deaths (see Table 18). Although both studies found lower crude rates for those receiving an ICD, neither reported whether the effect was statistically significant (AVID:⁷⁴ ICD 12.4%, AAD 18.5%, p not stated; CIDS:⁸⁶ ICD 20.4%, AAD 25.1%; p not stated). In addition, the CIDS trial⁸⁶ found no statistically significant difference between the interventions on annual crude mortality rates (ICD 6.7%, AAD 8.6%, relative risk reduction of 23.4% (95% CI, -5.7 to 44.5; p=0.104). However a meta-analysis of the two studies using a random effects model showed that ICDs had a statistically significant effect compared with AAD with a risk ratio of 0.74 (95% CI, 0.61 to 0.91; p=0.004) and no apparent heterogeneity ($\text{Chi}^2=0.84$, $\text{df}=1$, $\text{I}^2=0\%$) (see Figure 5).

Eight trials in people who had not suffered a life-threatening arrhythmia but were at increased risk assessed the effects of ICDs plus OPT compared with either OPT, amiodarone plus OPT, or placebo plus OPT on total cardiac deaths (see Table 18).^{71;80;84;97;99;101;105;110} Of these, only the MADIT II trial¹⁰⁵ on people remote from MI (ICD plus OPT 10.6%, OPT 16.3%, p<0.01) and the SCD-Heft trial¹¹⁰ on people with mild to moderate heart failure (ICD plus OPT 14.7%, placebo plus OPT 19.7%, amiodarone plus OPT 19.2%; HR 0.76, 95% CI, 0.60 to 0.95; p= 0.018) found statistically significant benefit for those receiving ICDs plus OPT. A similar difference was identified in the MADIT I trial¹⁰¹ on people remote from MI (ICD plus OPT 11.6%, OPT 26.7%), however statistical significance was not stated. A meta-analysis of the MADIT I¹⁰¹ and II¹⁰⁵ trials using a random effects model showed a statistically significant benefit for ICDs plus OPT with a risk ratio of 0.59 (95% CI, 0.42 to 0.83; p=0.003) and limited heterogeneity ($\text{Chi}^2=1.3$, $\text{df}=1$, $\text{I}^2=23\%$) (see Figure 5).

The DINAMIT⁹⁷ (ICD plus OPT 13.9%, OPT 14.3%, p=not stated) and IRIS⁹⁹ (ICD plus OPT 21.4%, OPT 21.9%, p=not stated) trials on those with a recent MI, the AMIOVIRT trial⁷¹ on those with cardiomyopathy (ICD plus OPT 8%, amiodarone plus OPT 10%, p=not stated) and the CABG Patch trial⁸⁰ on people scheduled for a CABG (ICD plus OPT 17.0%, OPT 17.4%, HR 0.97 (95% CI, 0.71 to 1.33; p=0.84) found limited difference in total cardiac deaths between those receiving ICD plus OPT compared with either OPT or amiodarone plus OPT (see Table 18). In contrast, the CAT trial⁸⁴ in people with cardiomyopathy reported higher total cardiac mortality among those receiving an ICD plus OPT compared with those receiving OPT (ICD plus OPT 8%, OPT 0%), although the statistical significance was not stated. When these trials were meta-analysed by patient group using random effects models, the lack of any statistically significant benefit was evident. Combining the DINAMIT⁹⁷ and IRIS⁹⁹ trials of people with a recent MI produced a risk ratio of 0.97 (95% CI, 0.79 to 1.20; p=0.8) with no apparent heterogeneity ($\text{Chi}^2=0$, $\text{df}=1$, $\text{I}^2=0\%$) (see Figure 5). The meta-analysis of the AMIOVIRT⁷¹ and CAT⁸⁴ trials of people with cardiomyopathy resulted in a risk ratio

of 2.03 (95% CI, 0.17 to 23.62; p=0.57) with some moderate heterogeneity ($\text{Chi}^2=2.59$, $\text{df}=1$, $\text{I}^2=61\%$) (see Figure 5).

Figure 5: Total cardiac deaths

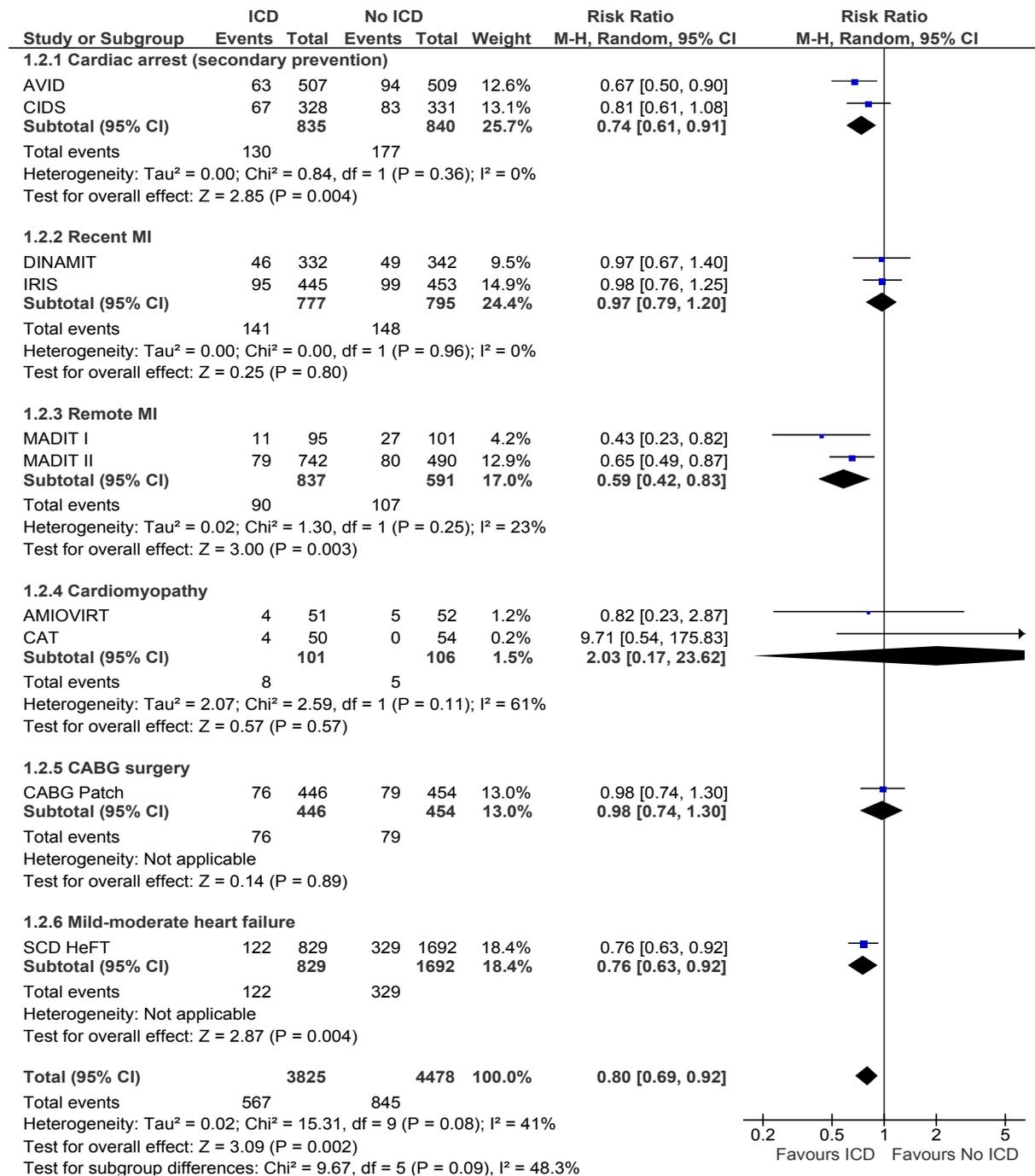


Table 18: Total cardiac deaths

Study	Follow-up, mean	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI , p value
<i>Cardiac arrest</i>					
AVID ⁷⁴	18.2 months (SD 12.2)	63/507 (12.4)	AAD: 94/509 (18.5)		
CIDS ⁸⁶	3 years	67/328 (20.4) [6.7]	Amiodarone: 83/331 (25.1) [8.6]	RRR 23.4	-5.7 to 44.5, 1.04
<i>Early post MI</i>					
DINAMIT ⁹⁷	average 30 months (SD 13)	46/332 (13.9)	49/342 (14.3)		
IRIS ⁹⁹	average 37 months	95/445 (21.4)	99/453 (21.9)		
<i>Remote from MI</i>					
MADIT I ¹⁰¹	average 27 months	11/95 (11.6)	27/101 (26.7)		
MADIT II ¹⁰⁵	average 20 months	79/742 (10.6)	80/490 (16.3)		<0.01
<i>Cardiomyopathy</i>					
AMIOVIRT ⁷¹	mean 2.0 years (SD 1.3)	4/51 (8)	Amiodarone plus OPT: 5/52 (10)		
CAT ⁸⁴	1-year (primary end point)	4/50 (8)	0/54 (0)		
<i>Scheduled for CABG</i>					
CABG Patch ⁸⁰	mean 32 months (SD 16)	76/446 (17.0)	79/454 (17.4))	HR 0.97	0.71 to 1.33, 0.84
<i>Heart Failure</i>					
SCD-Heft ¹¹⁰	Median for surviving patients 45.5months (range 24 to 72.6)	122/829 (14.7)	Amiodarone plus OPT: 162/845 (19.2) Placebo plus OPT: 167/847 (19.7)	HR 0.76	0.60 to 0.95, 0.018

4.2.2.3 Sudden cardiac death/arrhythmic deaths

Sudden cardiac and arrhythmic death rates were lower among people receiving an ICD compared with AAD in the four trials in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias (see Table 19).^{74;83;86;91} Both the CASH⁸³ (ICDs 13.0%, 95% CI, 7.9 to 19.6; AAD (either amiodarone or metoprolol) 33.0%, 95% CI, 27.2 to 41.8) and DEBUT⁹¹ (ICDs 0%; AAD 13.8%) trials reported lower rates of sudden cardiac death for those receiving an ICD compared with AAD, although only the CASH trial⁸³ showed a statistically significant difference. Similarly, the AVID⁷⁴ and CIDS⁸⁶ studies showed benefit for people receiving an ICD compared with AAD on crude rates of arrhythmic deaths (AVID:⁷⁴ ICDs 4.7%; AAD 10.8%; CIDS⁸⁶: ICDs 9.2%, AAD 13.1%), although neither demonstrated a statistically significant difference. The CIDS trial⁸⁶ also showed no statistically significant difference when comparing the interventions on annual crude mortality rates (ICDs 3.0%, AAD 4.5%, RRR 32.8%, 95% CI, -7.2 to 57.8; p=0.094). Combining the four studies through a random effects meta-analysis showed a statistically significant benefit for ICDs compared with AAD with a risk ratio of 0.49 (95% CI, 0.34 to 0.69; p<0.0001) and limited heterogeneity (Chi²=5.47, df =4, I²=27%), Figure 6.

All nine trials in people who had not suffered a life-threatening arrhythmia but were at increased risk reported sudden cardiac or arrhythmic deaths as an outcome (see Table 19).^{71;80;84;92;97;99;101;105;110} Although eight of the trials showed benefit for those receiving an ICD plus OPT compared with either OPT, amiodarone plus OPT or placebo plus OPT,^{71;80;92;97;99;101;105;110} only four identified these as being statistically significant.^{92;97;99;105} The DINAMIT⁹⁷ and IRIS⁹⁹ trials highlighted the benefits of ICDs plus OPT compared with OPT for people who had had a recent MI, reporting hazard ratios of 0.42 (95% CI, 0.22 to 0.83; p=0.009) and 0.55 (95% CI, 0.31 to 1.00; p=0.049) respectively (see Table 19). When meta-analysed a combined risk ratio of 0.45 (95% CI, 0.31 to 0.64; p<0.0001) resulted with no heterogeneity reported (Chi²=0.03, df =1, I²=0%) (see Figure 6).

The MADIT I¹⁰¹ (ICD plus OPT 3.2%, OPT 12.9%, p=not stated) and MADIT II¹⁰⁵ (ICD plus OPT 3.8%, OPT 10.0%, p<0.01) trials among people remote from MI showed lower rates of sudden cardiac or arrhythmic death among those with an ICD plus OPT compared with OPT. Meta-analysis through a random effects model showed significant benefit for ICD plus OPT with a risk ratio of 0.36 (95% CI, 0.23 to 0.55; p<0.00001) and no heterogeneity (Chi²=0.42, df =1, I²=0%)(see Figure 6).

The AMIOVIRT,⁷¹ CAT⁸⁴ and DEFINITE⁹² trials in people with cardiomyopathy reported differing outcomes. The DEFINITE trial⁹² found significantly fewer people with an ICD plus OPT (1.3%) died from sudden cardiac or arrhythmic death compared with those on OPT (6.1%), reflected in a hazard

ratio of 0.20 (95% CI, 0.06 to 0.71; $p=0.006$) (Table 19). Although the AMIOVIRT trial⁷¹ also found benefit for those receiving an ICD plus OPT (2.0%) compared with those receiving amiodarone plus OPT (3.9%), the benefit was not statistically significant ($p=0.7$). The CAT trial⁸⁴ reported no deaths from sudden cardiac or arrhythmic deaths in either the ICD plus OPT or OPT groups. A random effects meta-analysis of the three trials showed an overall statistically significant benefit for people with an ICD plus OPT compared with comparator treatment with a risk ratio of 0.26 (95% CI, 0.09 to 0.77; $p=0.02$) with no heterogeneity ($\text{Chi}^2=0.41$, $\text{df}=1$, $\text{I}^2=0\%$) (Figure 6).

The CABG Patch trial⁸⁰ in people who were scheduled for CABG surgery reported lower rates of sudden cardiac and arrhythmic death in the ICD plus OPT group (3.4%) compared with the OPT (6.2%), although the difference was marginally insignificant (HR 0.55, 95% CI, 0.29 to 1.03; $p=0.06$) (Table 19). In contrast, the SCD-HEFT trial¹¹⁰ found significantly lower sudden cardiac or arrhythmic mortality in the group receiving ICD plus OPT (4.6%) compared with the group receiving amiodarone plus OPT (9.5%) or placebo plus OPT (11.6%) with a risk ratio of 0.44 (95% CI, 0.31 to 0.61; $p<0.00001$) (Figure 6).

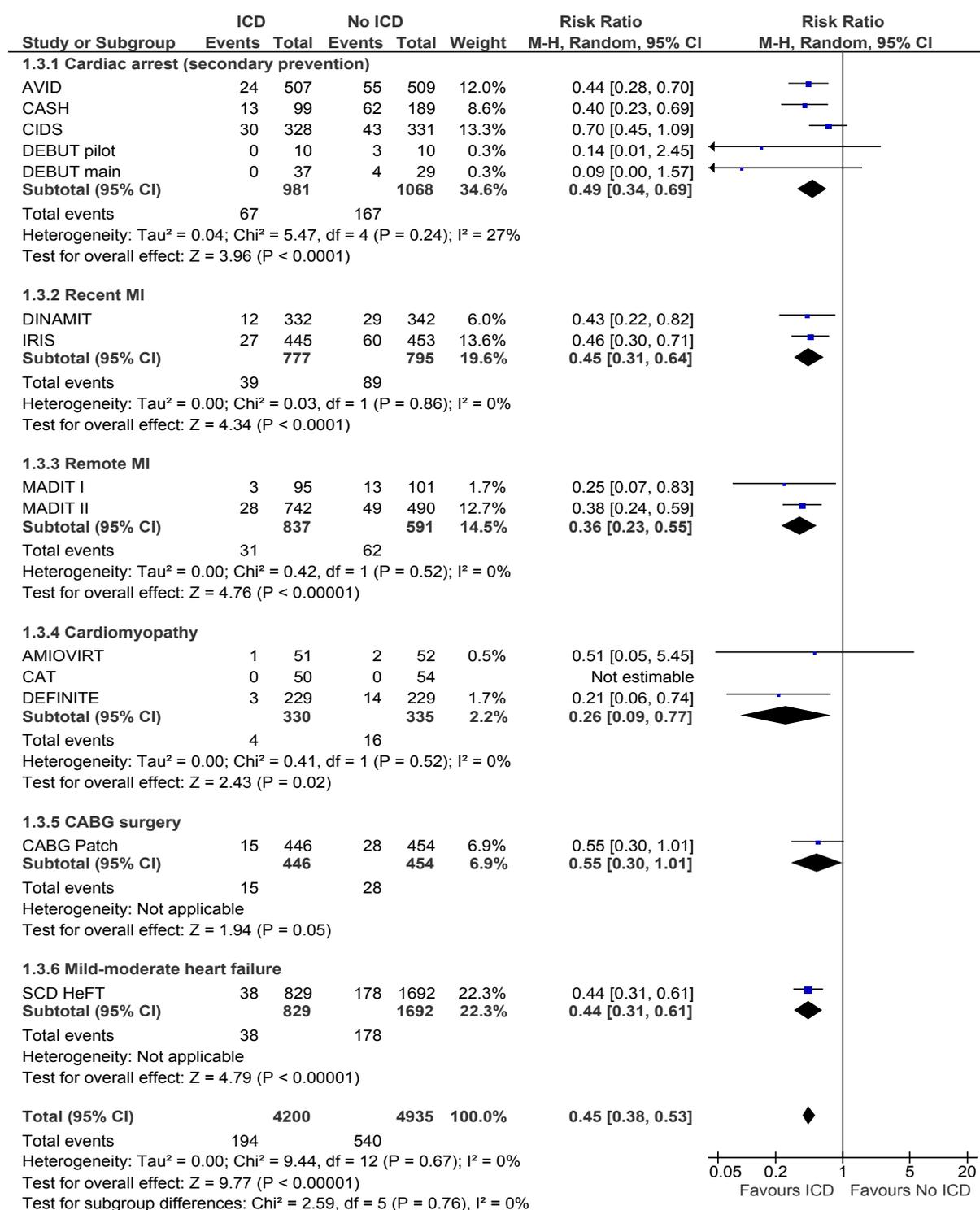
Table 19: Sudden cardiac deaths/arrhythmic deaths

Study	Follow-up	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI , p value
<i>Cardiac arrest</i>					
AVID ⁷⁴	Mean 18.2 months (SD 12.2)	24/507 (4.7)	AAD: 55/509 (10.8)		
CASH ⁸³	57 months (SD 34)	13/99 (13.0%, CI 7.9 to 19.6) ^a	Amiodarone: 27/92 (29.5%, CI 19.4 to 40.8) ^b Metoprolol: 34/97 (35.1%, CI 25.2 to 48.8) ^b Both: 62/189 (33.0%, CI 27.2 to 41.8) ^a		
CIDS ⁸⁶	Mean 3 years	30/328 (9.2) [3.0]	Amiodarone: 43/331 (13.1) [4.5]	RRR 32.8%	-7.2 to 57.8, 0.094
DEBUT ⁹¹ pilot study	Max. 3 years after randomisation	0/10 (0)	Propranolol: 3/10 (30)		
DEBUT ⁹¹ main study	3 years	0/37 (0)	Propranolol: 4/29 (13.8)		
<i>Early post MI</i>					
DINAMIT ⁹⁷	average 30 (SD 13) months	12/332 (3.6) [1.5]	OPT 29/342 (8.7) [3.5]	HR 0.42	0.22 to 0.83, 0.009
IRIS ⁹⁹	average 37 months	27/445 (6.1)	OPT 60/453 (13.2)	HR 0.55	0.31 to 1.00, 0.049
<i>Remote from MI</i>					
MADIT I ¹⁰¹	average 27 months	3/95 (3.2)	OPT 13/101 (12.9)		
MADIT II ¹⁰⁵	average 20 months	28/742 (3.8)	OPT 49/490 (10.0)		<0.01
<i>Cardiomyopathy</i>					
AMIOVIRT ⁷¹	mean 2.0 years (SD)	1/51 (2.0)	Amiodarone plus OPT 2/52 (3.9)		0.7

Study	Follow-up	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI , p value
	1.3)				
CAT ⁸⁴	1-year (primary end point)	0/50 (0)	OPT 0/54 (0)		
DEFINITE ⁹²	Mean (SD) 29.0 (14.4) months	3/229 (1.3)	OPT 14/229 (6.1)	HR 0.20	0.06 to 0.71, 0.006
<i>Scheduled for CABG</i>					
CABG Patch ⁸⁰	mean 32 (SD 16) months	15/446 (3.4)	OPT 28/454 (6.2)	0.55	0.29 to 1.03, 0.06
<i>Heart Failure</i>					
SCD-Heft ¹¹⁰	Median for surviving patients 45.5 months (range 24 to 72.6)	38/829 (4.6)	Amiodarone plus OPT 80/845 (9.5) Placebo plus OPT 98/847 (11.6)		

^a Crude death rate. ^b Level of CI not reported.

Figure 6: Sudden cardiac deaths/arrhythmic deaths



4.2.2.4 Cardiac non-arrhythmic deaths

Two trials in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias reported rates of non-arrhythmic deaths.^{74;86} The AVID⁷⁴ and CIDS⁸⁶ trials assessed the effects of

ICDs compared with AAD on crude non-arrhythmic cardiac deaths, with neither stating whether there was any statistically significant benefit (AVID⁷⁴: ICDs 7.7%, AAD 7.7%; CIDS⁸⁶: ICDs 11.3%, AAD 12.1%) (Table 20). The CIDS trial⁸⁶ also reported annual crude mortality rates (ICDs 3.7%, AAD 4.2%), which resulted in a non-significant relative risk reduction of 13.5% (95% CI, -35.4 to 44.7; $p=0.526$). A random effects meta-analysis confirmed the lack of statistically significant difference with a risk ratio 0.97 (95% CI, 0.72 to 1.31, $p=0.83$) with no heterogeneity ($\text{Chi}^2=0.06$, $\text{df}=1$, $I^2=0\%$) (Figure 7).

ICDs plus OPT appeared to have limited effect on the occurrence of non-arrhythmic cardiac deaths when compared with OPT, amiodarone plus OPT or placebo plus OPT in people who had not suffered a life-threatening arrhythmia but were at increased risk (Table 20). In people who had a recent MI, the DINAMIT⁹⁷ and IRIS trials⁹⁹ found statistically significant benefit for those on OPT only compared with those receiving an ICD plus OPT, reporting hazard ratios 1.72 (95% CI, 0.99 to 2.99; $p=0.05$) and 1.92 (95% CI, 1.29 to 2.84; $p=0.001$) respectively. Combining the studies through a random effects meta-analysis confirmed the statistically significant benefit for people on OPT with a risk ratio of 1.77 (95% CI, 1.30 to 2.40; $p=0.0002$) and no apparent heterogeneity ($\text{Chi}^2=0$, $\text{df}=1$, $I^2=0\%$) (Figure 7).

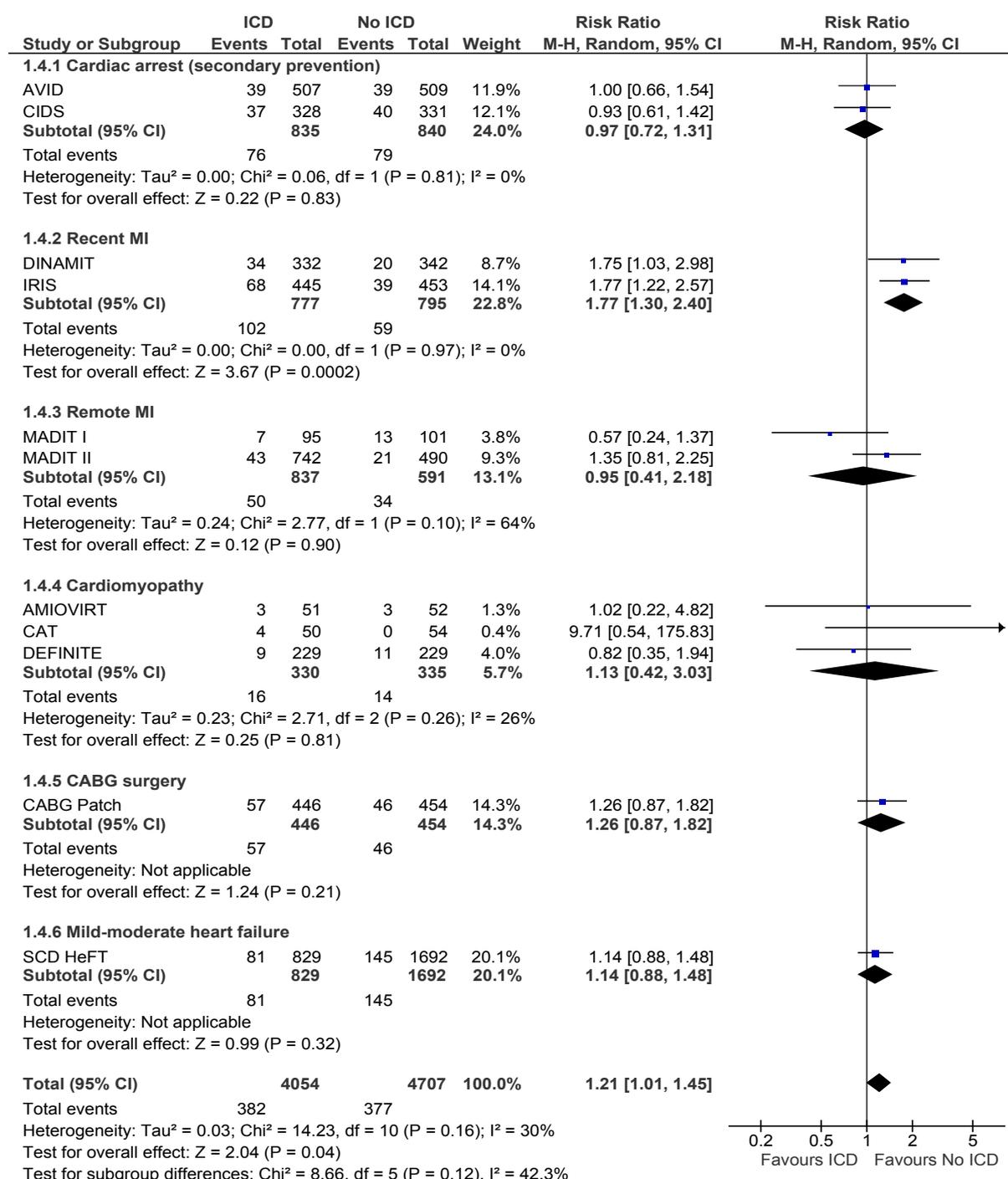
The effect of the different interventions on non-arrhythmic cardiac deaths in other patient sub-groups was more equivocal. The MADIT I¹⁰¹ and MADIT II¹⁰⁵ trials in people remote from MI reported contrasting mortality rates (MADIT I:¹⁰¹ ICDs plus OPT 7.4%, OPT 12.9%; MADIT II:¹⁰⁵ ICDs plus OPT 5.8%, OPT 4.3%), which when meta-analysed through a random effects model showed no statistically significant difference between the ICD plus OPT and OPT groups (RR 0.95, 95% CI, 0.41 to 2.18; $p=0.9$; $\text{Chi}^2=2.77$, $\text{df}=1$, $I^2=64\%$) (Figure 7). Similar variation was reported by the three trials assessing non-arrhythmic cardiac deaths among people with cardiomyopathy. The AMIOVIRT⁷¹ (ICDs plus OPT 5.9%, amiodarone plus OPT 5.8%), CAT⁸⁴ (ICDs plus OPT 8%, OPT 0%) and DEFINITE⁹² (ICDs plus OPT 3.9%, OPT 4.8%) trials reported differing mortality rates that when meta-analysed showed no statistically significant benefit (RR 1.13, 95% CI, 0.42 to 3.03; $p=0.81$; $\text{Chi}^2=2.71$, $\text{df}=2$, $I^2=26\%$) (Figure 7). Similarly the CABG Patch trial⁸⁰ in those who were scheduled for CABG surgery (RR 1.26, 95% CI, 0.87, 1.82; $p=0.21$) and SCD-Heft trial¹¹⁰ in people with mild-moderate heart failure (RR 1.14, 95% CI, 0.88 to 1.48; $p=0.32$) found no statistically significant benefit (Figure 7).

Table 20: Non-arrhythmic cardiac deaths

Study	Follow-up, mean	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI , p value
AVID ⁷⁴	18.2 months (SD 12.2)	39/507 (7.7)	AAD: 39/509 (7.7)		
CIDS ⁸⁶	3 years	37/328 (11.3) [3.7]	Amiodarone: 40/331 (12.1) [4.2]	RRR 13.5%	-35.4 to 44.7, 0.526
<i>Early post MI</i>					
DINAMIT ⁹⁷	average 30 (SD 13) months	34/332 (10.2) [4.1]	20/342 (5.8) [2.4]	HR 1.72	0.99 to 2.99, 0.05
IRIS ⁹⁹	average 37 months	68/445 (15.3)	39/453 (8.6)	HR 1.92	1.29 to 2.84, 0.001
<i>Remote from MI</i>					
MADIT I ¹⁰¹	average 27 months	7/95 (7.4)	13/101 (12.9)		
MADIT II ¹⁰⁵	average 20 months	43/742 (5.8)	21/490 (4.3)		
<i>Cardiomyopathy</i>					
AMIOVIRT ⁷¹	mean 2.0 years (SD 1.3)	3/51 (5.9)	Amiodarone plus OPT: 3/52 (5.8)		0.7
CAT ⁸⁴	1-year (primary end point)	4/50 (8)	0/54 (0)		
DEFINITE ⁹²	Mean (SD) 29.0 (14.4) months	9 ^a /229 (3.9)	11 ^a /229 (4.8)		
<i>Scheduled for CABG</i>					
CABG Patch ⁸⁰	mean 32 (SD 16) months	57/446 (12.8)	46/454 (10.1)	HR 1.24	0.84 to 1.84, 0.28
<i>Heart failure</i>					
SCD-Heft ¹¹⁰	Median for surviving patients 45.5 (range 24 to 72.6) months	81/829 (9.8)	Amiodarone plus OPT: 77/845 (9.1) Placebo plus OPT: 68/847 (8.0)		

^a Deaths from heart failure reported only.

Figure 7: Non-arrhythmic cardiac deaths



4.2.2.5 Other causes of death: non-cardiac deaths

Two trials in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias assessed non-cardiac causes of death as an outcome (see Table 21).^{74;86} The AVID⁷⁴ and CIDS⁸⁶ trials found no statistically significant difference between ICDs and AAD on other non-cardiac causes of death (AVID:⁷⁴ ICDs 3.4%, AAD 5.5%, RR 1.78 (95% CI, 0.98 to 3.26); p=0.053; CIDS:⁸⁶ non-cardiac vascular ICDs 0.9%, AAD 0.6%, RRR -36.6% (95% CI, -719.8 to 77.2), p=0.732; non-

vascular ICDs 4.0%, AAD 3.9%, RRR 4.5% (95% CI, -106.1 to 55.7), $p=0.908$) (see Table 21), reflected in a random effects meta-analysis (risk ratio 0.79, 95% CI, 0.45 to 1.37, $p=0.40$; $\text{Chi}^2=1.51$, $\text{df}=1$, $\text{I}^2=34\%$) (Figure 8). The CIDS trial⁸⁶ presented annual crude death rates for the ICDs and AAD groups for non-cardiac vascular (ICDs 0.3%, AAD 0.2%) and non-vascular (ICDs 1.3%, AAD 1.4%) causes,⁸⁶ finding limited difference.

Eight trials in people who had not suffered a life-threatening arrhythmia but were at increased risk assessed the effects of ICDs plus OPT with the different comparator treatments on other non-cardiac causes of death, finding no statistically significant benefit (see Table 21).^{71;80;84;97;99;101;105;110} Meta-analyses using random effects models of the DINAMIT⁹⁷ and IRIS⁹⁹ trials in people with a recent MI (RR 1.39, 95% CI, 0.86 to 2.27; $p=0.18$; $\text{Chi}^2=0.70$, $\text{df}=1$, $\text{I}^2=0\%$), the MADIT I¹⁰¹ and MADIT II¹⁰⁵ trials in people remote from MI (RR 1.06, 95% CI, 0.58 to 1.95; $p=0.84$; $\text{Chi}^2=0.55$, $\text{df}=1$, $\text{I}^2=0\%$), and the AMIOVIRT⁷¹ and CAT⁸⁴ trials in people with cardiomyopathy (RR 0.65, 95% CI, 0.13 to 3.29; $p=0.60$; $\text{Chi}^2=0.75$, $\text{df}=1$, $\text{I}^2=0\%$) all found no statistically significant effects (Figure 8). Similarly the CABG Patch trial⁸⁰ in people who were scheduled for CABG surgery (RR 1.50, 95% CI, 0.82 to 2.73; $p=0.19$) and the SCD-Heft¹¹⁰ trial in mild-to moderate heart failure (RR 0.92, 95% CI, 0.66 to 1.27; $p=0.60$) reported no statistically significant differences in deaths from other non-cardiac causes (Figure 8).

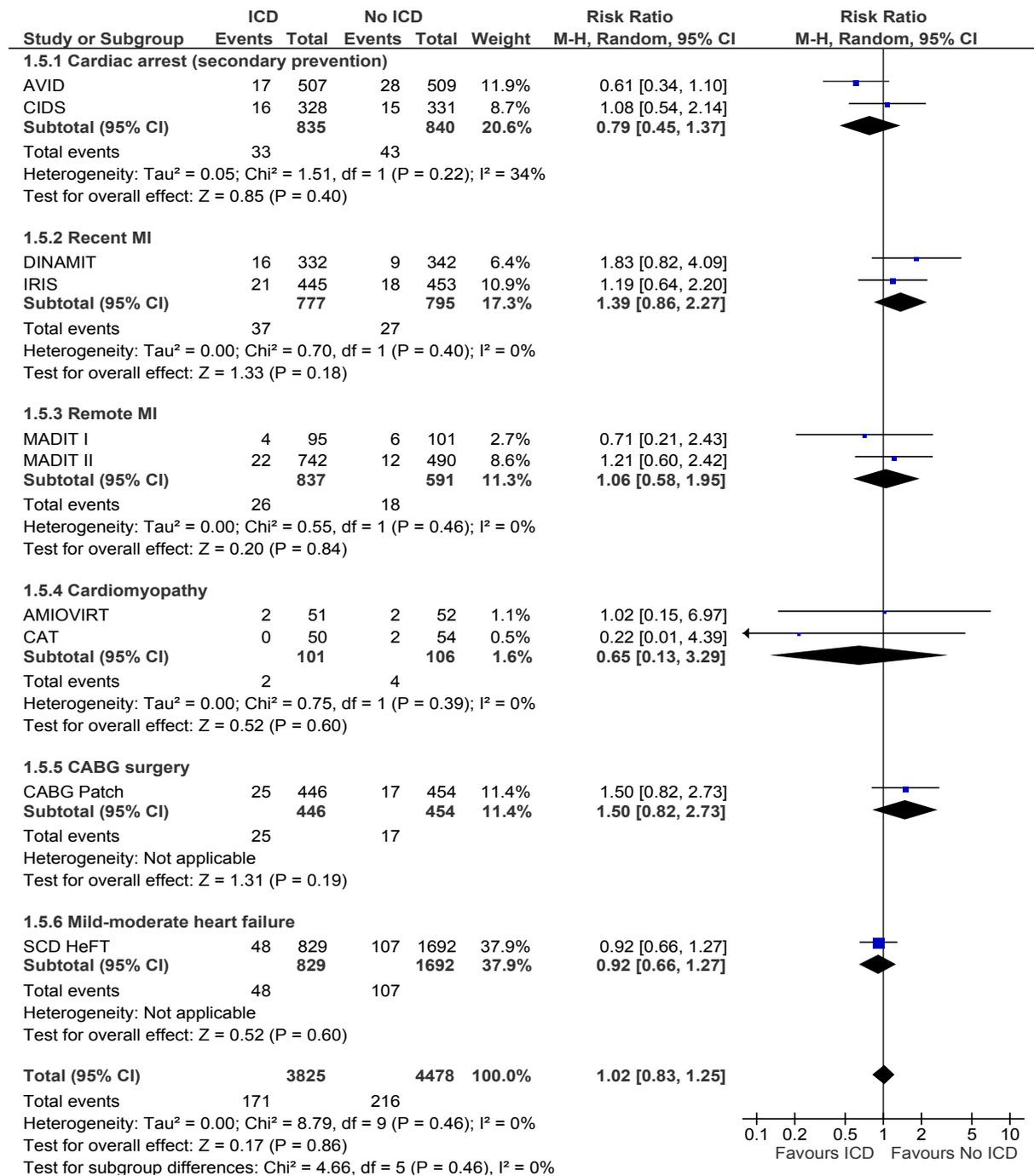
Table 21: Other causes of death (non-cardiac)

Study	Outcome, follow-up (mean)	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI, p value
<i>Cardiac arrest</i>					
AVID ⁷⁴	18.2 months (SD 12.2)	17/507 (3.4)	AAD: 28/509 ^a (5.5)	RR 1.78	0.98 to 3.26, 0.053
CIDS ⁸⁶	Non-cardiac vascular, 3 years	3/328 (0.9) [0.3]	Amiodarone: 2/331 (0.6) [0.2]	RRR -36.6%	-719.8 to 77.2, 0.732
	Non-vascular, 3 years	13/328 (4.0) [1.3]	13/331 (3.9) [1.4]	RRR 4.5%	-106.1 to 55.7, 0.908
<i>Early post MI</i>					
DINAMIT ⁹⁷	Non-cardiac vascular, average 30 months (SD 13)	5/332 (1.5) [0.6]	3/342 (0.9) [0.4]	HR 1.69	0.40 to 7.06, 0.47
	Non vascular	11/332 (3.3) [1.3]	6/342 (1.8) [0.7]	HR 1.85	0.68 to 5.01, 0.22
IRIS ⁹⁹	average 37 months	21/445 (4.7)	18/453 (4.0)	HR 1.23	0.51
<i>Remote from MI</i>					
MADIT I ¹⁰¹	Non-cardiac, average 27 months	4/95 (4.2)	6/101 (5.9)		
	Unknown (cardiac or non-cardiac)	0/95 (0)	6/101 (5.9)		
MADIT II ¹⁰⁵	Non-cardiac deaths, average 20 months	22/742 (3.0)	12/490 (2.4)		
	Unknown (cardiac or non-cardiac)	4/742 (0.5)	5/490 (1.0)		
<i>Cardiomyopathy</i>					
AMIOVIRT ⁷¹	mean 2.0 years (SD 1.3)	2/51 (3.9)	Amiodarone plus OPT: 2/52 (3.8)		0.9
CAT ⁸⁴	1-year (primary end point)	0/50 (0)	2/54 (3.7)		
<i>Scheduled for CABG</i>					

CABG Patch ⁸⁰	Non-cardiac, mean 32 mths (SD 16)	25/446 (5.6)	17/454 (3.7)	HR 1.49	0.80 to 2.76, 21
	Unknown	1/446 (0.2)	0/454 (0)		
<i>Heart Failure</i>					
SCD-Heft ¹¹⁰	Non-cardiac, median for surviving patients 45.5 mths (range 24 to 72.6)	48/829 (5.8)	Amiodarone plus OPT: 54/845 (6.4) Placebo plus OPT: 53/847 (6.3)	HR 0.80 ^b	0.57 to 1.12, ns
	Unknown deaths	12/829 (1.4)	Amiodarone plus OPT: 24/845 (2.8) Placebo plus OPT 24/847 (2.8)		ns

^a 3 attributed to pulmonary toxicity due to amiodarone. ^b Comparison of non-cardiac deaths for ICDs plus OPT compared with placebo plus OPT groups.

Figure 8: Other causes of death: Non-cardiac deaths



4.2.2.6 Cumulative mortality

The cumulative mortality risk for both total and arrhythmic mortality was assessed annually up to 3 years follow-up in the CIDS trial in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias.⁸⁶ Rates were consistently lower for those receiving an ICD compared with AAD with relative risk reduction for total mortality in year 1 of 15.4%, year 2 of 29.7% and year 3 of 13.7% and for arrhythmic mortality in year 1 of 29.9%, year 2 of 31.4% and year 3 17.8% (Table 22).

Four trials in people who had not suffered a life-threatening arrhythmia but were at increased risk reported other mortality outcomes.^{77;92;99;107} The IRIS trial⁹⁹ in people with a recent MI presented cumulative death rates annually up to 3 years (see Table 22). Although it found lower mortality rates for those with an ICD plus OPT (year 1 10.6%; year 2 15.4%; year 3 22.4%) compared with OPT (year 1 12.5%; year 2 18.2%; year 3 22.9%), the differences were not found to be statistically significant (p=0.76).⁹⁹ Similarly the DEFINITE trial⁹² in people with cardiomyopathy (year 1 ICDs plus OPT 2.6%, OPT 6.2%; year 2 ICDs plus OPT 7.9%, OPT 14.1%) and the SCD-Heft trial¹⁰⁷ in people with mild-moderate heart failure (Kaplan-Meier estimate 5 year: ICDs plus OPT 0.289; amiodarone plus OPT 0.340; placebo plus OPT 0.361) also reported lower all-cause mortality following implantation of an ICD (p not stated). In contrast, the CABG Patch trial⁷⁷ in people scheduled for CABG surgery reported higher actuarial mortality at 4 years follow-up in those with an ICD plus OPT (27%) compared with OPT (24%), although the difference was not statistically significant (HR 1.07, 95% CI, 0.81 to 1.42, p=0.64) (see Table 22).

4.2.2.7 Survival

Differences in mortality were reflected in the survival outcomes reported by the AVID^{73;74} and CASH⁸³ trials in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias.⁸³ The AVID trial reported statistically significant differences in overall survival during the 3 years follow-up (p<0.02),⁷³ survival free of cardiac death at 2 years (p=0.0042)⁷⁴ and survival to arrhythmic death at 2 years (p=0.0002)⁷⁴ favouring ICDs compared with AAD (see Table 23). Survival free of non-arrhythmic cardiac death did not differ significantly between those receiving ICD compared with AAD (p=0.8039).⁷⁴ Despite the CASH trial⁸³ finding benefits from ICDs compared with AAD on overall survival (HR 0.766, p=0.081) and survival free of cardiac arrest (HR 0.481, p=0.072), differences were not statistically significant. In contrast, the CASH trial⁸³ did report a significant benefit on survival free of sudden death for people who received an ICD compared with AAD (HR 0.423, p=0.005). The DEBUT trial⁹¹ reported mean survival times for the AAD group of 26.2 (SEM 1.4) months (no deaths in the ICDs group).

Only the AMIOVIRT⁷¹ and CAT⁸⁴ trials in people with cardiomyopathy reported survival (Table 23). The AMIOVIRT trial⁷¹ presented overall and arrhythmia-free survival rates for the ICD plus OPT group and the amiodarone plus OPT group at 1 and 3 years follow-up, showing no statistically significant difference (p=0.8).⁷¹ The CAT trial⁸⁴ presented cumulative survival data for ICDs plus OPT and OPT up to 6 years follow-up, finding no statistically significant difference (p=0.554) (Table 23).

4.2.2.8 Heart failure hospitalisations

Only the AVID study⁷³ in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias reported the proportion of patients re-hospitalised annually up to three years.

Significantly higher rates were reported for the ICD group compared with the AAD group (p=0.04) (Table 24). For both groups re-hospitalisation rates were above 55% at year 1, 65% at year 2 and 75% at year 3.

The MADIT II trial¹⁰³ among people remote from MI reported the proportion of hospitalisations due to heart failure (ICDs plus OPT 19.9%, OPT 14.9%, p not stated) and the number of patients hospitalised per 1000 months follow-up (ICDs plus OPT 11.3, OPT 9.4, p=0.09) with higher rates among those receiving ICDs plus OPT (Table 24).

4.2.2.9 Symptoms/complications related to arrhythmias

The CAT⁸⁴ and AMIOVIRT⁷¹ trials in people with cardiomyopathy reported the occurrence of syncope. Some 12% of people with an ICD plus OPT had syncope during ventricular tachycardias in the CAT trial⁸⁴ and 3.9% of ICD plus OPT and 5.8% of amiodarone plus OPT patients had syncope in the AMIOVIRT study⁷¹ (see Table 25). The MADIT II trial¹⁰⁵ among people remote from MI reported the number of adverse cardiac events in the week prior to sudden cardiac death (ICDs plus OPT 28, OPT 49) with comparable rates of syncope and angina pectoris (4% for both), lower rates of myocardial infarction for ICDs plus OPT (ICDs plus OPT 4%, OPT 10%) and higher rates of ventricular arrhythmia (ICDs plus OPT 25%, OPT 10%) and for congestive heart failure (ICDs plus OPT 43%, OPT 16%) for ICDs plus OPT compared with OPT.

Table 22: Cumulative mortality

Study	Outcome measure	ICD	OPT	Effect
<i>Cardiac arrest</i>				
CIDS ⁸⁶	Cumulative risks over time, Total mortality %		Amiodarone:	
	- 1 year	9.46%	11.18%	ARR 1.72%, RRR 15.4%
	- 2 years	14.75%	20.97%	ARR 6.22%, RRR 29.7%
	- 3 years	23.32%	27.03%	ARR 3.71%, RRR 13.7%
	Cumulative risks over time, arrhythmic mortality %			
	- 1 year	4.37%	6.23%	ARR 1.86%, RRR 29.9%
- 2 years	6.68%	9.74%	ARR 3.06%, RRR 31.4%	
- 3 years	9.77%	11.88%	ARR 2.11%, RRR 17.8%	
DEFINITE ⁹²	All-cause mortality rate at 1 year	2.6%	6.2%	
	All-cause mortality rate at 2 years	7.9%	14.1%	
IRIS ⁹⁹	Cumulative 1 year death rate ^a	10.6%	12.5%	
	Cumulative 2 year death rate ^a	15.4%	18.2%	
	Cumulative 3 year death rate ^a	22.4%	22.9%	
CABG Patch ⁷⁷	Actuarial mortality by 4 years follow-up	27%	24%	0.64
	Hazard ratio for death per unit time			HR 1.07 (95% CI 0.81 to 1.42)
SCD-Heft ¹⁰⁷	Kaplan-Meier estimates death from any cause	0.289	Amiodarone plus OPT: 0.340	
	- 5 year event rate		Placebo plus OPT: 0.361	

^a States that no significant difference in survival was detected between the groups, p-value of 0.76 given which may relate to these data, but reporting is unclear.

Table 23: Survival

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
<i>Cardiac arrest</i>					
AVID ⁷³	Overall survival, mean 18.2 months (SD 12.2)		AAD		<0.02
	- 1 year, %	89.3	82.3		
	- 2 year, %	81.6	74.7		
	- 3 year, %	75.4	64.1		
	Survival free of cardiac death ^{a 74} - at 1 year	90.9%	85.1%		0.0042
	- at 2 years	85.0%	81.2%		
	Survival to arrhythmic death ^{b74} - at 1 year	96.6%	91.9%		0.0002
	- at 2 years	94.2%	89.1%		
	Survival free of non-arrhythmic cardiac death ^c	presented in figure only	presented in figure only		0.8039
CASH ⁸³	57 months (SD 34)		AAD:		
	Overall survival, ICD vs amiodarone /metoprolol	HR 0.766			97.5% CI upper bound 1.112, 0.081
	Survival free of sudden death ICD vs amiodarone /metoprolol	HR 0.423			97.5% CI upper bound 0.721, 0.005
	Survival free of cardiac arrest ICD vs amiodarone /metoprolol	HR 0.481			97.5% CI upper bound 1.338, 0.072
DEBUT ⁹¹ main study	3 years Mean survival, months, mean (SEM)		26.2 (1.4)		
<i>Cardiomyopathy</i>					

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	Effect	95% CI , p value
AMIOVIRT ⁷¹	Survival rates %, - 1 year	96%	Amiodarone plus OPT: 90%		0.8 ^d
	- 3 year	88%	Amiodarone plus OPT: 87%		
	Arrhythmia-free survival rates %, - 1 year	78	82		0.1 ^e
	- 3 year	63	73		
CAT ⁸⁴	cumulative survival, - 2 year	92%	93%		0.554
	- 4-year	86%	80%		
	- 6-year	73%	68%		

^a Non-cardiac deaths censored. ^b Non-cardiac and non-arrhythmic deaths censored. ^c Non-cardiac and arrhythmic deaths censored. ^d Survival rates at 1 and 3 years. ^e Arrhythmic-free survival rates at 1 and 3 years.

Table 24: Hospitalisations

Study	Follow-up	ICD, n/N (%)	OPT, n/N (%)	Effect	95% CI , p value
<i>Cardiac arrest</i>					
AVID ⁷³	% of patients re-hospitalised (patients at risk n=1011)				0.04
	- at 1 year	59.5	55.6		
	- at 2 years	74.8	64.7		
	- at 3 years	83.3	75.5		
<i>Remote from MI</i>					
MADIT II ¹⁰³	Hospitalisation due to heart failure, n (%)	148 (19.9)	73 (14.9)		
	Patients hospitalised, per 1000 months of active follow-up	11.3	9.4		0.09

Table 25: Symptoms/complications related to arrhythmia

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	Effect (HR)	95% CI, p value
<i>Cardiomyopathy</i>					
CAT ⁸⁴	Syncope during VTS	6/50 (12)			
AMIOVIRT ⁷¹	Syncope	3.9% ^a	5.8%	0.7	
<i>Remote from MI</i>					
MADIT II ¹⁰⁵	Adverse cardiac events in week prior to SCD	(n=28)	(n=49)		
	Syncope	4%	4%		
	Angina pectoris	4%	4%		
	MI	4%	10%		
	Ventricular arrhythmia	25%	10%		
	Congestive HF	43%	16%		

^a VT or VF was the cause of syncope in each ICD patient in whom it occurred.

4.2.2.10 QoL

Two trials in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias, the AVID⁷⁶ and CIDS⁸⁹ trials, reported results from sub-studies using a range of generic and condition-specific measures of quality of life (QoL) (Table 26). The AVID trial⁷⁶ assessed QoL through the SF-36 physical (PCS) and mental (MCS) component summaries, 46 item patient concerns checklist, and the cardiac version of the QL index. Follow-up was for 12 months and assessments were made of the impact of adverse symptoms and ICD shocks. Comparison of PCS scores at baseline and 12 months follow-up showed no statistically significant difference between the ICD and AAD groups (baseline: ICDs 37.4, AAD 36.5, $p=0.3$; 12 months: ICDs 40.0, AAD 38.0, $p=0.3$). In contrast, the ICDs group had a lower (worse) mean score on the MCS at baseline compared with the AAD group that was statistically significant ($p=0.006$), although any difference had disappeared by 12 months follow-up. Scores on the patient concerns checklist did not differ significantly between the ICD and AAD groups at baseline (ICDs 15.9, AAD 16.2, $p=0.06$) or at 12 months follow-up ($p=0.1$). On the QL index the scores for the ICDs and AAD groups were similar at baseline (ICDs 22.1, AAD 21.9, p not stated) and at 12 months follow-up (scores and p values not stated).

The effects of adverse symptoms and ICDs shocks were assessed in the AVID trial⁷⁶ on PCS scores, MCS scores and patient concerns through multivariate analysis including age, sex, race, index arrhythmia, ejection fraction, history of heart failure and use of β -blockers at hospital discharge. Adverse symptoms led to a statistically significant worsening of PCS scores ($p<0.001$), MCS scores ($p=0.002$) and patient concern scores ($p<0.001$) for the ICDs group and on PCS scores ($p=0.009$) and patient concern scores ($p=0.03$) for the AAD group. The occurrence of ICD shocks had a similar adverse effect on QoL with statistically significant worsening on PCS scores ($p=0.03$), MCS scores ($p=0.04$) and patient concern scores ($p<0.001$).

A sub-study of the CIDS trial⁸⁹ reported the effects of ICDs and AAD on three domains of the Mental Health Inventory (MHI) and seven domains of the Nottingham Health Profile (NHP), with an additional assessment of the consequences of ICD shocks on these measures. At 12 months follow-up the ICDs group had shown significantly greater improvement than the AAD group on the MHI domains of 'total index' ($p=0.001$), 'psychological distress' ($p=0.001$) and 'psychological well-being' ($p=0.03$) and the NHP domains of 'energy level' ($p=0.0001$), 'physical mobility' ($p=0.002$), 'emotional reactions' ($p=0.002$), 'sleep disturbance' ($p=0.02$) and 'lifestyle impairment' ($p=0.005$). It was notable that none of the domains on MHI and NHP improved for the AAD group between baseline and 12 months follow-up, with the domains of energy level and physical mobility deteriorating.

The effects of ICD shocks on QoL were assessed in the CIDS trial⁸⁹ on the different domains of MHI and NHP through univariate comparisons between groups in terms of the numbers of shocks (i.e. ICD no shocks, ICD 1-4 shocks, ICD ≥ 5 shocks and AAD group without an ICD). It was evident that the ICD ≥ 5 shocks group, like the AAD group without an ICD, did not experience the significant improvements in QoL that were reported by the ICDs groups with < 5 shocks. At 12 months follow-up the ICDs ≥ 5 shocks sub-group scored significantly ($p < 0.05$) worse than both the ICDs no shocks and 1-4 shocks group on MHI 'total index' and 'psychological distress' domains, than 1-4 shocks on 'psychological well-being' domain and ICDs no shocks on NHP 'emotional reactions' domain. Although the ICDs ≥ 5 shocks group did not differ significantly from the AAD group without an ICD on any of the MHI and NHP domains, the ICDs no shocks and 1-4 shocks groups had significantly ($p < 0.05$) better QoL compared with the AAD group without an ICD on the MHI 'total index' and 'psychological distress' and the NHP 'energy level', 'physical mobility' (ICD no shocks only), 'emotional reactions' and 'lifestyle impairment' domains.

Five trials in people who had not suffered a life-threatening arrhythmia but were at increased risk assessed quality of life.^{71;82;96;106;109} The MADIT II trial¹⁰⁶ assessed quality of life in those remote from their MI through the Health Utility Index (HUI3), reporting the mean score, mean annual change and overall mean score (including death) for those alive at assessment annually to 3 years follow-up (Table 26). The mean annual change in HUI3 scores showed a worsening in HRQoL for the ICD plus OPT group compared with the OPT group annually, with statistically significant change in years 2 ($p = 0.05$) and 3 ($p = 0.10$).¹⁰⁶ Despite these changes, comparison of the HUI3 scores for the different interventions showed that they were not significantly different during follow-up, even when mortality was taken into account (valuing death as 0).¹⁰⁶

The AMIOVIRT study⁷¹ in people with cardiomyopathy assessed changes in quality of life using the Quality of Well Being Schedule (QWBS) and the State Trait Anxiety Inventory (STAI).⁷¹ Comparison of the ICD plus OPT group with the amiodarone plus OPT group at 1 year follow-up showed no statistically significant difference between the groups on well-being on the QWBS ($p = 0.5$) or anxiety on the STAI ($p = 0.4$).⁷¹ Although the DEFINITE trial⁹⁶ in people with cardiomyopathy assessed quality of life using the SF-12 mental (MCS) and physical (PCS) component scores and MLHFQ, stating that no statistically significant differences were found between the ICD plus OPT and OPT groups, no data were reported.

The CABG Patch trial⁸² in people scheduled for a CABG assessed HRQoL on measures of perception of health, ability to function and psychological well-being at 6 months follow-up. On all measures of HRQoL the group receiving OPT reported a higher QoL compared with the ICD plus OPT group, with statistically significant differences for the measures of perception of health transition ($p = 0.030$),

emotional role function ($p=0.003$), mental health ($p=0.004$), satisfaction with appearance ($p=0.008$) and satisfaction with scar ($p=0.040$).⁸² With 38.5% of people with an ICD plus OPT having received a shock in the 6 months prior to completing the QoL instrument, the CABG Patch trial⁸² assessed the effects on QoL scores. On ten of the 12 measures the OPT group had a higher QoL than the ICDs plus OPT group where the device either fired or did not fire.⁸² The scores for the ICD plus OPT group where the device did not fire were similar to those of the OPT group with no statistically significant differences (p not stated). In contrast for the ICD plus OPT group where the device did fire, the scores showed a lower QoL, with statistically significant ($p=0.05$) differences for perception of health transition, physical limitations, physical role functioning, emotional role functioning, mental health and satisfaction with appearance.⁸²

The SCD-Heft trial¹⁰⁹ in people with heart failure reported QoL through a comparison of the Duke Activity Status Index (DASI), Mental Health Inventory 5 (MHI-5), MLHFQ and the global health status for ICD plus OPT, amiodarone plus OPT and the placebo plus OPT groups at baseline, three, 12 and 30 months follow-up. The effects on quality of life for those experiencing shocks with an ICD plus OPT were compared with those not receiving a shock using the SF-36. When compared on DASI at baseline, three, 12 and 30 months no clinical (four point difference) or statistically significant difference was shown on median or mean scores.¹⁰⁹ On the MHI-5, outcomes were more equivocal. Although the differences in the median and mean scores comparing ICDs plus OPT and amiodarone plus OPT separately with placebo plus OPT were below clinically meaningful levels (i.e. five point difference), some were statistically significant.¹⁰⁹ Comparison of the median scores showed that the ICD plus OPT group had significantly better scores than the placebo plus OPT group (three months $p=0.01$, 12 months $p=0.003$).¹⁰⁹ By 30 months the scores for the ICD plus OPT group had declined to baseline levels. Similarly the mean scores for the ICDs plus OPT group, differed significantly from the placebo plus OPT group at three and 12 months ($p\leq 0.05$).¹⁰⁹ Although the amiodarone plus OPT group had a significantly higher MHI score at baseline than the placebo plus OPT group ($p\leq 0.05$), these differences disappeared during subsequent follow-up.¹⁰⁹

Similar improvements for the ICDs plus OPT group were reported on the MLHFQ in the SCD-Heft trial,¹⁰⁹ resulting in significantly better scores for the ICDs plus OPT group compared to the placebo plus OPT group at three ($p=0.006$) and 30 ($p=0.05$) months.¹⁰⁹ However, these differences were thought to be clinically insignificant (five point change).¹⁰⁹ In contrast, a comparison using a time-trade-off utility measure showed that the ICDs plus OPT and the placebo plus OPT group's health status declined from baseline with no statistically significant difference at 30 months follow-up ($p=0.18$).¹⁰⁹

The effects of ICD shocks on quality of life were assessed using the SF-36.¹⁰⁹ A comparison of the changes in scores for those who had received a shock within 1 month of a scheduled quality of life assessment with those who had not received a shock, showed a significant decrease in the quality of life of those who received a shock on their relative perceptions of general health ($p=0.002$), physical function ($p<0.001$), emotional function ($p=0.02$), social function ($p=0.009$) and self-related health ($p=0.009$).¹⁰⁹

Table 26: Quality of life outcomes

Study	Outcome, follow-up	Intervention, n/N (%)	Comparator(s), n/N (%)	95% CI , p value
<i>Cardiac arrest (secondary prevention)</i>				
AVID ⁷⁶	1 year follow-up	(n=416)	AAD (n=384)	
	SF-36 PCS score, mean (SD) - baseline	37.4 (10.9)	36.5 (11.2)	0.3
	- 12 months	40 (10.5) ^a	38 (17) ^a	
	SF-36 MCS score, mean (SD) - baseline	45.9 (11.8)	47.5 (11.5)	0.006
	- 12 months	49 (16.5) ^a	48 (17) ^a	
	Patient concerns checklist- baseline	15.9 (8.6)	16.2 (8.9)	0.06
	- follow-up	nr	nr	0.1
	QL index – baseline	22.1 (4.9)	21.9 (5.0)	
Impact of adverse symptoms on QoL ^b	- SF-36 PCS score	-2.25 (-3.32, -1.18) p<0.001	-1.64 (-2.89, -0.41) p=0.009	
	- SF-36 MCS score	-2.32 (-3.76, -0.88) p=0.002	-0.51 (-1.97, 0.94) p=0.5	
	- Patient concerns	1.84 (0.91, 2.76) p<0.001	0.91 (0.07, 1.75) p=0.03	
Impact of ICD shocks on QoL	- SF-36 PCS score	-1.45 (-2.74, -0.18) p=0.03		
	- SF-36 MCS score	-1.82 (-3.56, -0.08) p=0.04		
	- Patient concerns	2.15 (1.07, 3.23) p<0.001		
CIDS ⁸⁹		(n=86)	Amiodarone (n=92)	Time by group p value
	Domains of Mental Health Inventory, mean (SD):			

Total index ^c - baseline	173.2 (25.5)	180.4 (27.8)	
- 6 months	183.1 (30.2)	180.2 (31.1)	
- 12 months	184.3 (27.9)	178.3 (28.7)	0.001
Psychological distress ^d - baseline	51.3 (14.1)	47.8 (16.5)	
- 6 months	45.1 (17.6)	47.6 (18.3)	
- 12 months	43.4 (15.9)	48.8 (16.8)	0.001
Psychological well-being ^c - baseline	58.5 (12.7)	62.2 (12.3)	
- 6 months	62.2 (13.4)	61.8 (14.1)	
- 12 months	61.7 (13.2)	61.3 (13.3)	0.03
Domains of Nottingham Health Profile, mean (SD)	n=83	n= 88	
Energy level ^d - baseline	27.5 (32.2)	24.4 (32.4)	
- 6 months	18.6 (30.1)	27.8 (32.1)	
- 12 months	17.7 (26.1)	36.8 (37.3)	0.0001
Physical mobility	(n=84)	n=90	
- baseline	10.9 (12.0)	13.2 (20.5)	
- 6 months	10.5 (13.7)	15.1 (19.2)	
- 12 months	9.1 (13.6)	17.7 (19.2)	0.002
Social isolation ^d	n=81	n=88	
- baseline	8.5 (15.4)	9.9 (17.7)	
- 6 months	9.8 (18.6)	12.2 (22.4)	
- 12 months	8.5 (18.4)	11.1 (22.6)	0.9
Emotional reactions ^d	n=76	n=86	

	- baseline	17.3 (18.1)		14.3 (20.1)	
	- 6 months	11.1 (18.2)		15.3 (22.4)	
	- 12 months	8.3 (16.6)		14.5 (19.6)	0.002
	Pain ^d	n=83		n=90	
	- baseline	4.4 (7.9)		7.5 (15.1)	
	- 6 months	7.5 (17.1)		6.3 (13.6)	
	- 12 months	4.5 (9.9)		8.2 (15.4)	0.52
	Sleep disturbance ^d	n=78		n=88	
	- baseline	31.4 (27.4)		29.6 (31.5)	
	- 6 months	25.0 (29.7)		30.8 (31.0)	
	- 12 months	23.9 (29.4)		30.2 (32.4)	0.02
	Life impairment ^d	n=78		n=83	
	- baseline	2.0 (1.9)		1.6 (1.7)	
	- 6 months	1.6 (1.8)		1.9 (1.9)	
	- 12 months	1.6 (1.3)		1.8 (1.9)	0.005
	Effect of ICD shocks on HRQoL scores ⁸⁹	<u>ICDs</u> no shocks (n=66)	<u>ICDs</u> 1-4 shocks (n=27)	<u>ICDs</u> ≥5 shocks (n=15)	<u>Amiodarone</u> (n=95) Between group p value
	Domains of Mental Health Inventory, mean (SD)				
	Total index ^c				
	- baseline	175.9 (26.5)	171.7 (22.7)	171.2 (32.0)	177.9 (27.1)
	- 12 months follow-up	186.2 (26.9) ^{e, f}	186.6 (21.7) ^{e, f}	168.8 (41.2)	175.6 (29.2)
	Within group P value	0.001	0.001	0.725	0.001

	Psychological distress ^d					
	- baseline	50.2 (15.2)	50.8 (12.3)	51.9 (18.1)	49.8 (16.3)	
	- 12 months follow-up	42.5 (15.3) ^{e, f}	41.4 (11.7) ^{e, f}	52.7 (25.2)	50.9 (17.5)	0.001
	Within group P value	0.001	0.001	0.833		
	Psychological well-being ^c					
	- baseline	60.1 (12.5)	56.6 (11.6)	57.1 (15.0)	61.7 (12.0)	
	- 12 months follow-up	62.8 (13.1)	62.1 (10.9) ^f	55.6 (16.8)	60.6 (13.3)	0.02
	Within group P value	0.074	0.004	0.642		
	Domains of Nottingham Health Profile, mean (SD)					
	Energy level ^d	n=64	n=27	n=15	n= 90	
	- baseline	28.6 (32.5)	28.5 (30.5)	22.6 (34.2)	24.3 (30.8)	
	- 12 months follow-up	19.5 (27.1) ^e	24.8 (33.4) ^e	23.5 (29.5)	37.0 (37.6)	0.003
	Within group P value	0.02	0.115	0.859		
	Physical mobility ^d	n=65	n=27	n=15	n=93	
	- baseline	13.1 (15.0)	12.4 (10.2)	7.1 (9.8)	13.18 (20.1)	
	- 12 months follow-up	9.3 (12.4) ^e	15.5 (17.3)	8.0 (13.3)	17.2 (19.1)	0.02
	Within group P value	0.05	0.638	0.747		
	Social isolation ^d	n=66	n=27	n=15	n=92	
	- baseline	10.6 (16.7)	4.3 (9.2)	8.9 (16.1)	11.8 (18.5)	
	- 12 months follow-up	8.8 (19.5)	6.4 (15.5)	12.8 (23.9)	12.5 (23.0)	0.57
	Within group P value	0.03	0.991	0.817		
	Emotional reactions ^d	n=61	n=27	n=14	n=90	
	- baseline	16.2 (17.4)	16.3 (17.1)	21.6 (21.1)	16.3 (19.8)	

	- 12 months follow-up	7.1 (14.6) ^{e, f}	6.8 (10.2) ^e	22.0 (31.0)	15.9 (20.3)	0.001
	Within group P value	0.001	0.02	0.886		
	Pain ^d	n=66	n=27	n=15	n=92	
	- baseline	6.8 (11.8)	4.0 (8.5)	5.3 (8.3)	8.5 (15.6)	
	- 12 months follow-up	6.4 (14.7)	5.4 (11.7)	5.5 (7.1)	7.7 (14.5)	0.71
	Within group P value	0.086	0.710	0.721		
	Sleep disturbance ^d	n=62	N=27	N=14	n=89	
	- baseline	30.0 (26.9)	36.3 (31.4)	27.3 (27.1)	30.4 (30.5)	
	- 12 months follow-up	22.1 (28.1)	29.1 (33.9)	34.6 (35.4)	30.1 (33.6)	0.3
	Within group P value	0.002	0.042	0.680		
	Lifestyle impairment ^d	n=65	n=26	n=14	n=82	
	- baseline	2.0 (2.0)	2.4 (1.9)	2.2 (1.9)	1.7 (1.6)	
	- 12 months follow-up	1.3 (1.5) ^e	1.4 (1.5) ^e	1.4 (1.6)	1.9 (1.9)	0.03
	Within group P value	0.061	0.033	0.334		
<i>Remote from MI</i>						
MADIT II ¹⁰⁶	HU13 scores while alive, 36 months	(n=658)		(n=431)		
	Baseline mean	0.637		0.646		
	Baseline overall mean score including death ^g	0.637		0.646		
	Year 1, proportion alive	0.93		0.903		
	- Mean	0.627		0.659		
	- Mean annual change ^h	-0.019		-0.012		
	- Overall mean score including death ^g	0.584		0.595		
	Year 2, proportion alive	0.846		0.792		

	- Mean	0.622	0.667	
	- Mean annual change ^h	-0.027 ⁱ	-0.011	
	- Overall mean score including death ^g	0.526	0.529	
	Year 3, proportion alive	0.767	0.667	
	- Mean	0.601	0.678	
	- Mean annual change ^h	-0.019 ^j	-0.013	
	- Overall mean score including death ^g	0.461	0.452	
<i>Cardiomyopathy</i>				
AMIOVIRT ⁷¹	1 year	(n=51)	Amiodarone plus OPT (n=52)	
	Quality of Well Being Schedule, mean (SD)	74 (19)	70 (22)	0.5 ^k
	State Trait Anxiety Inventory, mean (SD)	61 (17)	67 (20)	0.4 ^k
DEFINITE ⁹⁶		(n= 227)	(n= 226)	
	- Long-term MCS scores ⁹⁶			0.89
	- Long-term PCS scores ⁹⁶			ns
	- Long-term MLHFQ subscale scores ⁹⁶			ns
<i>CABG</i>				
CABG Patch ⁸²	(6 months)	(n=262)	(n= 228)	p value ^l
	HRQoL, mean (SD):			
	Perception of health			
	- general health status	54.8 (22.9)	58.3 (23.6)	ns
	- perception of health transition ^m	2.4 (1.2)	2.1 (1.2)	0.030
	- physical limitations	41.7 (42.3)	49.2 (42.8)	0.055

- bodily pain	57.4 (24.6)		58.8 (24.8)	ns
Ability to Function				
- employment status	0.25 (0.4)		0.29 (0.5)	ns
- physical role functioning	58.3 (27.5)		61.8 (28.3)	ns
- emotional role functioning	55.4 (43.4)		67.3 (39.9)	0.003
- social functioning	70.5 (27.2)		70.8 (26.4)	ns
Psychological well-being				
- mental health	72.5 (18.3)		77.2 (17.0)	0.004
- satisfaction with appearance	6.0 (1.3)		6.3 (1.1)	0.008
- satisfaction with scar	7.0 (1.2)		7.2 (1.1)	0.040
Received a shock prior to completing the 6-month QoL instrument, n/N (%)	101/262 (38.5%)			
Health related quality of life at 6 months, mean (SD) ⁸²	ICD device did not fire (n=161)	ICD device fired (n=101)	OPT (n=228)	OPT vs ICD fired (95% CI) ⁿ
Perception of health				
- general health status	56.6 (23.3)	52.1 (22.1)	58.3 (23.6)	ns
- perception of health transition ^l	2.3 (1.2)	2.5 (1.3)	2.1 (1.2)	(-0.73 to -0.01) ^o
- physical limitations	44.8 (42.9)	36.8 (41.1)	49.2 (42.8)	(0.31 to 24.6) ^p
- bodily pain	57.8 (24.1)	56.8 (25.3)	58.8 (24.8)	ns
Ability to Function				
- employment status	0.30 (0.5)	0.18 (0.4)	0.29 (0.5)	ns

- physical role functioning	61.5 (27.5)	53.2 (27.0)	61.8 (28.3)	(0.7 to 16.6)
- emotional role functioning	59.5 (43.4)	49.1 (42.8)	67.3 (39.9)	(6.2 to 30.1)
- social functioning	71.6 (26.9)	68.8 (27.7)	70.8 (26.4)	ns
Psychological well-being				
- mental health	73.6 (43.4)	70.6 (18.5)	77.2 (17.0)	(1.5 to 11.6)
- satisfaction with appearance	6.0 (1.3)	6.0 (1.4)	6.3 (1.1)	(-0.01 to 0.71)
- satisfaction with scar	7.0 (1.2)	7.1 (1.2)	7.2 (1.1)	ns
Rate of re-hospitalisation prior to date of 6-month QoL	36.0%	55.5%	33.8%	

Heart failure

SCD-Heft ¹⁰⁹	DASI, mean score (SD)	(n= 816)	Amiodarone plus OPT (n= 830) Placebo plus OPT (n= 833)	Difference (95% CI) ^q , p value
	- baseline	(n=814) 24.6 (13.6)	(n=825) 25.3 (14.1) (n=829) 24.9 (14.1)	-0.34 (-1.68 to 1.00)
	- 3 months	(n=766) 26.9 (14.1)	(n=756) 26.2 (14.7) (n=768) 26.2 (14.3)	-0.69 (-0.73 to 2.11)
	- 12 months	(n=734) 26.8 (14.4)	(n=676) 26.1 (14.5) (n=697) 26.6 (14.8)	0.16 (-1.35 to 1.68)
	- 30 months	(n=665) 26.8 (14.3)	(n=575) 27.1 (15.3) (n=585) 25.9 (15.3)	0.89 (-0.75 to 2.53)
	MHI-5	ICDs plus OPT (n= 816)	Amiodarone plus OPT (n= 830) Placebo plus OPT (n= 833)	Difference (95% CI), ^q

- baseline	(n=814) 71.7 (20.5)	(n=827) 72.1 (20.1) (n=830) 70.0 (21.4)	1.64 (-0.39 to 3.67)
- 3 months	(n=764) 74.4 (19.3)	(n=759) 72.9 (20.6) (n=767) 71.3 (21.5)	3.15 (1.10 to 5.19), ≤0.05
- 12 months	(n=734) 74.5 (18.9)	(n=674) 72.9 (20.5) (n=693) 70.9 (21.5)	3.68 (1.58 to 5.78), ≤0.05
- 30 months	(n=654) 72.2 (19.1)	(n=560) 73.2 (20.3) (n=564) 71.0 (21.7)	1.24 (-1.06 to 3.53)
MLHFQ, median		Placebo plus OPT	p value
- baseline	41	43	0.77
- 3 months	30	36	0.006
- 12 months	32	36	0.07
- 30 months	32	36	0.05
Global health status, median		Placebo plus OPT	p value
- 3 months	75	70	0.002
- 12 months	75	70	0.05
- 30 months	70	70	0.18
	(n= 816)		p value
SF-36 score, mean change	Received shock (n=49)	No Shock	
- general health perceptions	-6.3	3.4	0.002
- physical function	-8	10.9	<0.001
- emotional function	-11	4.5	0.02

- social function	-5.3	4.6	0.009
- self-related health	-3.2	6.6	0.009

^a Values in italics obtained from Figure in paper using Engauge software. ^b Unit for outcome not given, assumed to be mean impact (change) in QoL score with 95% CI. ^c Higher values represents better functioning. ^d Higher values represents poorer functioning. ^e Groups that differed significantly from amiodarone without ICD group (P<0.05). ^f Groups that differed from the ICD ≥5 shocks group (p<0.05). ^g Mean HRQoL score (among n patients) after setting score for death to 0; ^h Equals (difference from baseline)/y. ⁱ p<0.05; ^j p<0.10; ^k P values were also reported within groups (not data extracted). ^l P-values for QoL outcomes represent significance of t-tests comparing mean scores of control versus ICD patients. ^m Lower score reflects a tendency to rate health as better now relative to 1 year ago. For all other QoL measures higher scores represent a more favourable score. ⁿ 95% CIs control the experiment-wise Type 1 error rate to be 0.5 using Tukey's method. ^o F test for analysis of variance (ANOVA) has p value of 0.0507. ^p F test for ANOVA has p value of 0.0549. ^q ICD vs placebo reported here. Amiodarone vs placebo can be viewed in data extraction forms (Appendix 8).

4.2.2.11 Adverse Events

All four trials comparing the use of ICDs with AAD in people at increased risk of sudden cardiac death due to previous ventricular arrhythmias reported adverse events (see Table 27).^{73;83;86;91}

Reported adverse events differed between the trials, limiting comparisons. Only the total number of adverse events and mortality rates were compared between the interventions in the DEBUT trial⁹¹ and the AVID⁷³ and CASH⁸³ trials respectively. The DEBUT trial⁹¹ reported that 30% of the ICDs group and 14% of the AAD group suffered adverse events (p not stated). The AVID trial⁷³ compared deaths within 30 days of initiation of therapy or by hospital discharge if 30 days after therapy began, finding no statistically significant difference between the ICDs (2.4%) and AAD (3.5%) groups (p=0.27). In contrast the CASH trial⁸³ found significantly (p=0.029) higher mortality rates during the perioperative period for the ICDs group (5.1%) compared to the AAD group (1.1%). The only other comparison between interventions was in the AVID trial,⁷³ finding that the use of thyroid replacement medication was higher for the AAD group at year 1 (10.0%) and 2 (16.0%) compared with that in the ICD group (year 1 and 2 1.0%) (p not stated).

Analysis of the adverse events reported for the ICDs groups in the four trials showed that these tended to be limited in occurrence (see Table 27).^{73;83;86;91} The most frequent were those related to the placement and operation of the device itself, including: defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia (19%);⁹¹ T-wave oversensing (8%);⁹¹ ICD product discomfort (7.6%);⁸⁶ ICD permanently or temporarily explanted due to infection, heart transplantation or patient preference (5%);⁸⁶ device dysfunction (5%);⁸³ pocket erosion requiring removal of ICD (3%);⁹¹ dislodgement or migration of system leads (3%);⁸³ ICD dislodgement/fracture (2.4%);⁸⁶ bleeding requiring reoperation or transfusion (1.2%);⁷³ and, unsuccessful first attempt at ICD implantation without thoracotomy (1.0%).⁷³ Other adverse events included: haematoma or seroma (6%);⁸³ serious haematoma (2.6%);⁷³ pleural effusion (3%);⁸³ infection (2.0% to 4.6%);^{73;86} and, pneumothorax (1.6%).⁷³

Adverse events reported for the AAD groups differed between the four trials (see Table 27).^{73;83;86;91} The CIDs trial⁸⁶ found that over 10% of people receiving amiodarone reported insomnia (19.3%), ataxia (17.2%), tremor (15.4%), visual symptoms (14.5%) or photosensitivity (10.3%). Other adverse events reported in the CIDs trial⁸⁶ included skin discolouration (6.3%) and pulmonary infiltrate (5.7%). In the CASH trial⁸³ 10% of people receiving amiodarone (9.8%) or metoprolol (10.3%) had to discontinue drug treatment. The AVID trial⁷³ reported that 5% of the AAD group had suspected pulmonary toxicity at two years. Other adverse events reported by the AVID,⁷³ CASH⁸³ and DEBUT⁹¹ trials affected under 5% of participants (see Table 27).

All nine trials comparing ICDs plus OPT with the differing comparator treatments in people who had not suffered a life-threatening arrhythmia but were at increased risk reported adverse events,^{71;77;84;92;97;99;101;103;107} with six trials focused predominantly on those related to the placement of ICDs (see Table 27).^{71;84;92;97;99;103} The type of adverse events reported differed between the trials, making comparisons difficult. Adverse events were thought to affect between 5%¹⁰⁷ and 61%⁷⁷ of people receiving an ICD, depending on the definition of an adverse event or complication and the period of follow-up. Only three trials reported adverse events for the different comparator treatments with rates varying from 12% to 55%.^{77;101;107}

Mortality rates associated with implantation of an ICD appeared low, with no deaths reported by four trials^{84;97;101;103} and crude death rates ranging from 1.6% to 5.4% in the IRIS⁹⁹ and CABG-Patch⁷⁷ trials respectively. Deaths among those receiving the comparator treatments were only reported in the CABG-Patch trial⁷⁷ with a crude death rate for the OPT group of 4.4%.

Lead, electrode or defibrillator generator related problems were reported in five trials,^{84;92;99;101;103} affecting between 1.8% and 14.0% of people. In the IRIS trial,⁹⁹ these led to surgical revision rates of 2.4%. Surgical or device related infections were reported in four trials affecting between 0.4% and 12.3% of people in the ICDs group,^{77;84;92;101} leading in three trials to surgical intervention or device removal/replacement in 0.7% to 4%.^{84;103;107}

Other non-device specific adverse events were reported by four trials.^{77;84;92;101} In the MADIT I¹⁰¹ and SCD-Heft⁷⁷ trials only syncope (5%) and hypothyroidism (6%) affected $\geq 5\%$ of people in the comparator groups. The CABG-Patch trial⁷⁷ reported adverse events in the post-operative period and following long-term follow-up for both the ICDs plus OPT and OPT groups, focusing predominantly on changes in underlying cardiac conditions. In the post-operative period the CABG-Patch trial⁷⁷ reported event rates $\geq 5\%$ for the ICDs plus OPT and/or OPT groups for atrial fibrillation (ICDs plus OPT 22.9%, OPT 20.7%), new or severe heart failure (ICDs plus OPT 15.7%, OPT 12.6%), conduction defect (ICDs plus OPT 14.1%, OPT 14.5%), sustained ventricular tachycardia (ICDs plus OPT 5.8%, OPT 6.8%), shock (ICDs plus OPT 9.2%, OPT 7.5%), pneumonia (ICDs plus OPT 8.5%, OPT 4.0%) and renal failure (ICDs plus OPT 6.7%, OPT 4.8%).⁷⁷ Events during long-term follow-up that affected $\geq 5\%$ of the ICDs plus OPT and/or OPT groups included new or worsening heart failure (ICDs plus OPT 42.5%, OPT 42.5%), angina pectoris (ICDs plus OPT 27.0%, OPT 27.5%), ventricular arrhythmias (ICDs plus OPT 19.4%, OPT 14.3%), and atrial fibrillation (ICDs plus OPT 14.7%, OPT 10.1%).

Table 27: Adverse events

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)		P value
<i>Cardiac arrest (secondary prevention)</i>					
AVID ⁷³	Non-fatal torsade-de-pointes ventricular tachycardia		1/509 (0.2)		
	Suspected pulmonary toxicity, % - at 1 year		3		
	- at 2 years		5		
	Death due to pulmonary toxicity		1/509 (0.2)		
	Thyroid replacement medication, % - at 1 year	1	10		
	- at 2 years	1	16		
	Death within 30 days of initiation of therapy ^a	12/507 (2.4)	18/509 (3.5)		0.27
	Bleeding requiring reoperation or transfusion	6/507 (1.2)			
	Serious haematoma	13/507 (2.6)			
	Infection	10/507 (2.0)			
	Pneumothorax	8/507 (1.6)			
	Cardiac perforation	1/507 (0.2)			
	Early dislodgment or migration of leads	3/507 (0.6)			
Unsuccessful first attempt at ICD implantation without thoracotomy	5/507 (1.0)				
Overall rate of nonfatal complications of implantation, %	5.7				
CASH ⁸³			Amiodarone	Metoprolol	
	- Drug related pulmonary toxicity		0/92 (0)		
	- Hyperthyroidism		3/92 (3.3)		

Study	Outcome, follow-up	ICD, n/N (%)		OPT, n/N (%)		P value
	- Drug discontinuation required			9/92 (9.8)	10/97 (10.3)	
	- Perioperative deaths, or for drug arms deaths within the same time frame	All ICDs 5/99 (5.1)		AAD 2/189 (1.1)		0.029
		epicardial ICDs 3/99 (5.4)	endocardial ICDs 2/99 (4.5)	Amiodarone 2/92 (2.2)	Metoprolol 0/0 (0)	
	Other complications - Infection	3/99 (3.0) (explantation required for 2)				
	- Haematoma or seroma	6/99 (6.1)				
	- Pericardial effusion	1/99 (1.0)				
	- Pleural effusion	3/99 (3.0)				
	- Pneumothorax	1/99 (1.0)				
	- Dislodgement or migration of system leads	3/99 (3.0)				
	- Device dysfunction	5/99 (5.1)				
	Overall complication rate	23.0% (including an explantation rate of 2.1%)				
CIDS ⁸⁶	30 day mortality in implanted patients (n=310)					
	- in patients with thoracotomy (n=33)	1/33 (3.0)				
	- in patients with non-thoracotomy lead system (n=277)	1/277 (0.4)				
	ICD permanently or temporarily explanted due to infection, heart transplantation or patient preference	16/310 (5.2)				

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	P value
	Adverse experiences ever reported:			
	Pulmonary infiltrate		18/331 (5.7) (1.9% per yr)	
	Visual symptoms (blurred, halo or decreased)		48/331 (14.5)	
	Bradycardia		10/331 (3.0)	
	Skin discolouration		21/331 (6.3)	
	Photosensitivity		34/331 (10.3)	
	Ataxia		97/331 (17.2)	
	Tremor		91/331 (15.4)	
	Insomnia		64/331 (19.3)	
	Peripheral neuropathy		1/331 (0.3)	
	ICD product discomfort	25/328 (7.6)		
	ICD malfunction	2/328 (0.6)		
	ICD pocket infection	15/328 (4.6) (1.4% per yr)		
	ICD dislodgement/fracture	8/328 (2.4)		
DEBUT ⁹¹	Operative mortality	0/0 (0)		
- pilot study	Adverse effects, n (%)	2/10 (20.0)		
	- defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia	1/10 (10.0)		
	- T-wave oversensing	0/0 (0)		
	ICD replaced because of insulation break	1/10 (10.0)		

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	P value
DEBUT ⁹¹ -main study	Operative mortality	0/0 (0)		
	Adverse effects, n (%)	11/37 (30)	4/29 (14)	
	Minor complications, corrected by reprogramming devices without major intervention, n			
	- defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia	7/37 (19.0)		
	- T-wave oversensing	3/37 (8.1)		
	Pocket erosion requiring removal of ICD	1/37 (2.7)		
Side-effects in B-Blocker group: - Impotence / decrease in libido			1/29 (3.4)	
	- Fatigue		1/29 (3.4)	
	- Profound bradycardia		1/29 (3.4)	
	- Hypotension plus central nervous system side effect		1/29 (3.4)	
<i>Early post MI</i>				
DINAMIT ⁹⁷	Number of death related to device implantation	0/310 (0)		
	In-hospital device-related complications	25/310 (8.1)		
IRIS ⁹⁹	Died within 30 days after implantation	7/415 (1.7) (n=4 MI, n=3 HF)		
	Died within 30 days of randomisation	9/415 (2.2)	11/453 (2.4)	
	Number of ICDs actually implanted	415	39 (median 7.6 months after randomisation)	
	Inserted lead entangled in tricuspid valve, removed surgically	1/415 (0.2)		

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	P value
	ICD explanted or permanently deactivated during follow-up (median 6.8 months after implantation)	14/415 (3.4)		
	Clinically significant complications requiring hospitalisation, surgical correction, or intravenous drug administration	65/415 (15.7) 76 complications		
	- up to 30 days after implantation	19/415 (4.6)		
	- during follow-up	48/415 (11.6)		
	Lead related problems requiring surgical revision (included in the above complications)	10/415 (2.4) (4 had lead replacements)		
<i>Remote from MI</i>				
MADIT I ¹⁰¹	Operative deaths in the first 30 days	0/95 (0)	0/101 (0)	
	Hypotension	0/95 (0)	1/101 (1.0)	
	Syncope	1/95 (1.1)	5/101 (5.0)	
	Hypothyroidism	0/95 (0)	1/101 (1.0)	
	Sinus bradycardia	3/95 (3.2)	3/101 (3.0)	
	Pulmonary fibrosis	0/95 (0)	3/101 (3.0)	
	Pulmonary embolism	1/95 (1.1)	1/101 (1.0)	
	Atrial fibrillation	4/95 (4.2)	0/101 (0)	
	Pneumothorax	2/95 (2.1)	0/101 (0)	
	Bleeding	1/95 (1.1)	0/101 (0)	
	Venous thrombosis	1/95 (1.1)	0/101 (0)	
	Surgical infection	2/95 (2.1)	0/101 (0)	

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	P value
	Problems with defibrillator lead	7/95 (7.4)	0/101 (0)	
	Malfunction of defibrillator generator	3/95 (3.2)	2/101 (2.0)	
	Total number of patients with adverse events	19/95 (20.0)	12/101 (12.0)	
MADIT II ¹⁰³	Adverse effects of treatment, death during implantation, n	0/742 (0)		
	Lead problems, n (%)	13/742 (1.8)		
	Non-fatal infections requiring surgical intervention, n (%)	5/742 (0.7)		
<i>Cardiomyopathy</i>				
AMIOVIRT ⁷¹	Discontinued amiodarone due to adverse effects, mean 17.8 months (SD 13.3)		25/52 (48.1)	
CAT ⁸⁴	Complications caused by ICD therapy			
	- deaths within 30 days of ICD implantation	0/50 (0)		
	- device dislocation & bleeding requiring revision	2/50 (4)		
	- electrode dislocation requiring revision	2/50 (4)		
DEFINITE ⁹²	Complications during implantation of ICD	3/229 (1.3)		
	- hemothorax	1/229 (0.4)		
	- pneumothorax	1/229 (0.4)		
	- cardiac tamponade	1/229 (0.4)		
	Procedure related deaths	0/229 (0)		

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	P value
	Complications during follow-up	10/229 (4.4)		
	- lead dislodgement or fracture	6/229 (2.6)		
	- venous thrombosis	3/229 (1.3)		
	- infection	1/229 (0.4)		
	Receipt of ICD upgrade during follow-up	13/229 (5.7)		
	- dual chamber ICD due to development of sinus-node dysfunction	2/229 (0.9)		
	- biventricular devices for NYHA class III or IV heart failure and prolonged QRS interval	11/229 (4.8)		
<i>Scheduled for CABG</i>				
CABG Patch ⁷⁷	Deaths in the first 30 days after randomisation	24/446 (5.4)	20/454 (4.4)	0.60
	Postoperative complications			
	- myocardial infarction	18 ^b /446 (4.0)	16 ^b /454 (3.5)	
	- sustained ventricular tachycardia	26 ^b /446 (5.8)	30 ^b /454 (6.8)	
	- ventricular fibrillation	15 ^b /446 (3.4)	24 ^b /454 (5.3)	
	- bradycardia	13 ^b /446 (2.9)	20 ^b /454 (4.4)	
	- atrial fibrillation	102 ^b /446 (22.9)	94 ^b /454 (20.7)	
	- shock	41 ^b /446 (9.2)	34 ^b /454 (7.5)	
	- new or more severe heart failure	70 ^b /446 (15.7)	57 ^b /454 (12.6)	
	- conduction defect	63 ^b /446 (14.1)	66 ^b /454 (14.5)	
	- residual central nervous system deficit	16 ^b /446 (3.6)	9 ^b /454 (2.0)	
	- bleeding treated with surgery	22 ^b /446 (4.9)	14 ^b /454 (3.1)	

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	P value
	- postpericardiotomy syndrome	4 ^b /446 (0.9)	3 ^b /454 (0.7)	0.01<p<0.05
	- deep sternal-wound infection	12 ^b /446 (2.7)	2 ^b /454 (0.4)	
	- infection at wound or catheter site	55 ^b /446 (12.3)	27 ^b /454 (5.9)	
	- pneumonia	38 ^b /446 (8.5)	18 ^b /454 (4.0)	
	- other infection	28 ^b /446 (6.3)	15 ^b /454 (3.3)	
	- renal failure	30 ^b /446 (6.7)	22 ^b /454 (4.8)	
	Events during long-term follow-up			0.01<p<0.05
	- angina pectoris	120 ^b /446 (27.0)	125 ^b /454 (27.5)	
	- myocardial infarction	2 ^b /446 (0.5)	19 ^b /454 (4.2)	
	- new or worsening heart failure	190 ^b /446 (42.5)	193 ^b /454 (42.5)	
	- ventricular arrhythmias	87 ^b /446 (19.4)	65 ^b /454 (14.3)	
	- atrial fibrillation	66 ^b /446 (14.7)	46 ^b /454 (10.1)	
	- hospitalisation	274 ^b /446 (61.4)	251 ^b /454 (55.2)	
	- repeat CABG surgery	0/446 (0.0)	3 ^b /454 (0.7)	
- PTCA or atherectomy	13 ^b /446 (2.9)	10 ^b /454 (2.1)		
- permanent cardiac pacemaker	13 ^b /446 (2.9)	22 ^b /454 (4.9)		
ICD removed	40/446 (9.0)			
- infection	19/446 (4.3)			
- ICD reached end of service period and not replaced	5/446 (1.1)			
- patient request	5/446 (1.1)			
<i>Heart Failure</i>				
SCD-Heft ¹⁰⁷		(n= 829)	Amiodarone plus OPT	

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	P value
			(n= 845) Placebo plus OPT (n= 847)	
	Implantation was unsuccessful, n	1/829 (0.1)		
	ICD removed during follow-up, n	32/829 (3.9)		
	Clinically significant ICD complications, ^c			
	- at time of implantation	5%		
	- later in the course of follow-up	9%		
	Increased tremor (amiodarone compared with placebo), at time of last follow-up		4%	
	Increased hypothyroidism (amiodarone compared with placebo), at time of last follow-up		6%	

^aOr by the time of hospital discharge if discharge occurred later than 30 days after therapy began. ^b Calculated from percentages by reviewer. ^c Defined as clinical events requiring surgical correction, hospitalisation, or new and otherwise unanticipated drug therapy.

4.2.2.12 Subgroup analyses reported by included RCTs

Six trials reported pre-specified subgroup analyses,^{73;77;92;99;105;107} although it should be noted that the trials were not powered to detect differences in subgroups.

The AVID trial⁷³ of people at increased risk of sudden cardiac death due to previous ventricular arrhythmias, presented four pre-specified subgroup analyses for all-cause mortality in a figure (age, LVEF, cause of arrhythmia and qualifying arrhythmia). No subgroup differed significantly from each other or the overall population. For most of the subgroups the 95% CIs crossed 1.0, apart from those for LVEF \leq 35%, cause of arrhythmia coronary artery disease and VF rhythm, which favoured ICD. Subgroup analyses for the index arrhythmia were also reported (baseline VF n=455; VT n=561).⁷⁴ ICDs improved survival free of arrhythmic death for people whose presenting arrhythmia was VT (p=0.025) or VF (p=0.0019). For nonarrhythmic cardiac death, there were no statistically significant differences in survival between ICD and AAD groups in people presenting with either VT (p=0.72) or VF (p=0.98).

The IRIS trial,⁹⁹ which included people in the early period post MI, pre-specified 13 subgroup analyses for all cause-mortality, nine of which were presented in a figure (age, gender, congestive heart failure on admission, criterion of inclusion (for definitions see Appendix 8), ST-elevation MI, early reperfusion for ST-elevation MI, number of vessels, smoking and NYHA class at discharge) and four of which were not presented but described as similar in the two study groups (diabetes, hypertension, lipid abnormalities, number of risk factors). For most of the subgroups the 95% CIs crossed 1.0, apart from those for thrombolytic therapy for early reperfusion of ST-elevation MI (favoured control, data in figure only) and left main artery (favoured ICD, data in figure only).

In people remote from their MI, the MADIT II trial¹⁰⁵ reported pre-specified subgroup analyses for all-cause mortality using baseline characteristics, five of which were presented in a figure only (age, gender, ejection fraction, NYHA class or QRS interval) and seven of which were not presented (hypertension, diabetes, left bundle-branch block, atrial fibrillation, the interval since the most recent MI, type of ICD, and blood urea nitrogen). The hazard ratios in all of the subgroups were similar, with no statistically significant interactions.

The DEFINITE trial,⁹² which included people with cardiomyopathy, presented six pre-specified subgroup analyses in a figure only (age, sex, LVEF, QRS interval, NHYA class and history of atrial fibrillation) for all-cause mortality. None of the differences between subgroups were statistically significant. For most of the subgroups the 95% CIs crossed 1.0, apart from those for men (RR 0.49,

95% CI 0.27 to 0.90, $p=0.018$), NYHA class III (RR 0.37, 95 % CI 0.15 to 0.90, $p=0.02$) and LVEF $\geq 20\%$ (favoured ICD, data in figure only).

The CABG Patch trial in people who were scheduled for a CABG⁷⁷ evaluated 10 pre-specified subgroups (age, gender, heart failure, NYHA class, LVEF, diabetes mellitus, QRS complex duration, use of ACE inhibitors, use of class I or class III antiarrhythmic drugs, and use of beta-adrenergic-blocking drugs). Hazard ratios for the ICD group compared with the control group were found to be similar among the subgroups for all-cause mortality (data not reported).

The SCD-HeFT trial in people with mild to moderate heart failure reported pre-specified subgroup analyses for all-cause mortality¹⁰⁷ and cause of death¹¹⁰ according to cause of congestive heart failure (ischaemic or nonischaemic) and NYHA class (class II or III), and also according to race¹⁰⁸ for all-cause mortality. Table 28 presents results for ICD versus placebo; subgroup results for the comparisons of amiodarone versus placebo can be seen in Appendix 8.

There was no interaction of ICD therapy ($p=0.68$) with the cause of congestive heart failure for all-cause mortality.¹⁰⁷ The HRs for those with ischaemic and non-ischaemic congestive heart failure were 0.79 (97.5% CI 0.60 to 1.04, $p=0.05$) and 0.73 (97.5% CI 0.50 to 1.07, $p=0.06$), respectively. Similarly, there was no significant interaction of ICD with the cause of congestive heart failure for each of the specified modes of death¹¹⁰ (Table 28). A significant reduction in sudden death presumed to be ventricular tachyarrhythmic was found for both ischaemic (HR 0.43, 95% CI 0.27 to 0.67) and non-ischaemic (HR 0.34, 95% CI 0.17 to 0.70) causes of congestive heart failure, whereas no significant reduction in other modes of death was found for either subgroup (Table 28).

There was a statistically significant interaction between ICD therapy and NYHA class ($p<0.001$).¹⁰⁷ Compared with placebo, ICDs reduced the risk of death in people with NYHA class II (HR 0.54, 97.5% CI, 0.40 to 0.74, $p<0.001$), but not in those with NYHA class III (HR 1.16, 97.5% CI, 0.84 to 1.61, $p=0.30$). The interaction between ICD therapy and NYHA class was statistically significant for cardiac mortality ($p=0.0004$) and sudden death presumed to be ventricular tachyarrhythmic ($p=0.0091$), but not for heart failure ($p=0.29$) or noncardiac ($p=0.11$) deaths.¹¹⁰ ICD therapy reduced the risk of cardiac mortality (HR 0.50, 95% CI 0.36 to 0.70) and sudden tachyarrhythmic death (HR 0.26, 95% CI 0.15 to 0.44) in people with NYHA class II, but not in those with NYHA class III (HR 1.17, 95% CI 0.84 to 1.64; and HR 0.73, 95% CI 0.41 to 1.29, respectively).

There was no significant interaction between ICD therapy and race ($p=0.53$); ICD therapy reduced the risk of death in both racial groups (African Americans HR 0.65, 95% CI, 0.43 to 0.99; whites HR 0.73 95% CI, 0.58 to 0.90).¹⁰⁸

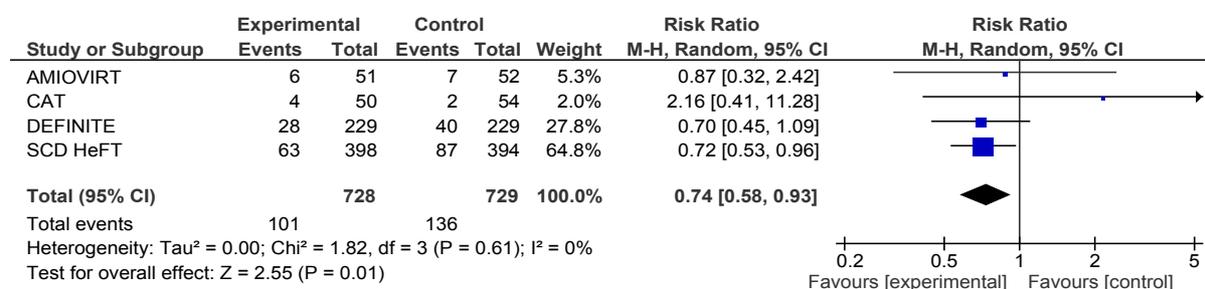
Table 28: SCD-HeFTsubgroups

Subgroup and outcome	HR ICD vs placebo (95% or 97.5%^a CI), p value
Ischemic CHF	
All-cause mortality ¹⁰⁷	0.79 (0.60 to 1.04 ^a), 0.05
Cause of death ¹¹⁰	
- cardiac	0.80 (0.60 to 1.05)
- sudden tachyarrhythmic	0.43 (0.27 to 0.67)
- heart failure	1.11 (0.74 to 1.67)
- noncardiac	0.79 (0.50 to 1.22)
Non-ischaemic CHF	
All-cause mortality ¹⁰⁷	0.73 (0.50 to 1.07 ^a), 0.06
Cause of death ¹¹⁰	
- cardiac	0.68 (0.44 to 1.03)
- sudden tachyarrhythmic	0.34 (0.17 to 0.70)
- heart failure	1.21 (0.67 to 2.18)
- noncardiac	0.81 (0.48 to 1.37)
NYHA II	
All-cause mortality ¹⁰⁷	0.54 (0.40 to 0.74 ^a), <0.001
Cause of death ¹¹⁰	
- cardiac	0.50 (0.36 to 0.70)
- sudden tachyarrhythmic	0.26 (0.15 to 0.44)
- heart failure	0.93 (0.56 to 1.54)
- noncardiac	0.63 (0.40 to 0.99)
NYHA III	
All-cause mortality ¹⁰⁷	1.16 (0.84 to 1.61 ^a), 0.30
Cause of death ¹¹⁰	
- cardiac	1.17 (0.84 to 1.64)
- sudden tachyarrhythmic	0.73 (0.41 to 1.29)
- heart failure	1.34 (0.86 to 2.09)
- noncardiac	1.10 (0.66 to 1.85)
Race: African American	
All-cause mortality ¹⁰⁸	0.65 (95% CI 0.43 to 0.99)
Race: white	
All-cause mortality ¹⁰⁸	0.73 (95% CI 0.58 to 0.90)

^a 97.5% CI. CHF = congestive heart failure.

Combining data from the SCD-Heft¹⁰⁷ non-*ischaemic* congestive heart failure subgroup with data from the three cardiomyopathy trials (AMIOVIRT,⁷¹ CAT,⁸⁴ DEFINITE⁹²) was considered appropriate by clinical experts. SCD-Heft¹⁰⁷ did not report the number of events for all-cause mortality occurring in each of the *ischemic* and non-*ischemic* subgroups, therefore these were estimated by reviewers and data from the non-*ischaemic* subgroup were combined in a meta-analysis (Figure 9). The SCD-Heft non-*ischemic* subgroup strongly influenced the analysis, and a statistically significant effect in favour of ICD with no statistical heterogeneity was found (RR 0.74, 95% CI 0.58 to 0.93, *p*=0.01). This in contrast to the non-significant result of meta-analysis of the three cardiomyopathy trials alone (Figure 4).

Figure 9: All-cause mortality, cardiomyopathy RCTs and SCD-Heft nonischemic CHF subgroup



4.2.3 Other relevant trials

Two trials (MUSTT,¹⁴⁷ 1999 and MAVERIC,¹⁴⁸ 2004) were excluded as the intervention did not meet the scope of the present review (many participants in the intervention arm did not receive ICD); however, these trials presented subgroup data comparing ICD versus no ICD that may be considered relevant. MUSTT and MAVERIC have not undergone formal data extraction and quality assessment but are presented here for information.

MUSTT was included in the previous TARs,^{65;66} although the authors noted that it did not meet their inclusion criteria if strictly applied (in that randomisation determined electrophysiological guided therapy not ICD therapy). The authors also state that caution should be used when assessing the results as the study did not randomise participants to drug therapy or ICD, and has the potential for bias and confounding of results.⁶⁵

The MUSTT study was designed to test the hypothesis that electrophysiological (EP) testing guided anti-arrhythmic therapy reduces sudden cardiac death. People with sustained, monomorphic ventricular tachycardia induced by any method of stimulation and those with sustained polymorphic

ventricular tachycardia (including ventricular flutter and fibrillation) induced by one or two extra stimuli were randomly assigned in equal numbers to receive either antiarrhythmic therapy guided by the results of EP testing or no antiarrhythmic therapy. ICD could be recommended for people randomised to EP testing after at least one unsuccessful drug test. Median follow-up was 39 months. Beta-blocker use was significantly higher in the no-therapy group (EP testing 29%, no therapy 51%, $p=0.001$).

All-cause mortality was significantly reduced in the ICD group compared with EP guided therapy without a defibrillator, RR 0.42 (95% CI, 0.29 to 0.61; $p<0.001$) and compared with no therapy, RR 0.49 (95% CI, 0.35 to 0.69; $p<0.001$).¹⁴⁷ The overall mortality rates at five years were 24% among patients who received a defibrillator and 55% among those who did not.

The risk of death from cardiac arrest or arrhythmia was significantly reduced in patients who received an ICD compared with those with EP-guided therapy without a defibrillator, RR 0.24 (95% CI, 0.13 to 0.43; $p < 0.001$) and compared with patients with no therapy, RR 0.28 (95% CI, 0.16 to 0.49; $p < 0.001$).¹⁴⁷

MAVERIC was in progress at the time of the previous TAR.⁶⁵ The multi-centre UK study was designed to test the possibility of prospectively identifying patients who would benefit most from ICD by electrophysiology study (EP) in the context of secondary prevention of sudden cardiac death. Survivors of sustained ventricular tachycardia, ventricular fibrillation or sudden cardiac death were randomised to EP-guided interventions (anti-arrhythmic drugs, coronary revascularisation and ICD) or empirical amiodarone therapy, with pre-stratification for haemodynamic status at index event. Median follow-up was 60 months.

Subgroup analysis was presented for ICD recipients versus non-ICD recipients, regardless of allocated treatment. As with the MUSTT trial, these results must be viewed with caution due to the lack of randomisation and possibility of bias and confounding. An ICD was received by 31 of 108 (29%) of patients randomised to EP [14/60 (23%) patients haemodynamically stable and 17/48 (35%) patients haemodynamically unstable at index event] and 5 of 106 (5%) patients randomised to amiodarone [4/62 (6%) patients haemodynamically stable and 1/44 (2%) patients haemodynamically unstable at index event]. ICD recipients were significantly younger [62.7 years (SD 9.0) vs 68.1 years (SD 9.8), $p=0.002$] and less likely to have diabetes (5.3% vs 18.8%, $p=0.042$) than non-ICD recipients; other baseline characteristics were similar.

Survival was significantly better in ICD recipients than non-ICD recipients [HR 0.54 (0.30 to 0.97, definition of interval not stated), $p=0.0391$]. Comparisons of ICD recipients versus non-ICD

recipients were also presented separately for patients haemodynamically stable [HR 0.71 (0.29 to 1.75, definition of interval not stated), $p=0.4537$] and unstable [HR 0.42 (0.20 to 0.92, definition of interval not stated), $p=0.0299$] at index event. Multivariate analysis on factors affecting survival found ICD implantation was associated with a non-statistically significant reduction in risk of death [OR 0.43 (0.17 to 1.11, definition of interval not stated), $p=0.080$].

4.2.4 Summary of clinical effectiveness: people at risk of sudden cardiac death as a result of ventricular arrhythmias

- A total of 13 RCTs were included comparing ICDs with medical therapy in people at risk of sudden cardiac death due to arrhythmias. The trials were synthesised according to the criteria they used to identify people at risk of sudden cardiac death.
- Risk of bias: as it was not possible to blind participants and personnel in these trials, they were judged to have a high risk of performance bias. Trials were judged to have a low risk of detection bias as assessment of mortality is unlikely to be influenced by lack of blinding, however the risk of detection bias is high for QoL outcomes. Five trials were judged to have a low risk of selection bias, but this was unclear in eight trials due to inadequate reporting.

Ventricular arrhythmia/cardiac arrest (secondary prevention)

- Four RCTs compared the effectiveness of ICDs with AAD. Average length of follow-up differed from 18 months to 57 months and sample sizes ranged from 66 to 1016. The proportion of participants with congestive heart failure differed. In two trials 100% of participants had congestive heart failure, with >80% in NYHA I and II. In the other 2 trials between approximately 60% and 90% had congestive heart failure with approximately 50% in both trials in NYHA I and II. LVEF also varied from 30% to 70% across all four studies.
- All four RCTs assessed all-cause mortality as the primary outcome measure, which when combined through meta-analysis was shown to be statistically significant (RR 0.75, 95% CI, 0.61 to 0.93; $p=0.01$). Differences were found in the 4 RCTs on the outcome of sudden cardiac/arrhythmic deaths, with statistically significant benefit for ICDs compared with AAD when combined through meta-analysis (RR 0.49, 95% CI, 0.34 to 0.69; $p<0.0001$).
- Meta-analysis of two trials showed statistically significant benefit for ICDs compared with AAD on total cardiac deaths (RR 0.74, 95% CI, 0.61 to 0.91; $p=0.004$), however no differences were found on non-arrhythmic cardiac deaths (RR 0.97, 95% CI, 0.72 to 1.31; $p=0.83$) or other non-cardiac causes of death (RR 0.79, 95% CI, 0.45 to 1.37; $p=0.40$). Two RCTs reported different measures of survival, finding statistically significant benefit for ICDs

compared with AAD on overall survival at 3 years (difference 11%, $p < 0.02$), survival free of cardiac death at 2 years (difference 4%, $p = 0.004$), survival to arrhythmic death at 2 years (difference 5%, $p = 0.0002$) in one trial, and survival free of sudden death at 57 months (HR 0.423, $p = 0.005$) in the other trial. One RCT found lower cumulative mortality annually over 3 years follow-up with ICD (difference year 1 14.5%, year 2 1.7%, year 3 4.1%).

- Two RCTs assessed quality of life through separate sub-studies on a range of measures. On one RCT there were no significant between group differences at follow-up. A second RCT found that QoL improved significantly for ICDs on 3 domains of MHI and 5 domains on NHP, while there were no changes for OPT. In this trial the QoL of those experiencing ≥ 5 ICD shocks did not differ significantly on MHI and NHP from the OPT group. The no shocks and 1-4 shocks group had significant improvements on MHI and NHP compared with the OPT group.
- One trial reported prespecified subgroup analyses for all-cause mortality. The subgroups for age, LVEF, cause of arrhythmia and qualifying arrhythmia did not differ significantly from each other or the overall population for all-cause mortality.

People with a recent myocardial infarction (within 6 to 41 days, or 31 days or less)

- Two RCTs compared ICD plus OPT with OPT. Length of follow-up ranged from an average of 30 and 37 months and sample sizes from 674 to 898. About 60% of participants in both trials were in NYHA class II, but the majority of the remaining participants had NYHA class III symptoms in one trial and NYHA class I symptoms in the other trial. Similarly, mean LVEF differed between the studies (28% and 35%), reflecting different eligibility criteria.
- Meta-analysis of the two trials found no difference in all-cause mortality (RR 1.04, 95% CI, 0.86 to 1.25; $p = 0.69$), total cardiac deaths (RR 0.97, 95% CI, 0.79 to 1.20; $p = 0.8$) or non-cardiac deaths (RR 1.39, 95% CI, 0.86 to 2.27; $p = 0.18$). People with ICD plus OPT had a lower risk of sudden cardiac death (RR 0.45, 95% CI, 0.31 to 0.64; $p < 0.0001$), but a higher risk of non-arrhythmic cardiac death (RR 1.77, 95% CI, 1.30 to 2.40; $p = 0.0002$). One trial reporting cumulative mortality found no statistically significant difference between groups. QoL was not reported.
- One trial reported pre-specified subgroup analyses for all cause-mortality. No significant differences were found for the 13 pre-specified subgroups.

People with remote myocardial infarction (more than three weeks or one month previously)

- Two RCTs compared ICD plus OPT with OPT, although the pharmacological therapy in one of these may not be considered optimal by current standards. Average length of follow-up

was between 27 and 20 months, and sample size was 196 and 1232. About two-thirds of participants had NYHA class II or III symptoms and one-third had NYHA class I symptoms. Mean LVEF differed between the studies (about 26% and 23%), reflecting different eligibility criteria.

- Meta-analysis of the two trials found a reduction in all-cause mortality (RR 0.57, 95% CI, 0.33 to 0.97; $p=0.04$), total cardiac deaths (RR 0.59, 95% CI, 0.42 to 0.83; $p=0.003$) and sudden cardiac death (RR 0.36, 95% CI, 0.23 to 0.55; $p<0.00001$) with ICD plus OPT compared with OPT. There was no difference in non-arrhythmic cardiac death (RR 0.95, 95% CI, 0.41 to 2.18; $p=0.9$) or non-cardiac death (RR 1.06, 95% CI, 0.58 to 1.95; $p=0.84$) between groups. One trial reporting hospitalisations found higher rates per 1000 months follow-up among people with ICDs (11.3 vs 9.4, $p=0.09$), with higher heart failure hospitalisations (19.9% vs 14.9%, $p=nr$).
- In one trial that assessed QoL with HU13, scores were lower in people with ICD plus OPT than with OPT at baseline. Differences were not statistically significant between groups at 3 years follow-up.
- One trial reported pre-specified subgroup analyses for all-cause mortality. The hazard ratios in all 12 of the subgroups were similar, with no statistically significant interactions.

People with non-ischemic or idiopathic dilated cardiomyopathy

- Three RCTs compared ICD plus OPT versus OPT, or ICD plus OPT versus amiodarone plus OPT. Mean follow-up was between 24 months (2 RCTs) to 29 months, and sample size was 103 to 458 participants. One trial enrolled people with recent onset of disease. Over half to two-thirds of participants were in NYHA class II; in one trial the remaining participants were in NYHA class III, but in two trials around 15 to 21% were in NYHA class I. Mean LVEF ranged between 21% to 25%.
- Meta-analysis found no significant difference in all-cause mortality (RR 0.77, 95% CI, 0.52 to 1.15; $p=0.20$), total cardiac deaths (RR 2.03, 95% CI, 0.17 to 23.62; $p=0.57$), non-arrhythmic cardiac death (RR 1.13, 95% CI, 0.42 to 3.03; $p=0.81$) or non-cardiac death (RR 0.65, 95% CI, 0.13 to 3.29; $p=0.60$). However a reduction was found in sudden cardiac deaths (RR 0.26, 95% CI, 0.09 to 0.77; $p=0.02$) with ICD.
- Two trials reported no significant difference in survival.
- Two trials reported no significant differences in QoL, assessed using the QWBS and STAI or the SF-12 MCS and PCS, and MLHFQ.
- One trial reported six pre-specified subgroup analyses for all-cause mortality. None of the differences between subgroups were statistically significant.

- Meta-analysis of the three cardiomyopathy trials and the non-ischaemic congestive heart failure subgroup of SCD-HeFT found a statistically significant reduction in all-cause mortality (RR 0.74, 95% CI 0.58 to 0.93, p=0.01) with ICD.

People scheduled for CABG surgery

- One trial compared ICD plus OPT versus OPT, although the pharmacological therapy would not be considered optimal by current standards. Mean follow-up was 32 months and 900 participants were randomised. The majority of participants were in NYHA class II or III, and mean LVEF was 27%.
- No significant difference was found in all-cause mortality (RR 1.08, 95% CI, 0.85 to 1.38; p=0.53), total cardiac deaths (HR 0.97, 95% CI, 0.71 to 1.33, p=0.84), non-arrhythmic cardiac death (HR 1.24, 95% CI, 0.84 to 1.84; p=0.28), non-cardiac death (RR 1.50, 95% CI, 0.82 to 2.73; p=0.19) or actuarial mortality at 4 years follow-up (HR 1.07, 95% CI, 0.81 to 1.42; p=0.64). Rates of sudden cardiac death were lower with ICD, but this did not reach statistical significance (HR 0.55, 95% CI, 0.29 to 1.03; p=0.06).
- HRQoL was higher among people with OPT compared with ICD for all measures, and this was statistically significant for some perception of health transition, emotional role function, mental health, satisfaction with appearance and satisfaction with scar.
- Hazard ratios for ICD compared with control for all-cause mortality were found to be similar among ten pre-specified subgroups.

A broad population of people with mild to moderate heart failure

- One three-arm trial compared ICD, amiodarone and placebo; all participants received OPT. Mean follow-up was 46 months and 2521 participants were randomised. Over two-thirds of participants were in NYHA class II, with the remaining participants in NYHA class III. Mean LVEF was 25%.
- All-cause mortality was significantly lower with ICD plus OPT than placebo plus OPT (HR 0.77 (97.5% CI, 0.62, 0.96; p=0.007). A significant reduction in total cardiac death (HR 0.76, 95% CI, 0.60 to 0.95; p=0.018) and sudden cardiac death (compared with placebo and amiodarone groups combined, RR 0.44, 95% CI, 0.31 to 0.61; p<0.00001) in favour of ICD was also found. There was no statistically significant difference in non-arrhythmic cardiac death (RR 1.14, 95% CI, 0.88 to 1.48; p=0.32) or deaths from non-cardiac causes (RR 0.92, 95% CI, 0.66 to 1.27; p=0.60) compared with placebo and amiodarone groups combined.
- Little difference was found in QoL assessed by DASI. Statistically significant differences in MHI score and global health status at 3 and 12 months were not maintained at 30 months, and the difference in MHI score was not clinically meaningful. A significant decrease in

perceptions of QoL was found using the SF-36 among people who had received an ICD shock within the previous month compared with those who had not received a shock.

- There was no interaction of ICD therapy ($p=0.68$) with the cause of congestive heart failure (ischaemic or non-ischaemic) for all-cause mortality or other specified modes of death. There was a statistically significant interaction between ICD therapy and NYHA class: compared with placebo, ICDs reduced the risk of all-cause mortality, cardiac mortality and sudden death presumed to be ventricular tachyarrhythmic in people with NYHA class II, but not in those with NYHA class III. The interaction between ICD therapy and NYHA class was not statistically significant for heart failure ($p=0.29$) or noncardiac ($p=0.11$) deaths.

Adverse events

- Adverse events were reported by all four RCTs of people with previous ventricular arrhythmias. Up to 30% of the ICDs groups reported adverse events, with most related to the placement and operation of the device. Rates for OPT appeared lower.
- The nine RCTS of people who had not suffered a life threatening arrhythmia reported adverse event rates between 5% and 61% of people with an ICD, depending on the definition of adverse event and length of follow-up. Adverse event rates for the comparator treatment were between 12% to 55% in the three RCTs reporting this. Lead, electrode or defibrillator generator related problems affected 1.8 to 14% of people in the five trials that reported it.

4.3 People with heart failure as a result of LVSD and cardiac dyssynchrony

4.3.1 Quantity and quality of research available

Four RCTs comparing CRT-P and OPT in people with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT, met the inclusion criteria.^{111;123;127} In addition, one of these RCTs compared CRT-P and CRT-D with OPT (COMPANION¹¹⁸).

Three of the trials reported their findings in more than one paper; a summary of the included papers for each trial can be seen in Table 29. All of these studies were included in the 2007 CRT TAR,⁴³ which also included CONTACT-CD.¹²⁸ This trial is discussed in section 4.4.

Table 29: Included RCTs for people with heart failure

Trial	Publication (Bold indicates primary or key publication)
CARE-HF	Cleland et al. 2005, ¹¹¹ 2001, ¹¹² 2006, ¹¹³ 2007, ¹¹⁴ 2009, ¹¹⁵ Gras et al. 2007, ³⁶ Gervais et al. 2009, ¹¹⁶ Ghio et al. 2009 ¹¹⁷
COMPANION	Bristow et al. 2004, ¹¹⁸ and 2000 ¹¹⁹ Carson et al. 2005, ¹²¹ FDA report 2004, ¹²⁰ Anand et al. 2009, ¹²²
MIRACLE	Abraham et al. 2002, ¹²³ and 2000, ¹²⁴ FDA report 2001, ¹²⁵ Sutton et al. 2003 ¹²⁶
MUSTIC	Cazeau et al. 2001 ¹²⁷

4.3.1.1 Characteristics of the included studies

Study characteristics are summarised in Table 30 and participant characteristics are summarised in Table 31. Further details can be found in the data extraction forms in Appendix 9.

Intervention and comparators

In MIRACLE¹²³ and MUSTIC,¹²⁷ all participants were implanted with a CRT-P device, and pacing was inactivated in the control group. Participants in CARE-HF¹¹¹ and COMPANION¹¹⁸ received either a device plus OPT or OPT only. Pharmacological therapy in all four trials would be considered optimal by current standards.

Participants

The trials included people with NYHA class III or IV heart failure, with the majority of participants in NYHA class III [82% (CARE-HF¹¹¹) to 100% (MUSTIC¹²⁷)]. All the trials included participants with LVEF ≤ 35%; average LVEF was about 22% in MIRACLE¹²³ and COMPANION,¹¹⁸ and 25% in CARE-HF.¹¹¹

The trials differed in their eligibility criteria for the QRS interval, with CARE-HF¹¹¹ and COMPANION¹¹⁸ requiring a QRS interval ≥ 120 ms, MIRACLE¹²³ ≥ 130 ms and MUSTIC¹²⁷ ≥ 150 ms. This is reflected in the average QRS interval at baseline in these studies, with the longest average QRS interval seen in MUSTIC (Table 31).¹²⁷ Where reported, the proportion of participants with ischemic heart disease ranged from 36% (CARE-HF¹¹¹) to 59% (COMPANION¹¹⁸).

The mean age of the participants in the studies was similar, ranging from around 64 years in MIRACLE¹²³ and MUSTIC¹²⁷ to 68 years in COMPANION¹¹⁸ (see Table 31). The majority of participants were men, equating to 73% and 74% in the CARE-HF trial arms,¹¹¹ 67%, 67% and 69% in the three COMPANION trial arms,¹¹⁸ 68% in both of the MIRACLE trial arms,¹²³ and 66% and 83% in both of the MUSTIC trial arms.¹²⁷

Table 30: Study characteristics

Parameter	Study name			
	CARE-HF ¹¹¹	COMPANION ¹¹⁸	MIRACLE ¹²³	MUSTIC ¹²⁷
Study design	RCT	RCT	RCT	Randomised cross-over
Target population	NYHA III or IV due to LVSD and cardiac dyssynchrony	Advanced chronic heart failure and intraventricular conduction delays	Moderate to severe heart failure	Severe heart failure and major intraventricular delay
Intervention	CRT-P plus medical therapy	CRT-P or CRT-D and OPT	CRT-P- ON and OPT	CRT-P ON and OPT
Comparator	Standard medical therapy	OPT	CRT-P OFF and OPT	CRT-P OFF and OPT
Country (no. of centres)	Europe (82) (including France, Germany, Italy, Switzerland and UK)	USA (128)	USA and Canada (45)	Europe (15) (France, Germany, Italy, Sweden, Switzerland and UK)
Sample size (randomised)	813	1520	453	58
Length of follow-up	Mean 29.4 months (mean 37.4 months with 8 month extension)	Primary end-point, median 11.9 to 15.7 months	6 months	3 months
Key inclusion criteria	HF for ≥ 6 weeks	Sinus rhythm	Heart failure due to ischemic or non-ischemic cardiomyopathy for > 1 month	Severe HF due to idiopathic or ischemic LVSD; Sinus rhythm,
- NYHA Class	NYHA class III or IV despite standard pharmacological therapy	NYHA class III, IV	NYHA III or IV	NYHA class III for ≥ 1 month whilst on OPT

Parameter	Study name			
	CARE-HF ¹¹¹	COMPANION ¹¹⁸	MIRACLE ¹²³	MUSTIC ¹²⁷
- LVEF	LVEF ≤ 35%	LVEF ≤ 35%	LVEF ≤ 35%	LVEF < 35%
- LVEDD	LVEDD ≥ 30 mm ^a	LVEDD ≥ 60mm	LVEDD ≥ 55 mm	LVEDD >60 mm
- QRS interval, ms	QRS interval ≥ 120 ms ^b	QRS ≥ 120 ms	QRS interval ≥ 130 ms	QRS interval > 150 ms
- Other	Aortic pre-ejection delay > 140 ms; Interventricular mechanical delay > 40 ms; Delayed activation of posterolateral left ventricular wall.	PR interval >150 ms	6-min walk distance ≤ 450 m	No standard indication for a pacemaker

^a Indexed to height. ^b QRS interval of 120 to 149 ms: patients need to meet 2/3 additional criteria for dyssynchrony.

Table 31: Key Participant characteristics

Parameter	Study name								
	CARE-HF ¹¹¹		COMPANION ¹¹⁸			MIRACLE ¹²³		MUSTIC ¹²⁷	
	CRT-P	OPT	CRT-P	CRT-D	OPT	CRT-P ON	CRT-P OFF	CRT-P ON	CRT-P OFF
Sample size, n	n= 409	n=404	n=617	n=595	n=308	n=228	n=225	n=29	n=29
Age, mean (SD)	67 (60-73) ^a	66 (59-72) ^a	67 ^b	66 ^b	68 ^b	63.9 (10.7)	64.7 (11.2)	64 (11)	64 (8)
Sex, % male	74	73	67	67	69	68	68	66	83
Ischemic heart disease, %	40	36	54	55	59	50	58		
Dilated cardio-myopathy, %	43	48							
NYHA I, %	0	0	0	0	0	0	0	0	0
NYHA II, %	0	0	0	0	0	0	0	0	0
NYHA III, %	94	93	87	86	82	90	91	100	100
NYHA IV, %	6	7	13	14	18	10	9	0	0
LVEF %, mean (SD)	25 ^b	25 ^b	20 ^b	22 ^b	22 ^b	21.8 (6.3)	21.6 (6.2)		
QRS interval, ms, mean (SD)	160 ^b (152-180) ^a	160 ^b (152-180) ^a	160 ^b	160 ^b	158 ^b	167 (21)	165 (20)	172 (22)	175 (19)
LBBB/RBBB, %			69/12	73/10	70/9				
6-min walk test, m, mean			274 ^b	258 ^b	244 ^b	305	291	354 (110)	346 (111)
Peak VO ₂ /kg, mL/kg ⁻¹ /min ⁻¹ , mean (SD)						14.0	13.7	13.5 (8.4)	14.1 (4.6)
Heart rate, bpm, mean (SD)	69 ^b	70 ^b	72 ^b	72 ^b	72 ^b	73 (13)	75 (13)	75 (12)	75 (14)

^a Range. ^b Median.

Pharmacological therapy

OPT was used in all of the trials (see Table 32). At least 90% of all participants received ACE inhibitors or angiotensin receptor blockers. Less than a third of participants used beta-blockers in the MUSTIC study (28%),¹²⁷ between 55-62 % in MIRACLE,¹²³ between 66-68% in COMPANION,¹¹⁸ and between 70-74% in CARE-HF.¹¹¹ Spironolactone use was not reported by the MIRACLE study,¹²³ but varied from 22% in MUSTIC,¹²⁷ to between 53-55% in COMPANION,¹¹¹ and 54-59% in CARE-HF.¹¹¹ Less than half of the participants in CARE-HF¹¹¹ used diuretics, which was around 94% in the other studies. Both CARE-HF¹¹¹ and MUSTIC¹²⁷ reported that less than half of the participants used digoxin, while around a third of the participants in MUSTIC¹²⁷ used amiodarone. In the MIRACLE trial,¹²³ around three quarters of participants used digitalis medication.

Outcomes

Whilst all four trials reported all-cause mortality, it was not a primary outcome. The primary outcome of two trials was a composite endpoint: all-cause mortality and all-cause hospitalisation in COMPANION,¹¹⁸ and all-cause mortality and unplanned hospitalisation for a major cardiovascular event in CARE-HF.¹¹¹ Composite outcomes can be seen in the data extraction forms (Appendix 9) but have not been discussed in this report. The primary outcome of MIRACLE¹²³ and MUSTIC¹²⁷ was distance walked in 6 minutes, changes in NYHA class and quality of life were also primary outcomes in MUSTIC.¹²⁷

All four trials reported mortality due to sudden cardiac death. In addition, COMPANION¹¹⁸ and MUSTIC¹²⁷ reported total cardiac death, while both CARE-HF¹¹¹ and COMPANION¹¹⁸ reported death due to heart failure. Heart failure hospitalisation was reported by all four trials. CARE-HF,¹¹¹ MIRACLE¹²³ and MUSTIC¹²⁷ reported details on worsening heart failure, while arrhythmias were reported by CARE-HF¹¹¹ and MUSTIC.¹²⁷ All trials except MUSTIC¹²⁷ reported change in NYHA class, but only CARE-HF¹¹¹ and MIRACLE¹²³ reported changes in LVEF. HRQoL and adverse events were reported by all trials.

Table 32: Medication at baseline

Medication, %	Study name								
	CARE-HF ¹¹¹		COMPANION ¹¹⁸			MIRACLE ¹²³		MUSTIC ¹²⁷	
	CRT-P	OPT	CRT-P	CRT-D	OPT	CRT-P ON	CRT-P OFF	CRT-P ON	CRT-P OFF
Sample size, n	n= 409	n=404	n=617	n=595	n=308	n=228	n=225	n=67^a	
Aldosterone antagonist (Spirinolactone)	54	59	53	55	55			22	
Amiodarone								31	
ACE inhibitor			70	69	69				
ACE inhibitor or angiotensin blocker	95	95	89	90	89	93	90	96	
Beta-blocker	70	74	68	68	66	62	55	28	
Digitalis						78	79		
Diuretic					94	94	93	94	
Loop diuretic	43	44	94	97					
Digoxin	40	45						48	

^aN=67 enrolled, n =58 randomised.

Setting

All four studies were multicentre trials, ranging from 15 (MUSTIC¹²⁷) to 128 (COMPANION¹¹⁸) centres. CARE-HF¹¹¹ and MUSTIC¹²⁷ were undertaken in Europe, both including centres in the UK. The COMPANION study¹¹⁸ was undertaken in the USA, while MIRACLE¹²³ had centres in the USA and Canada.

The MUSTIC study¹²⁷ used a randomised crossover design, with 3 months follow-up for each of the two cross-over periods. The length of follow-up for the MIRACLE study¹²³ was 6 months. Mean length of follow-up in the CARE-HF study¹¹¹ was 29.4 months, plus an 8 months extension (total mean follow-up 37.4 months). COMPANION¹¹⁸ reported a median follow-up for the composite endpoint of 11.9 months for OPT, 15.7 months for CRT-D and 16.2 months for CRT-P. Median follow-up for mortality was also reported as 14.8 months for OPT, 16.0 CRT-D and 16.5 months for CRT-P.

4.3.1.2 Risk of bias

Details of the risk of bias for each study can be found in the data extraction tables in Appendix 9, with a summary in Table 33.

Due to lack of reported details on randomisation methods and allocation concealment methods, the risk of selection bias for COMPANION,¹¹⁸ MIRACLE¹²³ and MUSTIC¹²⁷ was unclear. Risk of selection bias was low in CARE-HF.¹¹¹

MIRACLE¹²³ appeared to be at low risk of performance and detection bias, with both patients and physician unaware of treatment assignment (CRT-P on or off). MUSTIC¹²⁷ was at high risk of performance and detection bias, with only participants blinded to the treatment order (CRT-P on or off). Both CARE-HF¹¹¹ and COMPANION,¹¹⁸ were unblinded trials, placing them at high risk of performance bias. For detection bias, CARE-HF¹¹¹ was judged to be at low risk of bias for the composite endpoint of mortality and hospitalisation, using an end-points committee unaware of treatment assignment. However, without blinding, the trial was at high risk of detection bias for echocardiographic outcomes. The risk of detection bias for adverse events was unclear, with some adverse events classified by the endpoints committee, but others by an unblinded independent expert. The risk of detection bias in COMPANION¹¹⁸ was low, with a steering committee and endpoints committee unaware of treatment assignment.

Both COMPANION¹¹⁸ and MUSTIC¹²⁷ were at low risk of attrition bias. MUSTIC¹²⁷ reported both numbers and reasons for withdrawals, while COMPANION¹¹⁸ censored data in their ITT analysis for

participants who withdrew and data could not be obtained. CARE-HF¹¹¹ also reported ITT analyses and was at low risk of bias for mortality, hospitalisation and echocardiographic outcomes. However, the risk of bias for QoL and LV reverse remodelling was unclear due to unexplained differences in numbers. The risk of attrition bias in the MIRACLE study¹²³ was unclear for both the primary and secondary outcomes. While ITT analysis was used and attrition reported, the low numbers reported for the primary outcome of NYHA class and differences in sample size between primary and secondary outcomes were unexplained. Both CARE-HF¹¹¹ and COMPANION study¹¹⁸ were at low risk of selective reporting bias. Both studies have published protocol or rationale/design papers and there was no evidence of missing outcomes. However, MIRACLE¹²³ and MUSTIC¹²⁷ were at high risk of selective reporting bias. MIRACLE¹²³ assessed change in NYHA class but failed to report the data and MUSTIC¹²⁷ included the SF-36 in the study protocol,¹²⁴ but did not report the data.

There was an additional risk of bias in MUSTIC¹²⁷ due to the use of block randomisation without blinding. However, the use of the crossover design appears appropriate.

Table 33: Risk of bias

Judgement ^a	CARE-HF ¹¹¹	COMPANION ¹¹⁸	MIRACLE ¹²³	MUSTIC ¹²⁷
Selection bias				
Random sequence generation	Low	Unclear	Unclear	Unclear
Allocation concealment	Low	Unclear	Unclear	Unclear
Performance bias				
Blinding of participants and personnel	High	High	Low	High
Detection bias				
Blinding of outcome assessment	Composite ^b - Low	Low	Low	High
	Secondary ^c – High or Unclear			
Attrition bias				
Incomplete outcome data addressed	Composite ^b and Echocardiographic outcomes - Low LV remodelling outcomes - Unclear	Low	Unclear	Low
Reporting bias				
Selective reporting	Low	Low	High	High
Other bias				
Other sources of bias	Low	Low	Low	High

^a ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias. N/A, not applicable. ^b Morality and hospitalisation. ^c Echocardiographic outcomes – high risk, adverse events – unclear risk.

4.3.1.3 Methodological comments

Similarity of groups at baseline

The groups in the four studies were generally well balanced at baseline.

Sample size

All four of the included trials included a statistical power calculation. CARE-HF,¹¹¹ MIRACLE¹²³ and MUSTIC¹²⁷ appeared to be adequately powered to detect a difference in the relevant primary outcome measures. MUSTIC¹²⁷ randomised 58 participants, MIRACLE¹²³ randomised 453 participants and CARE-HF randomised 813 participants. COMPANION¹¹⁸ was stopped early when pre-established boundaries had been crossed, with 1520 participants randomised and 1000 primary end points already or almost met. The trial was designed with 2200 participants to detect a reduction of 25% in the primary endpoint.

Crossovers

By the end of the extension period in CARE-HF,¹¹¹ 24% of participants in the OPT group had a CRT device implanted and activated and 2% of participants in the CRT-P treatment arm received a CRT-D device. MIRACLE¹²³ reported that 4% of participants crossed over from OPT to CRT-P, but reported no details for the CRT-P treatment group. COMPANION¹²² reported that out of 78 cardiac procedures in the OPT group, 33 (42%) were for CRT implants. In addition, COMPANION¹²⁰ reported that there were substantial withdrawals in the OPT group (26%) to receive commercially available implants, whereas the withdrawal rate with CRT-P and CRT-D was 6% and 7%, respectively. ITT analysis was performed in the trials.

Other issues

Studies differed in the timing of implantation, baseline evaluation and randomisation. Two studies randomised participants prior to implantation. In the CARE-HF study¹¹¹ baseline measures were taken prior to randomisation and implantation, while in the COMPANION study¹¹⁸ randomisation was prior to implantation, but baseline measures were taken one week after successful implantation. The remaining two studies (MIRACLE¹²³ and MUSTIC¹²⁷) randomised participants after implantation. In the MIRACLE study¹²³ baseline measures were taken before implantation and randomisation, while in the MUSTIC study¹²⁷ baseline measures were taken after randomisation, which occurred two weeks after implantation. Thus only those participants with a successful implantation underwent randomisation in both studies, limiting the generalisability of these studies. These differences may affect comparability between studies.

MUSTIC¹²⁷ does not report all outcomes for both crossover periods. In addition, ten participants did not complete the both crossover periods (including five who did not complete the first period). The COMPANION trial¹¹⁸ had substantial withdraws from the OPT group (see *Crossovers*).

Funding

All four trials received funding grants from the device manufacturers, with three trials being funded by Medtronic^{111;123;127} and one by the Guidant corporation.¹¹⁸ In addition, three of the trials, MIRACLE,¹²³ MUSTIC,¹²⁷ and CARE-HF¹¹¹ reported conflicts of interests, as some/all authors were consultants or investigators for, or employees of, the company providing the funding. Both CARE-HF¹¹¹ and COMPANION¹¹⁸ stated that sponsors had no role in data analysis, while MIRACLE¹²³ stated that sponsors placed no restrictions or limitation on the investigators performing the data analyses.

4.3.2 Assessment of effectiveness

4.3.2.1 All-cause mortality

All four studies reported all-cause mortality (see Table 34), although it was not the primary outcome of the trials.

CRT-P vs OPT

CARE-HF¹¹¹ reported a statistically significant difference in all-cause mortality after a mean follow-up of 37.4 months including an 8 months extension period (CRT-P 24.7% vs OPT 38.1%, HR 0.60, 95% CI 0.47 to 0.77, $p < 0.0001$). Mortality rates at year 3 were nearly 10% lower for CRT-P (23.6% vs 35.1% OPT), although no statistical comparison was reported. After completion of the CARE-HF trial, long-term follow-up of people who survived and re-consented (343 of 813 originally enrolled) found that the effect of CRT persisted (HR 0.77, 95% CI 0.63 to 0.93, $p = 0.007$), despite implantation of CRT devices in more than 95% of those originally assigned to the control group (ITT analysis undertaken, with participants remaining in their assigned group regardless of subsequent treatment).¹⁵¹ In contrast, MIRACLE¹²³ found no statistically significant difference in all-cause mortality after 6 months follow-up (CRT-P 5.3% vs OPT 7.1%, HR 0.73, 95% CI 0.34 to 1.54, $p = 0.40$), while the difference in the 12 months rate from the COMPANION¹¹⁸ trial did not reach statistical significance (CRT-P 15% vs 19% OPT, HR 0.76, 95% CI 0.58 to 1.01, $p = 0.059$). MUSTIC¹²⁷ reported one death in the first crossover period (1/29, 3.4%) and two in the second crossover period (2/29, 6.9%) of the trial among those with CRT-P and none during the OPT period. No statistical comparison was reported.

The studies were considered sufficiently similar to combine in a meta-analysis (Figure 10). For meta-analysis of the MUSTIC cross-over trial,¹²⁷ all deaths in those with CRT-P or OPT from both cross-over periods were included. This method provides a conservative analysis, with the study being under-weighted rather than over-weighted.⁶⁷ There was evidence of moderate statistical heterogeneity between the studies (Chi^2 4.99, $\text{df}=3$, $I^2=40\%$). The risk ratio (RR) for CRT-P vs OPT for all-cause mortality with the random effects method was 0.75 (95% CI, 0.58 to 0.96; $p=0.02$) (see Figure 10). Excluding the MUSTIC trial¹²⁷ from the meta-analysis has little effect (RR 0.73, 95% CI, 0.60 to 0.89 $p=0.002$).

CRT-D vs OPT

COMPANION¹¹⁸ found a statistically significant reduction in mortality with CRT-D at 12 months (CRT-D 12% vs OPT 19%; HR 0.64, 95% CI 0.48 to 0.86; $p=0.003$), giving a reduction in risk of 36% for all-cause mortality.

CRT-P vs CRT-D

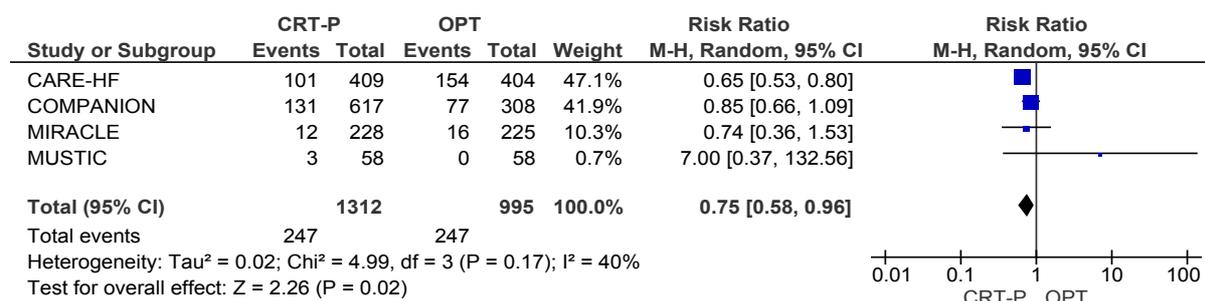
COMPANION¹¹⁸ included three treatment arms (CRT-P, CRT-D and OPT). All-cause mortality with CRT-P (21%) vs CRT-D (18%) was not statistically significant (RR 1.20; 95% CI, 0.96 to 1.52; $p=0.12$). However, all comparisons between CRT-P vs CRT-D should be treated with caution, as the trial was not powered for this comparison.

Table 34: All-cause mortality

Study	Follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ¹¹¹	First 90 days of trial	12/409 (2.9)	15/404 (3.7)		
	29.4 ^a	82/409 (20.0)	120/404 (29.7)	HR 0.64	0.48 to 0.85, <0.002
	37.4 ^{113a}	101/409 (24.7)	154/404 (38.1)	HR 0.60	0.47 to 0.77, <0.0001
	Mortality rate 1 year, ¹¹³ %	9.7	12.6		
	Mortality rate 2 year, %	18	25.1		
	Mortality rate 3 year, %	23.6	35.1		
MIRACLE ¹²³	6	12/228 (5.3)	16/225 (7.1)	HR 0.73	0.34 to 1.54, 0.40
MUSTIC ¹²⁷	6	1 st period: 1/29 (3.4 ^b) 2 nd period: 2/29 (6.9 ^b)	1 st period: 0/29 (0) 2 nd period: 0/29 (0)	RR 7.00 ^b	0.37 to 132.56, 0.19 ^b
COMPANION ¹¹⁸	CRT-P 16.5, OPT 14.8 ^c	131/617 (21.2)	77/308 (25.0)		
	12 months rate	93 ^b /617 (15)	59 ^b /308 (19)	HR 0.76	0.58 to 1.01, 0.059
		CRT-D, n/N (%)	OPT, n/N (%)		
	CRT-D 16.0, OPT 14.8 ^c	105/595 (17.6)	77/308 (25.0)	RR 0.71 ^b	0.54 to 0.92, 0.009 ^b
	12 months rate	71 ^b /595 (12)	59 ² /308 (19)	HR 0.64	0.48 to 0.86, 0.003
		CRT-P n/N (%)CRT	CRT-D, n/N (%)		
	CRT-P 16.5, CRT-D 16.0 ^c	131/617 (21)	105/595 (18)	RR 1.20 ^b	0.96 to 1.52, 0.12 ^b

^a Mean. ^b Calculated by reviewer. ^c Median.

Figure 10: All-cause mortality CRT-P vs OPT



4.3.2.2 Total cardiac deaths

Both COMPANION¹²¹ and MUSTIC¹²⁷ reported total cardiac deaths.

CRT-P vs OPT

COMPANION¹²¹ found no statistically significant difference between CRT-P and OPT (17.7% vs 18.8% respectively, p=0.334) in total cardiac deaths with a median follow-up of 16.5 months for CRT-P and 14.8 months for OPT (RR 0.94, 95% CI, 0.70 to 1.25; p=0.66) (Table 35). The three deaths that occurred in MUSTIC¹²⁷ were due to cardiac causes, with no significant differences between treatment arms (CRT-P 5.2% vs 0% OPT, RR 7.00, 95% CI, 0.37 to 132.56, p=0.19).

CRT-D vs OPT

COMPANION¹²¹ found that cardiac deaths were statistically significant lower with CRT-D compared with OPT (12.8% vs 18.8% respectively, p=0.006), with a median follow-up of 16.0 months for CRT-D and 14.8 months for OPT (RR 0.68, 95% CI, 0.50 to 0.93, p=0.02) (Table 35).

CRT-P vs CRT-D

Cardiac deaths in COMPANION¹²¹ were statistically significantly higher in those with CRT-P (RR 1.38; 95% CI, 1.06 to 1.81, p=0.02). However, all comparisons between CRT-P vs CRT-D should be treated with caution, as the trial was not powered for this comparison.

Table 35: Total cardiac deaths

Study	Follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
MUSTIC ¹²⁷	6	1 st period: 1/29 (3.4 ^a) 2 nd period: 2/29 (6.9 ^a)	1 st period 0/29 (0) 2 nd period 0/29 (0)	RR 7.00 ^a	0.37 to 132.56, 0.19 ^a
COMPANION ¹²¹	CRT-P 16.5, OPT 14.8 ^b % of deaths	109/617 (17.7 ^c) 83.2	58 ^d /308 (18.8) 75.3	RR 0.94 ^a	0.70 to 1.25, 0.66 ^a , (0.334 ^e)
		CRT-D, n/N (%)	OPT, n/N (%)		
	CRT-D 16.0, OPT 14.8 ^b % of deaths	76/595 (12.8) 72.4	58 ^d /308 (18.8) 75.3	RR 0.68 ^a	0.50 to 0.93, 0.02 ^a (0.006 ^e)
		CRT-P, n/N (%)	CRT-D, n/N (%)		
	CRT-P 16.5, CRT-D 16.0 ^b % of deaths	109/617 (17.7 ^c) 83.2	76/595 (12.8) 72.4	RR 1.38 ^a	1.06 to 1.81, 0.02 ^a

^a Calculated by reviewer. ^b Median. ^c States 109/617=17.1% in paper. ^d States 54/308 (18.8%) in paper, but cardiac causes total 58. ^e Statistical analysis reported by trial.

4.3.2.3 Heart failure deaths

Both the CARE-HF trial¹¹¹ and the COMPANION¹²¹ reported mortality due to HF.

CRT-P vs OPT

CARE-HF¹¹¹ found that mortality attributed to worsening heart failure was statistically significantly lower with CRT-P compared with OPT (around 9% vs 16% respectively), with a risk reduction of 45% (HR 0.55, 95% CI, 0.37 to 0.82, p=0.003) at 37.4 months mean follow-up. The risk of heart failure was reported to be 3.0% per annum for those with CRT-P compared with 5.1% per annum for those with OPT. COMPANION¹²¹ found no statistically significant differences between those with CRT-P and OPT (8.6% vs 11.0% respectively; HR 0.71, 95% CI, 0.46 to 1.09, p=0.112) at 16.5 months follow-up for those with CRT-P and 14.8 months for those with OPT (see Table 36).

The studies were considered sufficiently similar to combine in a meta-analysis. There was no evidence of statistical heterogeneity between the studies (Chi² 0.99, df=1, I²=0%). The random effects risk ratio for HF deaths with CRT-P vs OPT was 0.67 (95% CI, 0.51 to 0.88; p=0.004) (see Figure 11).

CRT-D vs OPT

COMPANION¹²¹ found no statistically significant differences in heart failure deaths between CRT-D (8.7%) and OPT (11.0%), with a HR of 0.73 (95% CI, 0.47 to 1.11; p=0.143) at 16.0 months follow-up for those with CRT-D and 14.8 months for those with OPT (see Table 36).

CRT-P vs CRT-D

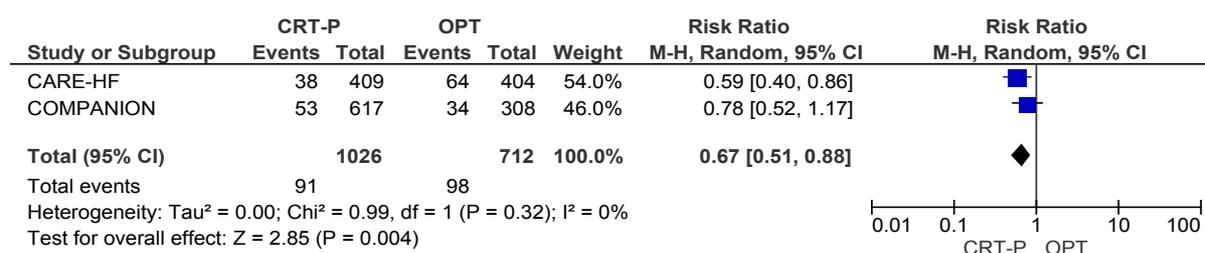
Heart failure deaths with CRT-P and with CRT-D in COMPANION¹²¹ were similar (8.6% vs 8.7% respectively); RR 0.98 (95% CI, 0.68 to 1.42; p=0.93).

Table 36: Heart failure deaths

Study	Mean follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ¹¹¹	29.4	33/409 (8.1)	56/404 (13.9)	RR 0.58	0.39 to 0.87, 0.009
	37.4 (with extension) ¹¹³	38/409 (8.8)	64/404 (15.8)	HR 0.55	0.37 to 0.82, 0.003
	Per annum	3.0%	5.1%		
COMPANION ¹²¹	CRT-P 16.5, OPT 14.8 ^a	53/617 (8.6)	34/308 (11.0)	HR 0.71	0.46 to 1.09, 0.112
	% of deaths	40.5	44.2		
		CRT-D, n/N (%)	OPT, n/N (%)		
	CRT-D 16.0, OPT 14.8 ^a	52/595 (8.7)	34/308 (11.0)	HR 0.73	0.47 to 1.11, 0.143
	% of deaths	49.5	44.2		
		CRT-P, n/N (%)	CRT-D, n/N (%)		
CRT-P 16.5, CRT-D 16.0 ^a	53/617 (8.6)	52/595 (8.7)	RR 0.98 ^b	0.68 to 1.42, 0.93 ^b	
% of deaths	40.5	49.5			

^a Median. ^b Calculated by reviewer.

Figure 11: Heart failure deaths CRT-P vs OPT



4.3.2.4 Sudden cardiac death

All trials reported sudden cardiac death, although there were uncertainties with the MIRACLE trial data.¹²³

CRT-P vs OPT

CARE-HF¹¹¹ found sudden cardiac deaths to be statistically significantly lower with CRT-P than with OPT (7.8% vs 13.4% respectively; HR 0.54, 95% CI, 0.35 to 0.84; p=0.005) at 37.4 months mean follow-up. The proportion of sudden deaths per year was reported to be 2.5% for those with CRT-P compared to 4.3% for those with OPT. There were two reported sudden deaths in the MUSTIC trial,¹²⁷ one (1/29, 3.4%) in the first crossover period (after 26 days of active pacing) and one (1/29, 3.4%) in the second crossover period (two hours after switching from inactive to active pacing). No statistical comparison was reported. CRT-P failed to reduce the risk of sudden death in the COMPANION trial,¹²¹ with more sudden deaths in those with CRT-P than those with OPT (7.8% vs 5.8% respectively; HR 1.21, 95% CI, 0.70 to 2.07; p=0.485) at 16.5 months follow-up for those with CRT-P and 14.8 months for those with OPT. The study also reported the proportion of deaths due to sudden cardiac death as 36.6% for those with CRT-P and 23.4% for those with OPT (see Table 37).

Meta-analysis of the three trials found evidence of substantial statistical heterogeneity between the studies (Chi² 7.22, df=2, I²=72%). Differences in sudden cardiac death between CRT-P and OPT were not statistically significant, with a random effects risk ratio of 0.97 (95% CI, 0.44 to 2.14; p=0.94) (Figure 12).

The FDA report¹²⁵ associated with MIRACLE reported SCD (CRT-P n=7, OPT n=5) at 9 months follow-up (the main publication reported outcomes at 6 months¹²³), however the numbers in each arm were not reported and the total sample size in the FDA report (n=536) differed from the number randomised in the main publication (n=453).¹²³ If the sample size in each arm is assumed to be the same as the main publication, the RR for the trial is 1.38, 95% CI 0.45 to 4.29. Combining the data in

the meta-analysis with CARE-HF, COMPANION and MUSTIC gives an overall of RR 1.02 (95% CI 0.54 to 1.94).

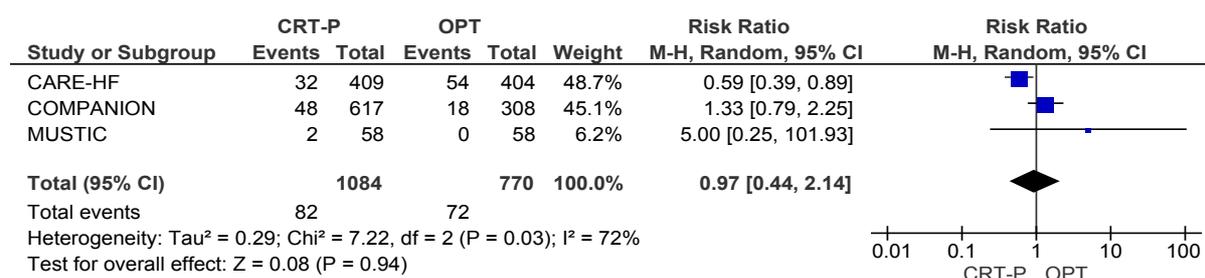
CRT-D vs OPT

COMPANION¹²¹ found sudden cardiac deaths to be statistically significantly lower in those with CRT-D compared with those with OPT (2.9% vs 5.8% respectively), with a HR of 0.44 (95% CI, 0.23 to 0.86; p=0.020) at 16.0 months follow-up for those with CRT-D and 14.8 months for those with OPT.

CRT-P vs CRT-D

Sudden cardiac deaths were statistically significantly higher in those with CRT-P compared with those with CRT-D in COMPANION¹²¹ (7.8% vs 2.9% respectively; RR 2.72, 95% CI, 1.58 to 4.68; p=0.0003). However, all comparisons between CRT-P vs CRT-D should be treated with caution, as the trial was not powered for this comparison.

Figure 12: Sudden cardiac death CRT-P vs OPT



4.3.2.5 Other causes of death

COMPANION¹²¹ found no statistically significant differences between those with CRT-P and those with OPT for non-cardiac deaths (p=0.122) or between those with CRT-D and those with OPT (p=0.717). Vascular, non-cardiac and unknown deaths appear to be similar between those with CRT-P and those with CRT-D (see Table 38).

Table 37: Sudden cardiac death

Study	Follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ¹¹¹	29.4 ^a	29/409 (7.1)	38/404 (9.4)	RR 0.75 ^b	0.47 to 1.20, 0.23 ^b
	37.4 ^{113a} Per annum	32/409 (7.8) 2.5%	54/404 (13.4) 4.3%	HR 0.54	0.35 to 0.84, 0.005
MUSTIC ¹²⁷	6	1 st crossover: 1/29 (3.4 ^b) 2 nd crossover: 1/29 (3.4 ^b)	1 st crossover: 0/29 (0) 2 nd crossover: 0/29 (0)	RR 5.00 ^b	0.25 to 99.82, 0.29 ^b
COMPANION ¹²¹	CRT-P 16.5, OPT 14.8 ^c % of deaths	48/617 (7.8) 36.6	18/308 (5.8) 23.4	HR 1.21	0.70 to 2.07, 0.485
		CRT-D, n/N (%)	OPT, n/N (%)		
	CRT-D 16.0, OPT 14.8 ^c % of deaths	17/595 (2.9) 16.2	18/308 (5.8) 23.4	HR 0.44	0.23 to 0.86, 0.020
		CRT-P, n/N (%)	CRT-D, n/N (%)		
	CRT-P 16.5, CTR-D 16.0 ^c % of deaths	48/617 (7.8) 36.6	17/595 (2.9) 16.2	RR 2.72 ^b	1.58 to 4.68, 0.0003 ^b

^a Mean. ^b Calculated by reviewer. ^c Median.

Table 38: Other causes of death

Study	Median follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
COMPANION ¹²¹	Vascular, CRT-P 16.5, OPT 14.8 % of deaths	5 /617 (0.8) 3.8	0		
	Non-cardiac % of deaths	14/617 (2.3) 10.7	11/308 (3.6) 14.3		0.122
	Unknown % of deaths	3 /617 (0.5) 2.3	8 /308 (2.6) 10.4		
		CRT-D, n/N (%)	OPT, n/N (%)		
	Vascular, CRT-D 16.0, OPT 14.8 % of deaths	3 /595 (0.5) 2.8	0		
	Non-cardiac % of deaths	21/595 (2.3) 10.7	11/308 (3.6) 14.3		0.717
	Unknown % of deaths	5/595 (0.8) 4.8	8/308 (2.6) 10.4		

4.3.2.6 Hospitalisations due to heart failure

All four trials reported hospitalisations due to heart failure. Additional hospitalisation outcomes reported by the trials, including cardiac and non-cardiac hospitalisations, are summarised in Appendix 7.

Number of people hospitalised due to heart failure

CRT-P vs OPT

CARE-HF¹¹¹ found that fewer people were hospitalised due to heart failure with CRT-P (17.9% vs 32.9% OPT; HR 0.48, 95% CI, 0.36 to 0.64; $p < 0.001$) at 29.4 months mean follow-up, as did MIRACLE¹²³ at 6 months follow-up (7.9% CRT-P vs 15.1% OPT; HR 0.50, 95% CI, 0.28 to 0.88; $p = 0.02$) and COMPANION¹¹⁸ at 16.2 months follow-up for CRT-P and 11.9 months for OPT (29% CRT-P vs 36% OPT; RR 0.80, 95% CI, 0.66 to 0.97; $p = 0.02$) (see Table 39). In the MUSTIC trial,¹²⁷ hospitalisations related to decompensated heart failure were lower in those with CRT-P (10.3% vs 31.0% OPT), but failed to reach statistical significance (RR 0.33, 95% CI, 0.10 to 1.11; $p < 0.07$).

The trials were combined in meta-analysis, however, MUSTIC¹²⁷ reported data for the first crossover period only. There was evidence of substantial statistical heterogeneity between the studies (Chi^2 8.50, $\text{df} = 3$, $I^2 = 65\%$), but the direction of effect is consistent. The risk ratio of hospitalisation due to heart failure for CRT-P vs OPT was 0.61 (95% CI, 0.44 to 0.83; $p = 0.002$), giving a relative risk reduction for hospitalisation related to heart failure with CRT-P of 39% (see Figure 13).

CRT-D vs OPT

There were significantly fewer people admitted to hospital due to heart failure with CRT-D compared with OPT in COMPANION,¹²¹ (28% vs 36% respectively) with a RR of 0.77 (95% CI, 0.63 to 0.93; $p = 0.008$) at a median follow-up of 15.7 months for those with CRT-D and 11.9 months for those with OPT.

CRT-P vs CRT-D

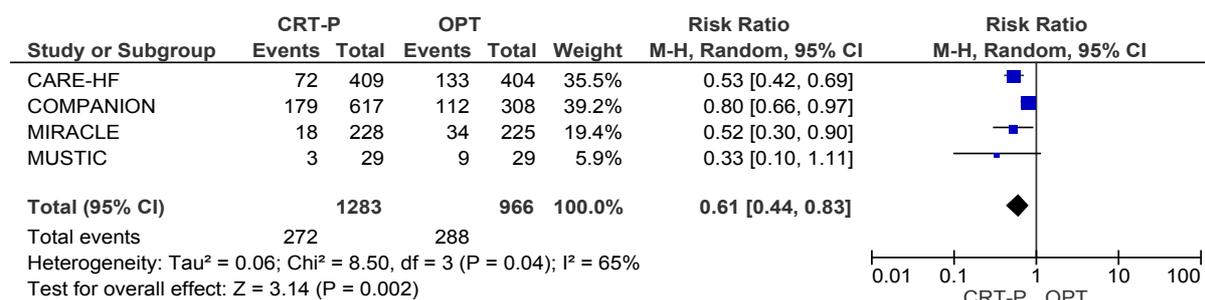
COMPANION¹¹⁸ states that no significant differences were found in any of the endpoints for those with CRT-P vs those with CRT-D, and results for the proportion of people hospitalised at least once with heart failure were similar (28% vs 29% respectively).

Table 39: Hospitalisations related to heart failure: number of people

Study	Outcome; follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ¹¹¹	Unplanned hospitalisation with worsening heart failure, 29.4 ^a	72/409 (17.9)	133/404 (32.9)	HR 0.48	0.36 to 0.64, <0.001
MIRACLE ¹²³	Hospitalisation for worsening heart failure, 6	18/228 (7.9)	34/225 (15.1)	HR 0.50	0.28 to 0.88, 0.02
MUSTIC ¹²⁷	Hospital admission because of decompensated heart failure; 3 ^b	3/29 (10.3)	9/29 (31.0)	RR 0.33 ^d	0.10 to 1.11, RR 0.07 ^{d,e}
COMPANION ¹¹⁸	Hospitalised ≥ 1 with heart failure; CRT-P 16.2, OPT 11.9 ^c	179/617 (29)	112/308 (36)	RR 0.80 ^d	0.66 to 0.97, 0.02 ^d
		CRT-D, n/N (%)	OPT, n/N (%)		
	Hospitalised ≥ 1 with heart failure; CRT-D 15.7, OPT 11.9 ^c	166/595 (28)	112/308 (36)	RR 0.77 ^d	0.63 to 0.93, 0.008 ^d

^a Mean. ^b Data reported for 1st crossover period only. ^c Estimated by the reviewer. ^e Median. ^d Calculated by reviewer. COMPANION¹¹⁸ states that no significant difference were found in any of the end-points for CRT-P vs CRT-D (no p values reported). ^e Analyses reported by paper, p<0.05.¹²⁷

Figure 13: Number of people hospitalised due to heart failure, CRT-P vs OPT



Number of events of heart failure hospitalisations

CARE-HF,¹¹¹ COMPANION¹²² and MIRACLE¹²³ reported events and/or number of days of hospitalisations due to heart failure. CARE-HF¹¹¹ reported the number unplanned hospitalisation of patients worsening heart failure. COMPANION¹²² reported the number of admissions, the percentage of total admissions and the number of average admission per patient year of follow-up, while MIRACLE¹²³ reported the total number of days hospitalised due to heart failure.

CRT-P vs OPT

In CARE-HF,¹¹¹ the 72 participants in the CRT-P group (n=409) who were hospitalised with worsening heart failure had a total of 122 hospitalisations, compared with a total of 252 hospitalisations for 133 patients in the OPT group (n=404). In COMPANION,¹²² 33% of total admissions were due to the heart failure among patients with CRT-P compared with 46% of total admissions among patients with OPT at a median 16.2 months follow-up for those with CRT-P and 11.9 months for those with OPT. The number of average admissions per patient year of follow up was also lower with CRT-P (0.41 vs 0.73 OPT). The average length of stay per admission was similar between the treatment groups (CRT-P 8.6 vs 8.2 days OPT). Similarly, MIRACLE¹²³ found that the total number of days hospitalised due to heart failure was lower with CRT-P compared with OPT (83 vs 363 days respectively) at 6 months follow-up, but no statistical comparison was reported. However, hospitalisation occurred twice as often in those with OPT (50 vs 25 events CRT-P).

The rate of events was calculated (no. of events/N*follow-up) for each trial and combined in a meta-analysis using the inverse variance method. Although statistical heterogeneity was present (Chi² 28.27, df 3, p<0.00001), the direction of the effect was fairly consistent (Figure 14). A significant reduction in the rate of heart failure hospitalisations was found with CRT-P (RR 0.58, 95% CI 0.35 to 0.96, p=0.03).

CRT-D vs OPT

In COMPANION,¹²² the proportion of total admissions was lower with CRT-D (36% vs 46%) at a median 15.7 months follow-up for those with CRT-P and 11.9 months for those with OPT. The number of average admissions per patient year of follow-up was lower in those with CRT-D (0.43 vs 0.73 OPT). The average length of stay per admission was similar for both treatment groups (CRT-D 8.8 vs 8.2 OPT).

CRT-P vs CRT-D

COMPANION¹²² stated that there were no significant differences between those with CRT-P vs those with CRT-D in any of the hospitalisation endpoints and results for the proportion of admissions that were related to heart failure were similar (33% vs 36% respectively). This was reflected in both the number of average admissions per patient year of follow-up (CRT-P 0.41 vs 0.43 CRT-D) and the average length of stay per admission (CRT-P 8.6 vs 8.8 CRT-D) (see Table 40).

Figure 14 Number of hospitalisations due to heart failure, CRT-P vs OPT

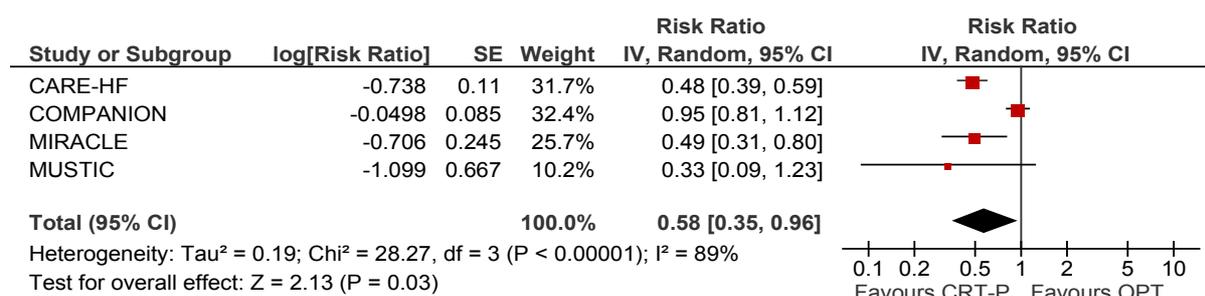


Table 40: Hospitalisations related to heart failure: number of events and/or days of admission

Study	Outcome; follow-up, months	CRT-P	OPT	Effect	95% CI, p value
CARE-HF ¹¹¹	Hospitalisation events, 29.4 ^a	122	252		
MIRACLE ¹²³	Total number of days ; 6	83	363		
	Number of hospitalisations	25	50		
COMPANION ¹²²	Number of admissions, (% of total admissions); CRT-P 16.2, OPT 11.9 ^b	329 (33)	235 (46)		
	Number of average admissions per patient year of follow-up	0.41	0.73		
	Average days per patient year of follow-up (average length of stay per admission)	3.6 (8.6)	5.9 (8.2)		
		CRT-D	OPT		
	Number of admissions , (% of total admissions); CRT-D 15.7, OPT 11.9 ^b	333 (36)	235 (46)		
	Number of average admissions per patient year of follow-up	0.43	0.73		
	Average days per patient year of follow-up (average length of stay per admission)	3.8 (8.8)	5.9 (8.2)		

^a Mean ^b Median. COMPANION¹¹⁸ states that no significant difference were found in any of the hospitalisation end-points for CRT-P vs CRT-D (no p values reported).

4.3.2.7 Arrhythmias

CARE-HF trial¹¹¹ reported atrial arrhythmias or ectopy, while MUSTIC trial¹²⁷ reported decompensation due to persistent atrial fibrillation. Due to the different outcome measures of the two trials, data were not pooled. No comparisons of CRT-D vs OPT or CRT-P vs CRT-D were reported.

CRT-P vs OPT

In CARE-HF,¹¹¹ the risk of arrhythmias or ectopy was significantly higher with CRT-P compared with OPT (15.6% vs 10.1% respectively; RR 1.54, 95% CI, 1.07 to 2.23, p=0.02). One reported case of decompensation due to persistent atrial fibrillation occurred in the OPT treatment group during the second crossover period of the MUSTIC trial¹²⁷ (RR 0.33, 95% CI, 0.01 to 8.02, p=0.50) (see Table 41).

4.3.2.8 Worsening heart failure

Three of the trials reported data on worsening heart failure (not defined by NYHA class), but outcome definitions differed.

CRT-P vs OPT

In CARE-HF,¹¹¹ fewer people with CRT-P experienced worsening heart failure than with OPT (46.7% vs 64.9% OPT; RR 0.72, 95% CI, 0.63 to 0.82, p<0.001). In MIRACLE,¹²³ heart failure requiring IV diuretics (5.7% vs 10.7% OPT; HR 0.51, 95% CI, 0.26 to 1.00, p=0.05), vasodilators or positive inotropic agents (CRT-P 2.6% vs OPT 6.2%; HR 0.41, 95% CI, 0.16 to 1.08, p=0.06) and medication for heart failure (CRT-P 7.0% vs OPT 15.6%; HR 0.43, 95% CI, 0.24 to 0.77, p=0.004) were lower in those with CRT-P than OPT (see Table 42). MUSTIC¹²⁷ reported one case of severe decompensation in the CRT-P OFF group, leading to a premature switch to active pacing (RR 0.33, 95% CI, 0.01 to 8.02, 0.50). Despite the differing definitions used by the trials, the risk of worsening heart failure was reduced with CRT-P when the trials were combined in a meta-analysis (RR 0.71, 95% CI 0.63 to 0.80, p<0.00001) (Figure 15). No significant statistical heterogeneity was observed.

Figure 15 Worsening heart failure, CRT-P vs OPT

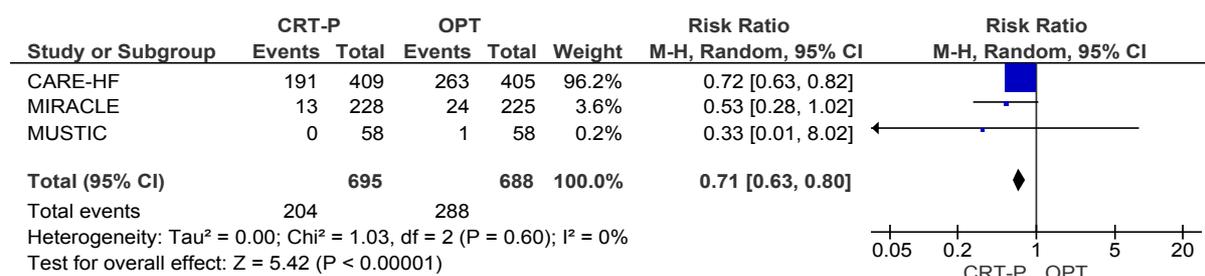


Table 41: Arrhythmias

Study	Outcome; follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ¹¹¹	Atrial arrhythmias or ectopy, 29.4 ^a	64/409 (15.6)	41/404 (10.1)	RR 1.54 ^b	1.07 to 2.23, 0.02 ^b
MUSTIC ¹²⁷	Decompensation due to persistent atrial fibrillation, 6 months	1 st period: 0/29 2 nd period: 0/29	1 st period: 1/29 (3.4) 2 nd period: 0/29	RR 0.33 ^b	0.01 to 8.02, 0.50 ^b

^a Mean. ^b Calculated by reviewer.

Table 42: Worsening heart failure

Study	Outcome; follow-up, months	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ¹¹¹	Worsening heart failure, 29.4 ^a	191/409 (46.7)	263/405 (64.9)	RR 0.72 ^b	0.63 to 0.82 ^b , <0.001
MIRACLE ¹²³	Heart failure requiring IV medication; 6				
	- diuretic agents	13/228 (5.7)	24/225 (10.7)	HR 0.51	0.26 to 1.00, 0.05
	- vasodilators or positive inotropic agents	6/228 (2.6)	14/225 (6.2)	HR 0.41	0.16 to 1.08, 0.06
	- medication for heart failure	16/228 (7.0)	35/225 (15.6)	HR 0.43	0.24 to 0.77, 0.004
MUSTIC ¹²⁷	Severe decompensation, 6 months	1 st period: 0/29 (0) 2 nd period: 0/29 (0)	1 st period: 1/29 (3.4) 2 nd period: 0/29 (0)	RR 0.33 ^b	0.01 to 8.02, 0.50 ^b

^a Mean. ^b Calculated by reviewer.

4.3.2.9 Change in NYHA class

CARE-HF trial,¹¹¹ COMPANION¹¹⁸ and MIRACLE¹²³ reported improvement in NYHA class. The three trials included people in NYHA class III and IV at baseline. CARE-HF¹¹¹ reported NYHA class at 18 months and mean NYHA class at 90 days, MIRACLE¹²³ reported improvements in NYHA class at 6 months, and COMPANION¹¹⁸ at 3 and 6 months. NYHA class was one of three reported primary endpoints in MIRACLE.¹²³

CRT-P vs OPT

All three trials reported a statistically significant greater proportion of participants with improvement in NYHA class with CRT-P than with OPT (see Table 43). CARE-HF¹¹¹ also reported an improvement in mean NYHA class with CRT-P [2.1 (SD 1.0) vs 2.7 (SD 0.9) OPT, $p < 0.001$]. There was no evidence of statistical heterogeneity between the studies (Chi^2 70, $\text{df}=2$, $I^2=0\%$) when the data were pooled in a random effects meta-analysis (see Figure 16). The pooled data from all three trials showed an increase in the proportion of people with an improvement in one or more NYHA class with CRT-P compared with OPT (RR 1.68; 95% CI, 1.52 to 1.86; $p < 0.00001$).

CRT-D vs OPT

In COMPANION,¹¹⁸ the proportion of people with an improvement in NYHA class was statistically significantly greater with CRT-D compared with OPT at both 3 (CRT-D 55% vs OPT 24%, $p < 0.001$) and 6 months follow-up (CRT-D 57% vs OPT 38%; $p < 0.001$).

CRT-P vs CRT-D

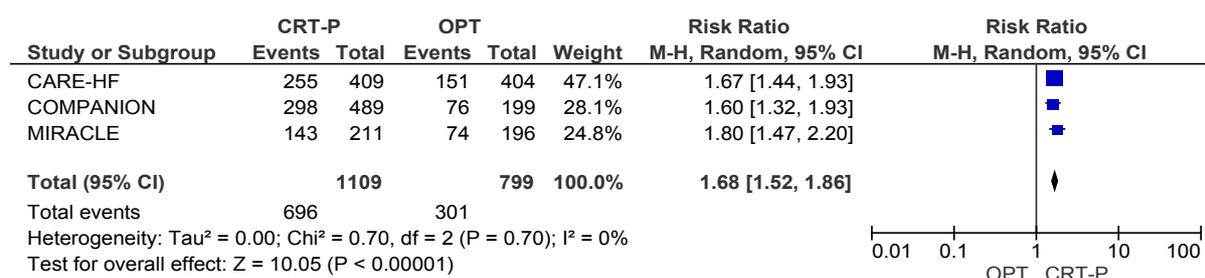
The proportion of people with an improvements in NYHA class was similar with CRT-P and with CRT-D at both 3 (58% vs 55% respectively) and 6 months follow-up (61% vs 57% respectively; RR 0.93; 95% CI, 0.84 to 1.04; $p=0.20$) in COMPANION.¹¹⁸ However, this comparison should be treated with caution as the trial was not powered it.

Table 43: Changes in NYHA class

Study	Outcome, follow-up	CRT-P, n/N (%)	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ¹¹¹	NYHA class at 18 months, Class I	105/409 (25.7)	39/404 (9.7)	RR 1.67 ^{a,b}	1.44 to 1.93, <0.00001 ^{a,b}
	Class II	150/409 (36.7)	112/404 (27.7)		
	Class III or IV	80/409 (19.6)	152/404 (37.6)		
	NYHA class, mean (SD) at 90 days	2.1 (1.0)	2.7 (0.9)	MD ^c 0.6	0.4 to 0.7, <0.001
MIRACLE ¹²³	improved ≥ 2 classes; 6 months	34/211 (16)	12/196 (6)	RR 1.80 ^b	1.47 to 2.20, <0.00001 ^b
	improved 1 class	109/211 (52)	62/196 (32)		
	no change	64/211 (30)	115/196 (59)		
	worsened	4/211 (2)	7/196 (4)		
COMPANION ¹¹⁸	Improvement in NYHA class symptoms, %				
	3 months	320 ^d /551 (58)	58 ^d /242 (24)		<0.001
	6 months	298 ^d /489 (61)	76 ^d /199 (38)	RR 1.60 ^b	1.32 to 1.93, <0.00001 ^{b,e}
		CRT-D	OPT		
	Improvement in NYHA class symptoms, %				
	3 months	299 ^d /543 (55)	58 ^d /242 (24)		<0.001
	6 months	283 ^d /497 (57)	76 ^d /199 (38)	RR 2.14 ^b	2.14 to 1.53, <0.00001 ^{b,e}
		CRT-P	CRT-D		
Improvement in NYHA class symptoms, %					
3 months	320 ^d /551 (58)	299 ^d /543 (55)			
6 months	298 ^d /489 (61)	283 ^d /497 (57)	RR 0.93 ^b	0.84 to 1.04, 0.20 ^b	

^a RR, 95% CI and p value for class 1 and 2 combined. ^b Calculated by reviewer. ^c MD, mean difference. ^d Numerator calculated by reviewer. ^e Analysis reported in paper, p<0.001.¹¹⁸

Figure 16: Participants with improvement in ≥ 1 NYHA class for CRT-P vs OPT



4.3.2.10 Change in LVEF

Only one trial reported LVEF. MIRACLE¹²³ reported absolute change in median LVEF at 6 months for those with CRT-P and with OPT. No comparisons of CRT-D vs OPT or CRT-P vs CRT-D were reported.

CRT-P vs OPT

MIRACLE¹²³ reported an improvement in median LVEF with CRT-P (+4.6, 95% CI, 3.2 to 6.4) but LVEF reduced with OPT (-0.2, 95% CI, -1.0 to 1.5). The difference between the two changes was statistically significant at 6 months follow-up (p<0.001).

4.3.2.11 Exercise capacity

COMPANION¹¹⁸ reported the mean increase in 6-minute walk at 3 and 6 months, while MIRACLE¹²³ reported median change from baseline in 6-minute walk and change in total exercise time. Change in 6-minute walk was one of three primary endpoints in this trial. MUSTIC¹²⁷ reported mean distance walked in 6 minutes at 3 months. Only CARE-HF¹¹¹ did not report 6-minute walk distance. Only two trials reported change in peak oxygen consumption. The MIRACLE trial¹²³ reported median change in VO₂ and MUSTIC¹²⁷ reported mean VO₂ uptake (see Table 45). No comparisons of CRT-D vs OPT or CRT-P vs CRT-D were reported.

CRT-P vs OPT

In all three trials, the distance walked in 6 minutes was statistically significantly greater for CRT-P compared with OPT (see Table 44). In MIRACLE,¹²³ CRT-P also had a superior outcome for change in total exercise time (81 sec vs 19 sec OPT, p=0.001).

The trials were combined in meta-analysis. For meta-analysis of the MUSTIC crossover trial,¹²⁷ data were combined from both periods. This method provides a conservative analysis, with the study being

under-weighted rather than over-weighted.⁶⁷ Trials reporting change values and final values were included in separate subgroups. There was some evidence of statistical heterogeneity between the studies with the inclusion of MUSTIC¹²⁷ (Chi^2 2.93, $\text{df}=2$, $I^2=32\%$). The improvement in distance walked in 6 minutes was statistically significantly greater for those with CRT-P than OPT (MD 38.14, 95% CI, 21.74 to 54.54; $p<0.00001$) (see Figure 17).

MIRACLE¹²³ reported statistically significantly greater improvements in VO_2 with CRT-P compared with OPT (+1.1 units vs +0.2 units respectively, $p=0.009$). In the MUSTIC trial,¹²⁷ authors combined the results of the crossover periods for statistical analysis, which demonstrated significantly greater uptake of VO_2 in those with CRT-P (16.2 units vs 15 units OPT; $p=0.029$).

CRT-D vs OPT

Improvement in 6-minute walk distance was statistically significantly greater with CRT-D compared with OPT at 3 (44 metres vs 9 metres respectively, $p<0.001$) and 6 months (46 metres vs 1 metre respectively, $p<0.001$) in COMPANION.¹¹⁸

CRT-D vs CRT-P

There were no statistically significant differences in 6-minute walk distance between those with CRT-D and those with CRT-P (MD -6.0, 95% CI, -19.87 to 7.87; $p=0.40$). However, all comparisons between CRT-P vs CRT-D should be treated with caution, as the trial was not powered for this comparison.

Figure 17: Change in 6-minute walk distance at 6 months

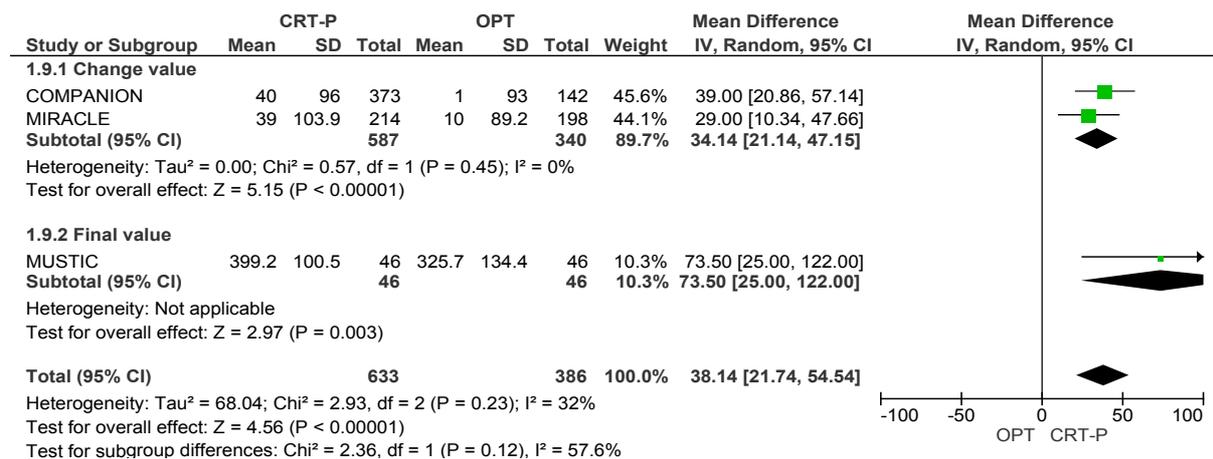


Table 44: Change in 6-minute walk

Study	Outcome; follow-up, month	CRT-P	OPT	Effect	95% CI, p value
MIRACLE ¹²³	Change in 6-minute walk, m, median (95% CI; SD); 6	+ 39 (26 to 54; 103.9 ^a) (n=214)	+ 10 (0 to 25; 89.2 ^a) (n=198)		0.005
	Change in total exercise time, sec, median (95% CI)	+81 (62 to 119) (n=159)	+19 (-1 to 47) (n=146)		0.001
MUSTIC ¹²⁷	Distance in 6-minute, m, mean (SD)				
	Group 1 (CRT-P ON, CTR-P OFF) n=22	384.1 (78.9)	336.1 (128.3)		
	Group 2 (CRT-P OFF, CRT-P ON) n=24	412.9 (116.9)	316.2 (141.8)		
	Both groups n=46	399.2 (100.5)	325.7 (134.4)		<0.001
COMPANION ¹⁸	Change in 6-minute walk, m, mean change (SD)				
	3 months	33 (99) (n=422)	9 (84) (n=170)		<0.001
	6 months	40 (96) (n=373)	1 (93) (n=142)		<0.001
		CRT-D	OPT		
	Change in 6-minute walk, m, mean change (SD)				
	3 months	44 (109) (n=420)	9 (84) (n=170)		<0.001
	6 months	46 (98) (n=378)	1 (93) (n=142)		<0.001
		CRT-P	CRT-D		
	Change in 6-minute walk, m, mean change (SD)				
	3 months	33 (99) (n=422)	44 (109) (n=420)		
6 months	40 (96) (n=373)	46 (98) (n=378)	MD -6.0 ^a	-19.87 to 7.87, 0.40 ^a	

^a Calculated by reviewer.

Table 45: Change in peak oxygen consumption

Study	Outcome; follow-up, months	CRT-P	OPT	Effect	p value
MIRACLE ¹²³	Change in VO ₂ , ml/kg/ min, median (95% CI); 6	+ 1.1 (0.6 to 1.7) (n=158)	+ 0.2 (-0.2 to 0.8) (n=145)		0.009
MUSTIC ¹²⁷	VO ₂ uptake, ml/kg of body weight/min, mean (SD); 3				
	Group 1 (CRT-P ON, CTR-P OFF) n=18	15.9 (5.8)	15.3 (5.9)		
	Group 2 (CRT-P OFF, CRT-P ON) n=20	16.4 (3.6)	14.8 (3.9)		
	Both groups n=38	16.2 (4.7)	15 (4.9)		0.029

4.3.2.12 QoL

All four studies reported change in QoL assessed by the Minnesota Living with Heart Failure Questionnaire (MLWHFQ). Change in MLWHFQ scores was the primary outcome in MUSTIC.¹²⁷ CARE-HF¹¹⁵ also reported EQ-5D (European Quality of Life Questionnaire – 5 Dimensions), mean Quality-Adjusted Life-Year score (QALY) and mean life-years (see Table 46).

CRT-P vs OPT

All four trials showed statistically significant improvements in MLWHFQ scores with CRT-P compared with OPT (lower scores indicate improved QoL). The trials were combined in a meta-analysis. COMPANION¹¹⁸ and MIRACLE¹²³ reported mean change from baseline for MLWHFQ scores, while CARE-HF¹¹⁵ and MUSTIC¹²⁷ reported final mean values. MUSTIC¹²⁷ reported data per crossover period and combined data for both crossover periods (see Figure 18).

For meta-analysis of the MUSTIC cross-over trial,¹²⁷ the combined data from both cross-over periods were included, as this method provides a conservative analysis, with the study being under-weighted rather than over-weighted.⁶⁷ There was some evidence of statistical heterogeneity between the studies (Chi^2 4.39, $\text{df}=3$, $I^2=32\%$), but the direction of effect was consistent. The mean difference was -10.33 (95% CI, -13.31 to -7.36) and MLWHFQ scores were statistically significantly lower in those with CRT-P compared with OPT ($p=0.00001$), indicating improved QoL.

Other QoL measures with statistically significant improvements reported on by CARE-HF¹¹⁵ were EQ-5D and QALY. The mean value of the EQ-5D was statistically significantly higher in those with CRT-P at each follow-up (90 days 0.70 vs 0.63 OPT, $p<0.001$; 3 months 0.69 vs 0.61 OPT, $p<0.0001$; 18 months 0.61 vs 0.51 OPT, $p<0.0001$; end of study 0.56 vs 0.43 OPT, $p<0.0001$), although scores appeared to be lower by the end of the study (37.4 months) compared with those at baseline in both treatment arms. Mean QALY was statistically significantly higher in those with CRT-P at 18 months (0.95 vs 0.82 OPT, $p<0.0001$) and at the end of the study (1.45 vs 1.22, <0.0001).

CRT-D vs OPT

The reduction in MLWHFQ scores, indicating improved QoL, in COMPANION¹¹⁸ was statistically significantly greater in those with CRT-D at both 3 (-24 vs -9 OPT, $p<0.001$) and 6 months (-26 vs -12 OPT, $p<0.001$).

CRT-P vs CRT-D

In COMPANION,¹¹⁸ improvements in MLWHFQ scores were similar in those with CRT-P and in those with CRT-D at 6 months (-25 vs -26, MD 1.00, 95% CI, -2.46 to 4.46; $p=0.57$).

Table 46: Quality of Life Measures

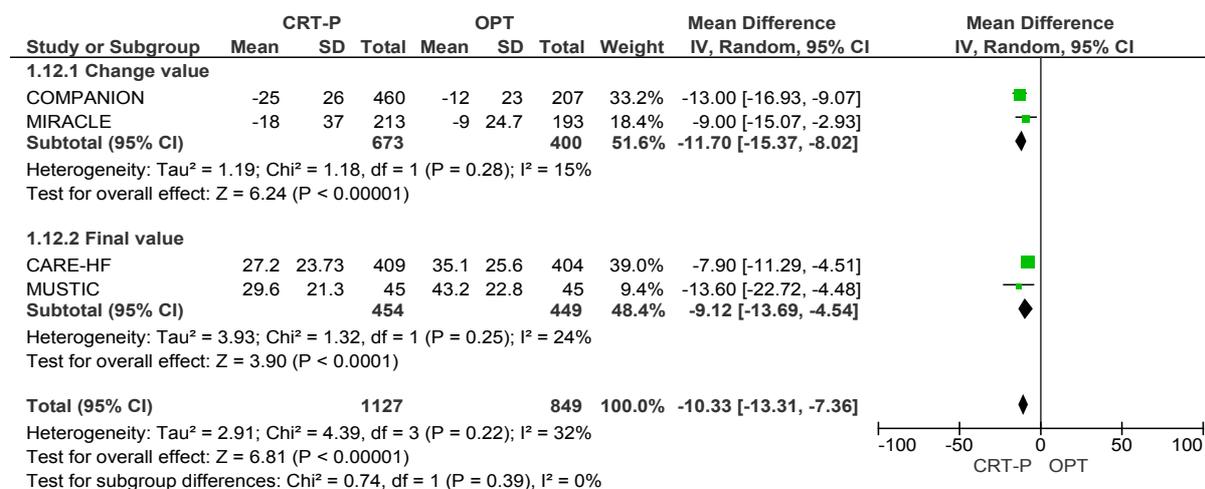
Study	Outcomes, follow-up	CRT-P	OPT	MD (95% CI), p value
CARE-HF ¹¹⁵	QALY, mean (95% CI)	(n= 409)	(n= 404)	
	3 months	0.16 (0.15-0.16)	0.15 (0.14-0.15)	0.01 (0.001 to 0.018), 0.285
	18 months	0.95 (0.91-0.99)	0.82 (0.78-0.86)	0.13 (0.07 to 0.018), <0.0001
	End of study, mean 37.4 months	1.45 (1.38-1.53)	1.22 (1.15-1.29)	0.23 (0.13 to 0.33), <0.0001
	Life-years, mean (95% CI)			
	3 months	0.241 (0.238-0.244)	0.241 (0.238-0.244)	0.0003 (-0.004 to 0.0045), 0.90
	18 months	1.37 (1.34-1.40)	1.33 (1.29-1.37)	0.04 (-0.01 to 0.09), 0.13
	End of study, mean 37.4 months	2.07 (1.99-2.15)	1.96 (1.88-2.05)	0.10 (-0.01 to 0.22), 0.07 ^a
	EQ-5D, mean (95% CI)			
	Baseline	0.60 (0.58-0.63)	0.60 (0.57-0.63)	-
	90 days, (SD) ¹¹¹	0.70 (28)	0.63 (0.29)	0.08 (0.04 to 0.12), 0.001
	3 months	0.69 (0.66-0.72)	0.61 (0.59-0.64)	0.08 (0.04 to 0.11), <0.0001
	18 months	0.61 (0.58-0.64)	0.51 (0.48-0.54)	0.10 (0.06 to 0.15), <0.0001
	End of study, mean 37.4 months	0.56 (0.52-0.59)	0.43 (0.39-0.46)	0.13 (0.08 to 0.18), <0.0001 ^b
	MLWHFQ, mean			
	Baseline (95% CI)	44.6 (42.5-46.7)	43.7 (41.5-45.8)	-
	90 days, (SD) ¹¹¹	31 (22)	40 (22)	-10 (-8 to -12), <0.001
	3 months (95% CI)	30.1 (27.9-32.3)	38.9 (36.6-41.2)	-10.6 (-8.1 to -13.1), <0.0001 ^c
	18 months (95% CI)	28.4 (26.2-30.5)	36.0 (33.5-38.5)	-10.7 (-7.6 to -13.8), <0.0001 ^c
	End of study, mean 37.4 months (95% CI) (SD)	27.2 (24.9-29.5) (23.7)	35.1 (32.6-37.6) (25.6)	-10.1 (-6.8 to -13.3), <0.0001 ^c
MIRACLE ¹²³	Change in MLWHFQ score; 6 months, median	(n=213)	(n=193)	

Study	Outcomes, follow-up	CRT-P	OPT	MD (95% CI), p value
	(95% CI) SD	-18 (-22 to -12) 37	-9 (-12 to -5) 24.7	0.001
MUSTIC ¹²⁷	MLWHFQ score, mean (SD)			
	Group 1 (CRT-ON, CRT-P OFF), n=23	33.3 (22)	42.6 (20.9)	
	Group 2 (CRT-OFF, CRT-P ON), n=22	25.7 (20.4)	44.0 (25)	
	Both Groups, n=45	29.6 (21.3)	43.2 (22.8)	<0.001
COMPANION ¹¹⁸	MLWHFQ, % increase, mean (SD)			
	3 months	-24 (27) (n=510)	-9 (21) (n=243)	<0.001
	6 months	-25 (26) (n=460)	-12 (23) (n=207)	<0.001
	MLWHFQ, % increase, mean (SD)	CRT-D	OPT	
	3 months	-24 (28) (n=514)	-9 (21) (n=243)	<0.001
	6 months	-26 (28) (n=478)	-12 (23) (n=207)	<0.001
	MLWHFQ, % increase, mean (SD)	CRT-P	CRT-D	
	3 months	-24 (27) (n=510)	-24 (28) (n=514)	
	6 months	-25 (26) (n=460)	-26 (28) (n=478)	1.00 (2.46 to 4.46), 0.57 ^d

MLWHFQ – 21 questions rated on a 6-point scale (total score 105), with higher scores indicating poorer quality of life.^a Calculated by reviewer.

^b P-value based on restricted mean survival used to estimate QALYs. This is not the best estimator of survival differences between groups (statistically inefficient), see instead all-cause mortality above. ^c Decline in EQ-5D despite maintained effect with Minnesota Living with Heart Failure Questionnaire (MLWHFQ) scores is because death has a health use of zero in EQ-5D and is not included in the MLWHFQ. ^d MLWHFQ scores include last value carried forward for missing items. Patients who died were not included. Difference between groups accounts for baseline NYHA class and MLWHFQ score.

Figure 18: Change in MLWHF scores



4.3.2.13 Adverse events

Reporting of adverse events was limited, as can be seen in Table 47 and Table 48. All participants in MIRACLE¹²³ and MUSTIC¹²⁷ were implanted with a CRT-P device, with pacing inactive in the control (OPT) group. Both trials randomised only those people who had a successful implantation, although MIRACLE¹²³ also reported adverse events for all enrolled participants (including 71 participants who were part of a pilot phase and not included in the effectiveness results) (Table 47).

CARE-HF¹¹¹ and COMPANION¹¹⁸ randomised participants to receive either a CRT-P (or CRT-D) device or OPT only (Table 48). However, CARE-HF¹¹¹ limited reporting of adverse events to device-related complications. Only COMPANION¹¹⁸ reported any statistical comparison of CRT-P or CRT-D versus OPT for adverse events.

Between 4.6%¹¹¹ and 12.6%¹¹⁸ of device implantations were unsuccessful in the trials (Table 47, Table 48). Death due to adverse clinical events during the implantation procedure occurred among 0.4% of all participants in MIRACLE,¹²³ and in COMPANION¹¹⁸ 0.8% of CRT-P recipients and 0.5% of CRT-D recipients died due to procedural complications. Mortality rate 30 days after randomisation was not statistically significantly different between OPT only (1.2%) and CRT-P (1.0%, p=0.34) or CRT-D (1.8%, p=0.97),¹¹⁸ or between CRT-P and CRT-D (RR 0.53, 95% CI 0.20 to 4.41, p=0.2). Device related death occurred among 0.2% of participants randomised to CRT-P in CARE-HF,¹¹¹ and in 0.2% of those randomised to OPT (after receiving a device), although the time period was not reported.¹¹¹

Moderate or severe adverse events related to the implantation procedure occurred in 10% of the CRT-P group and 8% of the CRT-D group in COMPANION.¹¹⁸ The most common reported adverse events were coronary sinus/venous dissection (0.3% CRT-P, 0.5% CRT-D¹¹⁸ 4.0%,¹²³ 2.4%¹¹¹) or perforation (1.1% CRT-P, 0.8% CRT-D,¹¹⁸ 2.1%¹²³) and lead related events (6%,^{111;123} 13.8%¹²⁷). Hospitalisation for repositioning or replacement of LV lead was more frequent in those with CRT-P-ON (4.8%) than CRT-P OFF (1.3%) in participants who were successfully implanted and randomised in MIRACLE.¹²³

The proportion of moderate or severe adverse events from any cause was statistically significantly higher in those with CRT-D compared with OPT only (69% vs 61% respectively, $p=0.03$), but not between those with CRT-P and those with OPT only (66% vs 61% respectively, $p=0.15$),¹¹⁸ or between those with CRT-P and CRT-D (RR 0.95, 95% CI 0.88 to 1.03, $p=0.25$). Authors of CARE-HF¹¹¹ state that the frequency of respiratory tract infections, hypotension, falls or syncope, acute coronary syndromes, renal dysfunction, ventricular arrhythmias or ectopy, and neurologic events were similar in the CRT-P and OPT only groups.

Table 47: Adverse events for participants with a CRT device (randomised to CRT-P on or off)

Study	Adverse events	CRT device, n/N (%)
MIRACLE ¹²³	<i>All participants undergoing implantation (n=571)</i>	
Enrolled n=571	Unsuccessful implantation	43/571 (7.5)
Successfully implanted n=528	Complete heart block requiring permanent cardiac pacing	2/571 (0.4)
Randomised n=453	Death due to clinical events during implant procedure (progressive hypotension; asyctole)	2/571 (0.4)
CRT-P n=228	Coronary-sinus dissection	23/571 (4.0)
OPT n=225	Cardiac vein or coronary-sinus perforation ^a	12/571 (2.1)
	<i>Participants who had successful implantation (n=528)</i>	
	Left ventricular lead repositioned	20/528 (3.8)
	Left ventricular lead replaced	10/528 (1.9)
	Pacemaker-related infection requiring explantation	7/528 (1.3)
	Hospitalised for repositioning/replacement of LV lead	
	CRT-P-ON	11/228 (4.8)
	CRT-P-OFF	3/225 (1.3)
MUSTIC ¹²⁷	Unsuccessful implantation	5/64 (7.8)
Enrolled n=67	Early lead dislodgement	8/58 (13.8)
Randomised n=58	<i>CRT-P-ON</i>	
CRT-ON, CRT-P	Uncorrectable loss of left ventricular pacing efficacy	2/58 (3.4)
OFF n =29	Decompensation attributed to rapidly progressive aortic stenosis	1/58 (1.7)
CRT-P OFF, CRT-P ON n=29	<i>CRT-P-OFF</i>	
	Severe decompensating leading to a premature switch to active pacing	1/58 (1.7)
	Decompensation due to persistent atrial fibrillation	1/58 (1.7)

^a 3 of these recovered and continued in study.

Table 48: Adverse events for participants randomised to CRT-P or OPT (no device)

Study	Adverse events	CRT-P, n/N (%)	OPT, n/N (%)	RR (95% CI), p value
CARE-HF ¹¹¹ Enrolled and randomised n=813 CRT-P n=409 OPT n=404 (CRT-P OFF)	Unsuccessful implantation	19/409 (4.6)		
	Device related death			
	- heart failure aggravated by lead displacement	1/409 (0.2)		
	- septicaemia after receiving a device		1/404 (0.2)	
	Most common adverse device- or procedure- related events			
	Lead displacement	24/409 (5.9)		
	Coronary-sinus dissection	10/409 (2.4)		
	Pocket erosion	8/409 (2.0)		
Pneumothorax	6/409 (1.5)			
Device related infection	3/409 (0.7)			
COMPANION ¹¹⁸ Enrolled and Randomised n=1520 CRT-P n=617 CRT-D n=595 OPT n=308	Unsuccessful implantation	78/617 (12.6)		
	Deaths due to procedural complications	5/615 (0.8)		
	Mortality rate 30 days after randomisation	6 ^b /617 (1.0)	4 ^b /308 (1.2)	p=0.34
	Moderate or severe adverse event from any cause	407 ^b /617 (66)	188 ^b /308 (61)	p=0.15
	Moderate or severe adverse event related to implantation procedure	62 ^b /617 (10)		
	Coronary venous dissection	2 ^b /617 (0.3)		
	Coronary venous perforation	7 ^b /617 (1.1)		
	Coronary venous tamponade	3 ^b /617 (0.5)		
		CRT-D, n/N (%)	OPT, n/N (%)	
	Unsuccessful implantation	54/595 (9.1)		

Study	Adverse events	CRT-P, n/N (%)	OPT, n/N (%)	RR (95% CI), p value
	Deaths due to procedural complications	3/595 (0.5)		
	Mortality rate 30 days after randomisation	11 ^b /595 (1.8)	4/308 (1.2)	p=0.97
	Moderate or severe adverse event from any cause	411 ^b /595 (69)	188/308 (61)	p=0.03
	Moderate or severe adverse event related to implantation procedure	48 ^b /595 (8)		
	Coronary venous dissection	3 ^b /595 (0.5)		
	Coronary venous perforation	5 ^b /595 (0.8)		
	Coronary venous tamponade	2 ^b /595 (0.3)		
		CRT-P, n/N (%)	CRT-D, n/N (%)	
	Mortality rate 30 days after randomisation	6 ^b /617 (1.0)	11 ^b /595 (1.8)	0.53 (0.20, 1.41), 0.20 ^c
	Moderate or severe adverse event from any cause	407 ^b /617 (66)	411 ^b /595 (69)	0.95 (0.88, 1.03), 0.25 ^c

^a Number of patients per treatment arm not reported. ^b Denominator calculated by reviewer. ^c Calculated by reviewer.

4.3.2.14 Subgroup analyses reported by included RCTs

Only CARE-HF¹¹¹ presented subgroup analyses that were clearly pre-defined (Table 49 and Table 50). The trial reported LVEF in people with or without ischaemic heart disease. A statistically significant interaction between CRT-P and aetiology was found ($p=0.003$), whereby people with non-ischaemic heart disease experienced a greater change in LVEF (Table 49).

The effect of CRT-P on the composite endpoint (death from any cause or unplanned hospitalisation for a major cardiovascular event) in pre-defined subgroups with analysis stratified for NYHA class (except the subgroup analyses of NYHA class) can be seen in Table 50. The overall effect of CRT-P on the composite end-point was HR 0.63 (95% CI, 0.51 to 0.77) and there was little difference in this outcome for any of the pre-defined subgroups.

Table 49: Changes in LVEF for ischemic or non-ischemic heart disease

Study	Median follow-up, months	CRT-P		OPT		p value
		IHD, n=168	non-IHD, n=197	IHD, n=135	non-IHD, n=235	
CARE-HF ¹¹⁷	LVEF % at baseline, median (IQR)	25 (22-29)	24 (21-29)	26 (22-30)	24 (21-29)	0.1867 (IHD vs non-IHD)
	mean (SD) change at 18 months, % ^a	6.1 (1.2)	10.9 (1.5)	1.3 (0.7)	2.4 (1.7)	0.003 for interaction between CRT and aetiology

IHD, ischemic heart disease. ^a Values estimated by reviewer from figure using Engauge digitising software (not stated but error bars presumed to show SD).¹¹⁷

Table 50: Effect of CRT-P on death from any cause or unplanned hospitalisation for a major cardiovascular event failure in pre-defined subgroups

Study	Subgroups	Patients with event/ Total no. of patients ^a	Hazard ratio (95% CI)
CARE- HF ¹¹¹	Overall with primary end point	383/813	0.63 (0.51 to 0.77)
	Age ^b <66.4 year	163/406	0.55 (0.40 to 0.75)
	Age ^b ≥66.4 year	220/407	0.68 (0.52 to 0.89)
	Sex male	290/597	0.62 (0.49 to 0.79)
	Sex female	93/215	0.64 (0.42 to 0.97)
	NYHA class III	349/763	0.64 (0.52 to 0.80)
	NYHA class IV	34/50	0.50 (0.25 to 1.01)
	Dilated cardiomyopathy - No	238/443	0.68 (0.53 to 0.88)
	Dilated cardiomyopathy - Yes	145/370	0.51 (0.36 to 0.73)
	Systolic blood pressure ^b <117 mmHg	208/401	0.60 (0.46 to 0.80)
	Systolic blood pressure ^b ≥117 mmHg	170/402	0.66 (0.48 to 0.89)
	NT-BNP ^c <214.5 pg/ml	122/366	0.53 (0.36 to 0.76)
	NT-BNP ^c ≥214.5 pg/ml	224/366	0.70 (0.54 to 0.91)
	Ejection fraction ^b <24.7%	205/372	0.65 (0.49 to 0.86)
	Ejection fraction ^b ≥24.7%	152/373	0.62 (0.44 to 0.85)
	End-systolic volume index ^b <119.2 ml/m ²	156/366	0.71 (0.52 to 0.98)
	End-systolic volume index ^b ≥119.2 ml/m ²	193/366	0.54 (0.40 to 0.73)
	QRS interval <160 ms	152/290	0.74 (0.54 to 1.02)
	QRS interval ≥160 ms	222/505	0.60 (0.46 to 0.79)
	Interventricular mechanical delay ^b <49.2 ms	199/367	0.77 (0.58 to 1.02)
	Interventricular mechanical delay ^b ≥49.2 ms	147/368	0.50 (0.36 to 0.70)
	Mitral-regurgitation area ^b <0.218	114/302	0.86 (0.60 to 1.25)
	Mitral-regurgitation area ^b ≥0.218	175/303	0.56 (0.41 to 0.75)
	Glomerular filtration rate ^b <60.3 ml/min/1.73m ²	196/369	0.67 (0.50 to 0.89)
	Glomerular filtration rate ^b ≥60.3 ml/min/1.73m ²	142/370	0.57 (0.40 to 0.80)
	Beta-blockers, No	131/227	0.72 (0.51 to 1.02)
	Beta-blockers, Yes	252/586	0.59 (0.46 to 0.76)
Spironolactone, No	166/356	0.58 (0.43 to 0.79)	

	Spironolactone, Yes	217/457	0.67 (0.51 to 0.88)
	Loop diuretics <80 mg of furosemide or equivalent	181/461	0.56 (0.42 to 0.76)
	Loop diuretics ≥80 mg of furosemide or equivalent	202/352	0.69 (0.53 to 0.92)
	Digoxin, No	218/467	0.66 (0.50 to 0.86)
	Digoxin, Yes	165/346	0.59 (0.43 to 0.81)

^a Authors state that due to missing baseline data, not all subgroup numbers total 813. ^b Divided according to the median value in the study population – this lead to some inequality in the sizes if the subgroups. ^c NT-BNP, N-terminal probrain natriuretic peptide.

4.3.3 Summary of clinical effectiveness: people with heart failure as a result of LVSD and cardiac dyssynchrony

- Four RCTs, with a combined total of 2844 participants, were included comparing CRT-P (and CRT-D in one trial) with OPT in people with heart failure as a result of LVSD and cardiac dyssynchrony. The trial comparing CRT-P and CRT-D with OPT randomised participants to each of the three groups, but did not perform a direct comparison of CRT-D and CRT-P.
- There was some risk of bias in the trials in relation to performance, detection and reporting bias; although the risk was unclear in some cases due to inadequate reporting.
- Length of follow-up in the trials varied: 3 months, 6 months, median 11.9-15.7 months and mean 37.4 months including an extension period. Sample size ranged from 58 to 1520 participants. The majority of participants had NYHA class III symptoms, the remaining few had NYHA class IV symptoms.

CRT-P vs OPT:

- Meta-analysis found that CRT-P significantly reduced the risk of all-cause mortality (4 trials, RR 0.75, 95% CI 0.58 to 0.96, p=0.02), heart failure deaths (2 trials, RR 0.67, 95% CI 0.51 to 0.88, p=0.004) and heart failure hospitalisations (4 trials, RR 0.61, 95% CI 0.44 to 0.83, p=0.002).
- Combining three RCTs in a meta-analysis demonstrated no significant difference in sudden cardiac death (RR 0.97, 95% CI 0.44 to 2.14, p=0.94). One RCT (COMPANION) reported no statistically significant difference in total cardiac deaths (CRT-P 17.7% vs OPT 18.8%, p=0.334) or non-cardiac deaths (CRT-P 2.3% vs OPT 3.6%, p=0.122).
- More people with CRT-P had an improvement of one or more NYHA class (RR 1.68, 95% CI 1.52 to 1.86, p<0.00001) in the three trials reporting this outcome.
- One RCT reported change in LVEF and reported a statistically significant improvement with CRT-P compared with OPT (4.6% vs -0.2%, p,0.001) at 6 months.

- There was a greater improvement in exercise capacity with CRT-P, as measured by the distance walked in 6 minutes (6 MWT) (meta-analysis of three trials, change from baseline or final values, MD 38.14 m, 95% CI 21.74 to 54.54, $p < 0.00001$). A statistically significant improvement in peak oxygen consumption was also reported by two of these RCTs.
- All four RCTs found statistically significant improvements in QoL (MLWHFQ) score with CRT-P (change scores or final values MD -10.33, 95% CI -13.31 to -7.36). One trial (CARE-HF) also reported statistically significant improvements in EQ-5D (MD 0.13, 95% CI 0.08 to 0.18, $p < 0.0001$) and QALYs (0.23, 95% CI 0.13 to 0.33, $p < 0.00001$) with CRT-P at end of study (mean 37.4 months).
- One trial reported prespecified subgroup analysis. A significant interaction between CRT-P and aetiology was found, whereby people with non-IHD had a greater change in LVEF. There was little difference in the effect of CRT-P on the composite outcome (death from any cause or unplanned hospitalisation for a major cardiovascular event) for 16 pre-defined subgroups.

CRT-D vs OPT:

- One trial compared CRT-D with OPT. All-cause mortality (HR 0.64, 95% CI 0.48 to 0.86, $p = 0.003$), total cardiac deaths (RR 0.68, 95% CI 0.50 to 0.93, $p = 0.02$), sudden cardiac deaths (HR 0.44, 95% CI 0.23 to 0.86, $p = 0.02$) and heart failure hospitalisations (RR 0.77, 95% CI 0.63 to 0.93, $p = 0.008$) were reduced with CRT-D compared with OPT.
- There were no significant differences in heart failure deaths (HR 0.73, 95% CI 0.47 to 1.11, $p = 0.143$) or non-cardiac deaths (CRT-D 2.3% vs OPT 3.6%, $p = 0.717$) in those with CRT-D compared with those with OPT.
- The proportion of people with an improvement of one or more NYHA class (57% vs 38%, $p < 0.001$), improvements in exercise capacity (change in 6 MWT 46 m vs 1 m, $p < 0.001$), and QoL (MLWHFQ) score (-26 vs -12, $p < 0.001$) at 6 months were statistically significantly greater with CRT-D.

CRT-P vs CRT-D:

- One three-arm trial compared both CRT-P and CRT-D with OPT, but the trial was not powered for a statistical comparison of CRT-P with CRT-D. Statistical comparisons of CRT-P versus CRT-D have been undertaken for the purposes of this review but should be viewed with caution.
- Total cardiac deaths (RR 1.38, 95% CI 1.06 to 1.81, $p = 0.02$) and sudden cardiac deaths (RR 2.72, 95% CI 1.58 to 4.68, $p = 0.0003$) were higher with CRT-P than CRT-D. All-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, $p = 0.12$), heart failure deaths (RR 0.98, 95% CI 0.68 to 1.42, $p = 0.93$), and heart failure hospitalisations (28% vs 29%) were similar for those with CRT-P and those with CRT-D.

- Changes in NYHA class, exercise capacity and QoL were similar for CRT-P and CRT-D.

Adverse events:

- Two trials randomised people with successful implantation only. The other two trials reported device-related deaths between 0.2% and 0.8% for those with CRT-P and 0.5% for those with CRT-D. Moderate or severe adverse events related to implantation procedure were reported as 10% for those with CRT-P and 8% for those with CRT-D by one trial, with 13% and 9% of CRT-P and CRT-D implantations unsuccessful. Moderate or severe adverse events from any cause were more common among those with CRT-D than OPT (CRT-D 69%, CRT-P 66%, OPT 61%, CRT-D vs OPT $p=0.03$, CRT-P vs OPT, $p=0.15$). Reported complications included lead displacements, infections and coronary-sinus dissections.

4.4 People with both conditions

4.4.1 Quantity and quality of research available

Nine RCTs comparing CRT-D and ICD in people at risk of sudden cardiac death due to ventricular arrhythmia and with heart failure as a result of LVSD and cardiac dyssynchrony met the inclusion criteria. Five of these trials reported their findings in more than one paper; a summary of the included papers for each trial can be seen in Table 51.

One of these studies (CONTAK-CD¹²⁸) was included in the 2007 TAR on CRT,⁴³ however participants in CONTAK-CD¹²⁸ were required to have VT as an indication for ICD and defibrillating capacity was available to the control group, and is therefore discussed here rather than in the Section 4.3.

No trials comparing CRT-D with OPT or comparing CRT-D with CRT-P were identified for this population.

Table 51: Included RCTs for people with both conditions

Trial	Publication (Bold indicates primary or key publication)
CONTAK-CD	Higgins <i>et al.</i>, 2003¹²⁸ , Lozano <i>et al.</i> , 2000 ¹³⁰ , FDA report ¹³¹ , Saxon <i>et al.</i> , 1999 ¹²⁹
MADIT-CRT	Moss <i>et al.</i>, 2009,^{132;133} Solomon <i>et al.</i> 2010, ¹³⁴ Goldenberg <i>et al.</i> 2011, ^{136;146} Arshad <i>et al.</i> 2011 ¹⁵²
MIRACLE ICD	Young <i>et al.</i>, 2003¹³⁷
MIRACLE ICD II	Abraham <i>et al.</i>, 2004¹³⁸
Piccirillo 2006	Piccirillo <i>et al.</i>, 2006¹³⁹
Pinter 2009	Pinter <i>et al.</i>, 2009¹⁴⁰
RAFT	Tang <i>et al.</i>, 2010;¹⁴¹ Tang <i>et al.</i> , 2009 ¹⁴²
RethinQ	Beshai <i>et al.</i>, 2007;¹⁴³ Beshai & Grimm, 2007 ¹⁴⁴
RHYTHM ICD	Summary of Safety and Effectiveness 2004^{145;146}

4.4.1.1 Characteristics of the included studies

Study characteristics are summarised in Table 52 and participant characteristics are summarised in Table 53. Further details can be found in the data extraction forms in Appendix 10.

Intervention and comparators

The participants in six of these trials^{128;137;138;140;143;145} were implanted with a device that could provide both CRT and ICD therapy, and the devices in the comparator groups provided back-up ventricular pacing and active ICD therapy only (CRT-off). In three of the trials the comparator group received an ICD only device.^{132;139;141} Participants in both groups of all trials also received OPT (discussed further below).

Participants

Participants included in eight of these studies were required to have guideline indications for ICD therapy (Table 52). Piccirillo¹³⁹ states that the participants were undergoing prophylactic treatment with the ICD or CRT-D. Pinter¹⁴⁰ and colleagues enrolled people ‘without a conventional CRT indication at the time of the study’, however these would now be considered a conventional indication

The trials differed in their eligibility criteria for severity of heart failure (Table 52). The majority of participants in MADIT-CRT,¹³² MIRACLE ICD II¹³⁸ and RAFT¹⁴¹ were in NYHA class II; in CONTAK-CD,¹²⁸ MIRACLE ICD,¹³⁷ RethinQ¹⁴³ and RHYTHM ICD¹⁴⁵ the majority of participants were in NYHA class III; and the majority of participants in Piccirillo¹³⁹ were in NYHA class IV (Table 53). NYHA class was not reported by Pinter,¹⁴⁰ although the eligibility criteria required mild to moderate heart failure. The proportion of participants with ischaemic heart disease varied between the trials, from around 52% (RethinQ¹⁴³) to 100% (Piccirillo¹³⁹). RethinQ¹⁴³ enrolled people with ischemic or non-ischaemic cardiomyopathy and Piccirillo¹³⁹ enrolled people with ischemic dilated cardiomyopathy.

RethinQ¹⁴³ differed from the other trials in the criteria used to define cardiac dyssynchrony. Conventionally, a wide QRS interval indicates electrical dyssynchrony. RethinQ,¹⁴³ however, recruited people with a narrow QRS interval (<130 ms) and evidence of mechanical dyssynchrony on echocardiography. Mean QRS interval in this trial was about 107 ms, and approximately one quarter of participants had a QRS duration of 120 ms or more.

Mean QRS interval in the other eight trials, where reported, ranged from 156 ms (CONTAK-CD¹²⁸) to 169 ms (RHYTHM ICD¹⁴⁵). Pinter¹⁴⁰ did not report baseline QRS duration, but required a minimum duration of 120 ms for study eligibility. MADIT-CRT¹³² required participants to have a QRS duration of at least 130 ms, and reported that around 65% of participants had a QRS interval of 150 ms or more at baseline. Mean LVEF ranged from 21% (CONTAK-CD¹²⁸) to 26% (RethinQ¹⁴³).

The mean age of the participants in the trials was similar, ranging from 63 (MIRACLE ICD II¹³⁸) to 67 (MIRACLE ICD¹³⁷) years. The majority [75% (MADIT-CRT¹³²) to 90% (MIRACLE ICD II¹³⁸)] of participants were men.

Pharmacological therapy

Table 54 displays medication at baseline. The majority of participants in all studies received ACE inhibitors and/or angiotensin receptor blockers, although the proportion receiving beta-blockers varied between the studies. Less than half of participants in the CONTAK-CD study,¹²⁸ around 60% of participants in MIRACLE ICD¹³⁷ and MIRACLE ICD II,¹³⁸ and around 80-95% of participants in MADIT-CRT,¹³² Piccirillo,¹³⁹ RAFT,¹⁴¹ RethinQ¹⁴³ and RHYTHM ICD received beta-blockers. Antiarrhythmic drugs use also varied between the studies; around 33-35% of participants in MIRACLE ICD II,¹³⁸ 33-42% of participants in MIRACLE ICD,¹³⁷ less than a quarter of participants in RHYTHM ICD,¹⁴⁵ around 15% of participants in RAFT,¹⁴¹ 8-12% in RethinQ¹⁴³ and around 7% in MADIT-CRT¹³² were receiving antiarrhythmic drugs. Pharmacological therapy in each of these trials would be considered optimal or close to optimal by current standards, although beta-blocker use in the MIRACLE ICD trials was slightly low.

Table 52: Study characteristics

Parameter	Study name								
	CONTAK-CD ¹²⁸	MADIT-CRT ¹³²	MIRACLE ICD ¹³⁷	MIRACLE ICD II ¹³⁸	Piccirillo ¹³⁹	Pinter ¹⁴⁰	RAFT ¹⁴¹	RethinQ ¹⁴³	Rhythm ICD ¹⁴⁵
Study design	Crossover / Parallel RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Intervention	CRT-D + OPT	CRT-D + OPT	CRT-D + OPT	CRT-D + OPT	CRT-D	CRT-D	CRT-D + OPT	CRT-D + OPT	CRT-D
Comparator	CRT-off + OPT	ICD + OPT	CRT-off + OPT	CRT-off + OPT	ICD	CRT-off + OPT	ICD + OPT	CRT-off + OPT	CRT-off + OPT
Country (no. of centres)	USA (47)	USA (88) Canada (2) Europe (20)	USA, Canada (63)	USA, Canada (63)	Italy (1)	Canada (7)	Canada (24) Europe & Turkey (8) Australia (2)	USA (34)	Unclear (50)
Sample size randomised	490	1820	369	186	31	72	1798	172	179
Length of follow-up	max 6 months	Average 2.4 years	6 months	6 months	1 year	6 months	Mean 40 months (SD 20)	6 months	Average 12.1 (3.4) months,
Key inclusion criteria	IV conduction delay and malignant VT/VF	Ischaemic or non-ischaemic CM	CHF. Stable drug regimen for ≥ 1 month	Chronic HF.	Chronic HF secondary to ischemic dilated CM	Symptoms of on climbing ≤ 2 flights or 6-MWD \leq	Ischemic or non-ischemic causes. OPT	Ischemic or non-ischemic CM, narrow QRS,	Symptomatic HF for ≥ 6 months, ≥ 90 days OPT

Parameter	Study name								
	CONTAK-CD ¹²⁸	MADIT-CRT ¹³²	MIRACLE ICD ¹³⁷	MIRACLE ICD II ¹³⁸	Piccirillo ¹³⁹	Pinter ¹⁴⁰	RAFT ¹⁴¹	RethinQ ¹⁴³	Rhythm ICD ¹⁴⁵
						450 m; ≥ 2 weeks drugs ^a		IV dyssyn-chrony. OPT	
- NYHA Class	II, III, IV	I, II	III, IV	II			II, III	III	III, IV
- LVEF	≤35%	≤30%	≤ 35%	≤ 35%	≤ 35%	≤ 35%	≤ 30%	≤35	≤ 35%
- QRS interval, ms	≥120	≥130	≥130	≥130	>120	>120	≥120 or paced ≥200	<130	≥ 150
- Other		Sinus rhythm	LVEDD ≥ 55 mm	LVEDD ≥ 55 mm	Sinus rhythm	Sinus rhythm	Sinus rhythm or permanent AF ^b		
- ICD indication requirement	Conventional indications for an ICD.	Met guideline indication for ICD therapy.	Cardiac arrest due to VT or VF.	Indication for ICD.	Prophylactic treatment with ICD or CRT-D.	High risk of sudden death and eligible for an ICD.	Planned ICD implantation, primary or secondary prevention.	Approved indication for ICD.	ICD indication for VT.

CHF, congestive heart failure. CM, cardiomyopathy. HF, heart failure. IV, intra-ventricular. 6-MWD, 6-minute walk distance. ^a Max doses of ACE inhibitors or beta-blockers. ^b Or flutter, controlled ventricular rate or planned AV junction ablation.

Table 53: Key Participant characteristics

	CONTAK- CD ¹²⁸		MADIT- CRT ¹³²		MIRACLE ICD ¹³⁷		MIRACLE ICD II ¹³⁸		Piccirillo ¹³⁹		Pinter ¹⁴⁰		RAFT ¹⁴¹		RethinQ ¹⁴³		Rhythm ICD ¹⁴⁵	
	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD
Sample size, n	245	245	1089	731	187	182	85	101	16	15	36	36	894	904	87	85	119	59
Age, mean (SD)	66 (11)	66 (11)	65 (11)	64 (11)	66.6 (11.3)	67.6 (9.2)	63.0 (12.8)	63.1 (12.1)	65 (4)	65 (8)	66.3 (8.6)	66.1 (8.8)	66.1 (9.3)	66.2 (9.4)	60 (12)	58 (14)	nr	nr
Sex, % male	85	83	74.7	75.6	75.9	77.5	88.2	90.1	81	80	77.8	80.6	84.8	81.0	71	58	nr	nr
IHD, %	67	71	55	55	64.0	75.8	55.3	58.4	100	100	77.8	80.6	68.7	64.9	54	51	nr	nr
NYHA I, %	0	0	14.0	15.5	0	0	0	0	0	0	nr	nr	0	0	0	0	0.8	3.4
NYHA II, %	32	33	86	84.5	0	0	100	100	0	0	nr	nr	79.2	80.8	0	0	5.0	6.8
NYHA III, %	60	57	0	0	88.2	89.6	0	0	31.3	33.3	nr	nr	20.8	19.2	100	99 ^b	87.4	84.7
NYHA IV, %	8	10	0	0	11.8	10.4	0	0	68.8	66.7	nr	nr	0	0	0	0	6.7	5.1
LVEF %, mean (SD)	21 (7)	22 (7)	24 (5)	24 (5)	24.2 (6.5)	23.9 (6.0)	24.4 (6.6)	24.6 (6.7)	23 (4)	22 (8)	21.2 (7.9) ^a	24.0 (8.3) ^a	22.6 (5.4)	22.6 (5.1)	25 (5)	26 (6)	25.6 (8.3)	23.3 (6.4)
QRS interval, ms	160	156			165	162	166	165	160	159	nr	nr	157	158.3	107	106	169	167
- mean (SD)	(27)	(26)			(22)	(22)	(25)	(23)	(4)	(8)			(23.6)	(24.0)	(12)	(13)	(16)	(15)
- ≥ 150, %			64.2	65.1														
- < 120, %															76	71		
- ≥ 120, %															24	29		
LBBB/RBBB, %	54/14	55/12	70/13	71/13	nr/13	nr/13	nr/12	nr/21					73/8	71/10				

nr, not reported. IHD, Ischaemic heart disease. ^a Measured by echocardiogram; also measured by quantitative resting radionuclide angiogram (MUGA): CRT-D 24.2 (SD 7.5), ICD 26.8 (SD 8.4). ^b NYHA class of one participant not reported.

Table 54: Medication at baseline

Medication, %	CONTAK-CD ¹²⁸		MADIT-CRT ¹³²		MIRACLE ICD ¹³⁷		MIRACLE ICD II ¹³⁸		Piccirillo ¹³⁹		RAFT ¹⁴¹		RethinQ ¹⁴³		Rhythm ICD ¹⁴⁵	
	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD
Sample size	245	245	1089	731	187	182	85	101	16	15	894	904	87	85	119	59
ACE inhibitor			77.0	77.0	92.5	89.0	97.6	95.0	100	100						
ACE inhibitor / substitutes/ARB	86	89									96.1	97.1	89	91	71.4	74.6
Angiotensin-receptor blocker			20.8	20.2											20.2	16.9
Antiarrhythmic					42.3	33.0	35.3	32.7					8	12	24.4	22.0
-Amiodarone			7.2	7.0							15.7	13.7				
- Other anti-arrhythmia drug											1.3	0.9				
- Class I antiarrhythmic			1.1	0.4												
Anti-coagulants and anti-platelets															85.7	81.4
-Acetylsalicylic acid (Apirin)									100	93	65.3	68.8				
- Clopidogrel											15.0	16.0				
- Warfarin											34.7	33.0				
Beta-blocker	48	46	93.3	93.2	62.0	58.2	63.5	63.4			90.4	89.0	97	93	79.8	88.1

Medication, %	CONTAK-CD ¹²⁸		MADIT-CRT ¹³²		MIRACLE ICD ¹³⁷		MIRACLE ICD II ¹³⁸		Piccirillo ¹³⁹		RAFT ¹⁴¹		RethinQ ¹⁴³		Rhythm ICD ¹⁴⁵	
	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD
Sample size	245	245	1089	731	187	182	85	101	16	15	894	904	87	85	119	59
- Biskoprolol									13	7						
- Carvedilol									81	80						
Calcium-channel blocker											11.3	9.2			9.2	15.3
Diuretic	88	83	75.7	72.9	93.1	94.5	87.1	80.2			84.7	83.6	84	87	86.6	91.5
- Furosemide									100	100						
- Aldosterone antagonist			32.3	30.9												
- Spironolactone									56	67	41.6	41.8				
Nitrates															32.8	39.0
Positive inotropics / glycoside															61.3	66.1
- Digitalis			26.7	24.2												
- Digoxin	69	68							75	73						
Statin			67.5	67.2							67.9	68.4				

Note: Pinter 2009 did not report base line medication, but inclusion criteria state ≥ 2 weeks treatment with maximal tolerated doses of ACE inhibitors or beta-blockers unless adverse effects or contraindicated.

Key outcomes

The primary outcomes differed between the trials. All nine trials reported all-cause mortality, but none as a primary outcome. Also reported were total cardiac deaths (seven trials: CONTAK CD,¹²⁸ MIRACLE ICD II,¹³⁸ Piccirillo,¹³⁹ Pinter,¹⁴⁰ RAFT,¹⁴¹ RethinQ,¹⁴³ Rhythm ICD),¹⁴⁵ death due to heart failure (four trials: CONTAK CD,¹²⁸ MIRACLE ICD II,¹³⁸ Piccirillo,¹³⁹ Pinter¹⁴⁰), sudden cardiac death (six trials: CONTAK CD,¹²⁸ MIRACLE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ Piccirillo,¹³⁹ RethinQ,¹⁴³ Rhythm ICD¹⁴⁵) and death from other causes (six trials: CONTAK CD,¹²⁸ MIRACLE ICD II,¹³⁸ Piccirillo,¹³⁹ Pinter,¹⁴⁰ RethinQ,¹⁴³ Rhythm ICD¹⁴⁵). Three trials (CONTAK CD,¹²⁸ Piccirillo,¹³⁹ RAFT¹⁴¹) reported hospitalisation due to heart failure, six trials reported NYHA class (CONTAK CD,¹²⁸ MIRACLE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ Piccirillo,¹³⁹ RethinQ,¹⁴³ Rhythm ICD¹⁴⁵), and eight trials reported LVEF (CONTAK CD,¹²⁸ MADIT-CRT,¹³² MIRACLE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ Piccirillo,¹³⁹ Pinter,¹⁴⁰ RethinQ,¹⁴³ Rhythm ICD¹⁴⁵). Six trials reported exercise capacity assessed by the six minute walk test and/or peak oxygen consumption, and quality of life assessed by the Minnesota Living with Heart Failure questionnaire (CONTAK CD,¹²⁸ MIRACLE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ Pinter,¹⁴⁰ RethinQ,¹⁴³ Rhythm ICD¹⁴⁵). The primary outcome of three trials^{128;132;141} was a composite outcome, these can be seen in the data extraction forms (Appendix 10) but have not been presented in the report.

Setting

Other than the single-centre study by Piccirillo and colleagues,¹³⁹ the trials were multicentre with the majority of the centres in USA and Canada. Only one of the studies had a centre in the UK (MADIT-CRT¹³²).

The number of participants randomised ranged from 31 (Piccirillo¹³⁹) to 1820 (MADIT-CRT¹³²). The length of follow-up was 6 months in CONTAK-CD,¹²⁸ MIRACE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ Pinter¹⁴⁰ and RethinQ,¹⁴³ 12 months in Piccirillo and RHYTHM ICD,¹⁴⁵ and an average of 2.4 years in MADIT-CRT¹³² and 40 months in RAFT.¹⁴¹

4.4.1.2 Risk of bias

The risk of bias in the included studies is summarised in Table 55 and further details for each study can be found in the data extraction tables in Appendix 10. Only three of the studies (MIRACLE ICD I¹³⁷ and II,¹³⁸ RethinQ¹⁴³) were at low risk of selection bias. MADIT-CRT¹³² did not report the randomisation method used, although sufficient details were reported to establish that the allocation sequence was adequately concealed. The remaining studies did not report details of randomisation method or allocation sequence concealment, therefore the risk of selection bias is unclear.

There is a high risk of performance bias and detection bias in MADIT-CRT,¹³² treating physicians were aware of study group assignments, and diagnosis of heart failure and decisions on therapy or hospital admission were made by physicians aware of assignments, although members of the mortality and heart failure committees were unaware of study group assignments. Details of blinding of participants and personnel were not reported by Piccirillo,¹³⁹ and although spectral recording assessment was blinded, details of blinding of other outcomes were not reported. RethinQ¹⁴³ and RHYTHM ICD¹⁴⁵ are described as ‘double-blind’, but further details such as who was blinded and how this was maintained were not reported. However, outcome assessors were unaware of treatment assignment in RethinQ.¹⁴³ There was a low risk of performance bias and detection bias in CONTAK-CD,¹²⁸ MIRACLE ICD I¹³⁷ and II,¹³⁸ RAFT¹⁴¹ and Pinter.¹⁴⁰

Risk of attrition bias in CONTAK-CD¹²⁸ was low for the primary outcome, but high for other outcomes. MADIT-CRT¹³² was judged to have a low risk of bias for survival, but high risk of bias for ventricular remodelling outcomes. Risk of attrition bias was unclear for primary outcomes and high for secondary outcomes in MIRACLE ICD,¹³⁷ and unclear in MIRACLE ICD II.¹³⁸ RethinQ¹⁴³ was judged to have a low risk of attrition bias for primary and secondary outcomes, but a high risk of bias for additional outcomes where missing data were not accounted for. RAFT,¹⁴¹ RHYTHM ICD,¹⁴⁵ Pinter¹⁴⁰ and Piccirillo¹³⁹ had a low risk of attrition bias.

RAFT¹⁴¹ was considered to have a high risk of selective reporting bias, as outcomes stated in the protocol (for example, QoL) were not reported in the publication. However, it is noted that this was a recent study and data may have been published after the completion of this report. The RHYTHM ICD study report was only available from the FDA website and does not appear to have been published in a journal. It is not clear whether selected outcomes have been presented to meet the needs of the FDA approval process. CONTAK-CD,¹²⁸ MADIT-CRT,¹³² MIRACLE ICD I¹³⁷ and II, Pinter,¹⁴⁰ Piccirillo¹³⁹ and RethinQ¹⁴³ were judged to have a low risk of selective reporting bias.

The risks of other sources of bias were unclear in three studies. The study design, primary outcome measure and length of follow-up were changed during the course of the CONTAK-CD study,¹²⁸ but the potential for these issues to introduce a bias into the results is unknown. Due to a lack of details in the RHYTHM ICD report,¹⁴⁵ the risk of other sources of bias is unclear. Sponsors (Medtronic Inc) of the MIRACLE ICD study¹³⁷ appear to have been involved in all aspects of the study, though the risk of bias of this is unclear. MADIT-CRT,¹³² MIRACLE ICD II,¹³⁸ RAFT,¹⁴¹ Pinter¹⁴⁰ Piccirillo¹³⁹ and RethinQ¹⁴³ were judged to have a low risk of bias.

Table 55: Risk of bias

Judgement ^a	CONTAK- CD ¹²⁸	MADIT- CRT ¹³²	MIRACLE ICD ¹³⁷	MIRACLE ICD II ¹³⁸	Piccirillo 139	Pinter 140	RAFT 141	RethinQ ¹⁴³	Rhythm ICD ¹⁴⁵
<i>Selection bias</i>									
Random sequence generation	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Allocation concealment	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
<i>Performance bias</i>									
Blinding of participants & personnel	Low	High	Low	Low	High	Low	Low	Unclear	Unclear
<i>Detection bias</i>									
Blinding of outcome assessment	Low	High	Low	Low	High	Low	Low	Low	Unclear
<i>Attrition bias</i>									
Incomplete outcome data addressed	Primary - Low Other - High	Survival –Low Other - High	Primary- Unclear Other-High	Unclear	Low	Low	Low	Primary ^b - Low Other - High	Low
<i>Reporting bias</i>									
Selective reporting	Low	Low	Low	Low	Low	Low	High	Low	Unclear
<i>Other bias</i>									
Other sources of bias	Unclear	Low	Unclear	Low	Low	Low	Low	Low	Unclear

^a ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias. ^b Also QoL, NYHA and mortality.

4.4.1.3 Methodological comments

Similarity of groups at baseline

The groups were generally well balanced at baseline (see Table 53). However, the ICD group of MIRACLE ICD¹³⁷ had a higher proportion of participants with ischemic heart disease. In RHYTHM ICD,¹⁴⁵ the ICD group performed significantly better in the exercise test for peak VO₂ (a primary outcome) and had a lower proportion of men, although the authors state none of the differences were significant (statistical analysis not presented).

Sample size

Four of the trials were adequately powered to show a difference in their primary outcome(s), these were MIRACLE ICD¹³⁷ (a difference in NYHA class of 0.75, QoL of 13 points, or 6MWT distance of 50 m), Pinter¹⁴⁰ (12% decrease in end-systolic volume), RAFT¹⁴¹ (25% relative reduction in the composite outcome) and RethinQ¹⁴³ (difference of 23% in the proportion of patients who achieved the primary end point).

The actual event rate observed in CONTAK-CD¹²⁸ was approximately half that expected in the original study design and consequently the authors state that the study was not adequately powered to detect a statistically significant difference in HF events. MADIT-CRT¹³² was stopped on the recommendation of the independent data and safety monitoring board when the monitoring statistic reached the prespecified efficacy boundary. The study was then unblinded and analyses were limited to events occurring before trial termination. MIRACLE ICD¹³⁷ was not powered to detect a morbidity or mortality difference. Piccirillo¹³⁹ was a small study of 31 participants. The paper does not report details of a sample size calculation, and mortality and NYHA were not primary outcomes therefore it is assumed it was not powered for these outcomes. MIRACLE ICD II¹³⁸ and RHYTHM ICD¹⁴⁵ do not report sample size calculations.

Crossovers

Crossovers between groups were reported by six of the trials. Crossover from ICD to CRT-D occurred in 2.8% (Pinter¹⁴⁰) to 12.4% (MADIT-CRT¹³²) of participants, the most common reason for crossover was heart failure events (Table 56). Crossover from CRT-D to ICD occurred in 0% (RethinQ¹⁴³) to 7.5% (MADIT-CRT¹³²) of participants, most commonly due to difficulties with the LV/CRT pacing lead (Table 56).

Table 56: Crossovers to alternative device

Study	CRT-D, n/N (%)	ICD, n/N (%)
MADIT-CRT ¹³²	82/1089 (7.5) (technical difficulties positioning CRT pacing lead)	91/731 (12.4) (30 before reaching an endpoint, 61 after heart failure event)
MIRACLE ICD ¹³⁷	10/187 (5) - 2 ventricular lead dislodgement - 2 diaphragmatic stimulation - 6 programming errors	14/182 (8) - 11 worsening HF - 2 bradycardia - 1 programming error
MIRACLE ICD II ¹³⁸	2/85 (2) LV lead dislodgement in 1 patient and diaphragmatic stimulation in biventricular and right ventricular pacing modes in 1 patient	5/101 (5) bradycardia in 3 patients, centre error in 1 patient, and pacemaker dependency after AV node ablation for atrial flutter in 1 patient
Pinter ¹⁴⁰	1/36 (2.8) (Late LV capture failure)	1/36 (2.8) (worsening congestive heart failure)
RAFT ¹⁴¹	Not reported	96/904 (10.6%) (36 before primary outcome, 60 after heart failure hospitalisation)
RethinQ ¹⁴³	0/87 (0)	3/85 (3.5) due to worsening heart failure

Other issues

There were some differences between studies in the timing of implantation, baseline evaluation and randomisation. MADIT-CRT,¹³² Piccirillo¹³⁹ and RAFT¹⁴¹ randomised participants before or at the time of implantation. CONTAK-CD¹²⁸ implanted the device first because of the immediate need for ICD therapy, then programmed the randomised therapy after a minimum 30 day period with no CRT, during which time investigators were permitted to optimise pharmacologic therapy.

The other studies (MIRACLE ICD I¹³⁷ and II,¹³⁸ Pinter,¹⁴⁰ RethinQ¹⁴³ and RHYTHM ICD¹⁴⁵) randomised only those participants who were successfully implanted. In MIRACLE ICD¹³⁷ randomisation occurred within 7 days of successful implant, in Pinter¹⁴⁰ participants were randomly assigned following completion of baseline procedures 14-28 days post implant, and in RethinQ¹⁴³ and RHYTHM ICD¹⁴⁵ baseline evaluation occurred 14 days post implant, followed by randomisation.

The study design of CONTAK-CD¹²⁸ was modified due to regulatory concerns about morbidity and mortality associated with CRT and the length of follow-up in the randomised mode. This meant that

the design changed from a randomised crossover design with crossover to occur after 3 months of randomised therapy (Phase I), to a parallel RCT design with 6 months of follow-up (Phase II). Data from both phases are reported.

Piccirillo¹³⁹ was a small study that aimed to assess whether spectral indexes obtained by power spectral analysis of heart rate variability could predict malignant ventricular arrhythmias in patients. These data are beyond the scope of this report and have not been included. The study also reported mortality and NYHA class, although these were not specified as primary or secondary outcomes.

RAFT¹⁴¹ enrolled both NYHA class II and III patients during the first part of the study, until a protocol revision was made in February 2006 to include only NYHA class II patients. Primary and secondary outcomes for patients with NYHA class II or III heart failure were therefore analysed separately.

RHYTHM ICD¹⁴⁵ has not been published in a journal. Data have been extracted from the FDA report, but limited methodological details are reported.

Funding

Eight of the trials received funding from the device manufacturers. RHYTHM ICD¹⁴⁵ was the basis of an FDA report by St Jude Medical, Sunnvale, CA. Piccirillo did not report funding or competing interests.

4.4.2 Assessment of effectiveness

4.4.2.1 All-cause mortality

All nine trials reported data on all-cause mortality, although only two compared events between groups statistically (MADIT-CRT,¹³² RAFT¹⁴¹) (see Table 57). MADIT-CRT¹³² found no statistically significant difference in all-cause mortality after an average follow-up of 2.4 years (CRT-D 6.8% vs ICD 7.3%, HR 1.00, 95% CI 0.69 to 1.44, p=0.99), whilst RAFT¹⁴¹ found a statistically significant reduction in mortality with CRT-D (CRT-D 20.8% vs ICD 26.1%, HR 0.75, 95% CI 0.62 to 0.91, p=0.003). Analysis of the remaining trials [CONTAK-CD¹²⁸ (CRT-D 4.5% vs ICD 6.5%, RR 0.69, 95% CI 0.33 to 1.45, p=0.33), MIRACLE ICD¹³⁷ (CRT-D 7.5% vs ICD 8.2%, RR 0.91, 95% CI 0.45 to 1.83, p=0.79), MIRACLE ICD II¹³⁸ (CRT-D 2.4% vs ICD 2.0%, RR 1.19, 95% CI 0.17 to 8.26, p=0.86), Piccirillo¹³⁹ (CRT-D 0% vs ICD 0%), Pinter¹⁴⁰ (CRT-D 2.8% vs ICD 2.8%, RR 1.00, 95% CI 0.07 to 15.38, p=1.00), RethinQ¹⁴³ (CRT-D 5.7% vs ICD 1.2%, RR 4.89, 95% CI 0.58 to 40.95, p=0.14) and RHYTHM ICD¹⁴⁵ (CRT-D 10.8% vs ICD 7.0%, RR 1.55, 95% CI 0.44 to 5.44, p=0.49)]

demonstrated no statistically significant difference in all-cause mortality between devices in each of the trials. Length of follow-up was up to 6 months in six of the studies, 12 months in Piccirillo,¹³⁹ and an average of 28.8 months in MADIT-CRT¹³² and 40 months in RAFT.¹⁴¹

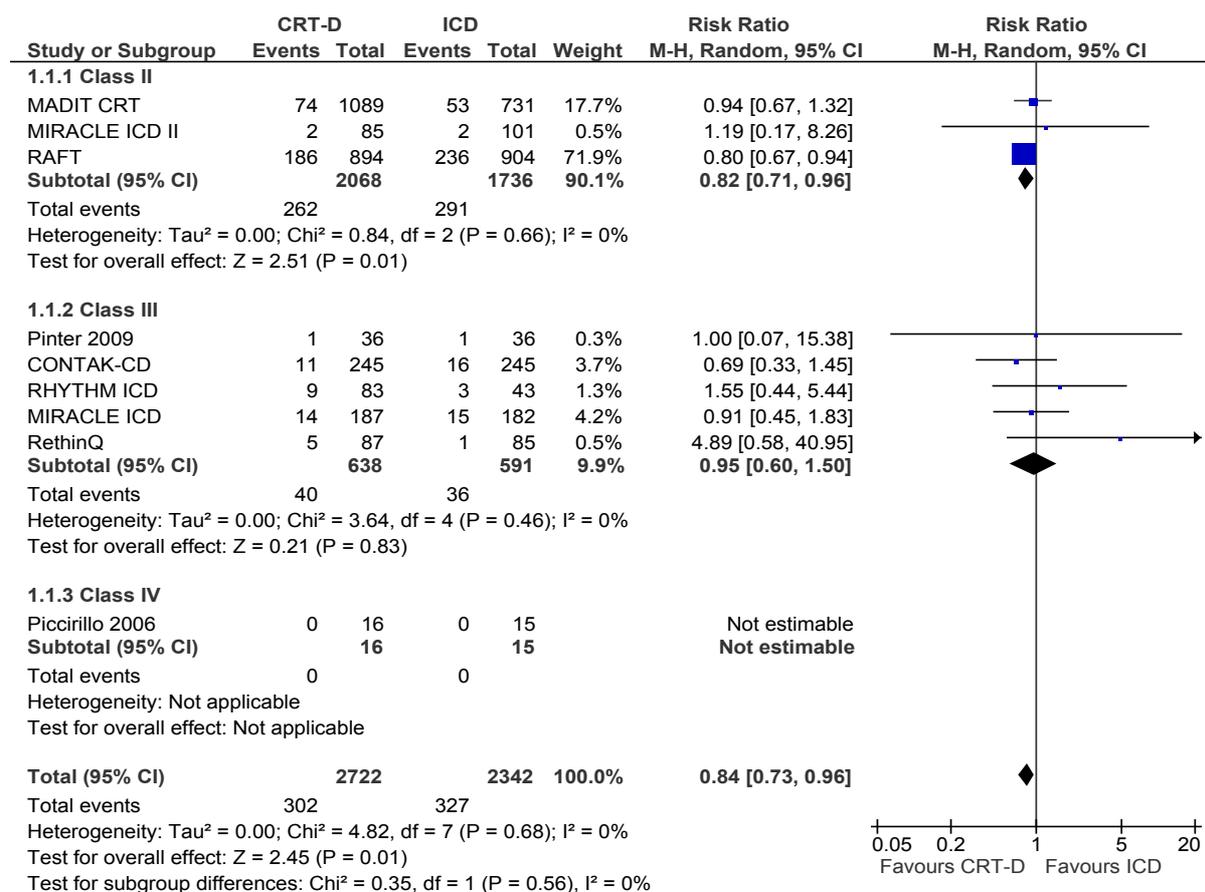
The trials were considered sufficiently similar to combine in a random effects meta-analysis, and were grouped according to the NYHA class of the majority of the participants in each trial. There was no evidence of significant statistical heterogeneity between the studies ($\text{Chi}^2 = 4.82$, $\text{df} = 7$, $I^2 = 0\%$). Note that the Piccirillo study¹³⁹ was not estimable within the meta-analysis as zero events were observed in both groups. The risk ratio for CRT-D vs ICD was 0.84 (95% CI 0.73 to 0.96, $p=0.01$), (Figure 19), giving a relative risk reduction of 16% with CRT-D for all-cause mortality. The results were strongly influenced by the large RAFT study¹⁴¹ with 40 months follow-up, and when this study was removed from the analysis the results were no longer statistically significant (RR 0.95, 95% CI 0.72 to 1.24, $p=0.69$).

Table 57: All-cause mortality

Study	Follow-up, months	CRT-D n/N (%)	ICD n/N (%)	Effect	95% CI, p value
CONTAK-CD ¹²⁸	3-6	11/245 (4.5)	16/245 (6.5)	RR 0.69 ^a	0.33 to 1.45 ^a , 0.33
MADIT-CRT ¹³²	Average 2.4 years	74/1089 (6.8)	53/731 (7.3)	HR 1.00	0.69 to 1.44, 0.99
MIRACLE ICD ¹³⁷	6	14/187 (7.5)	15/182 (8.2)	RR 0.91 ^a	0.45 to 1.83, 0.79 ^a
MIRACLE ICD II ¹³⁸	6	2/85 (2.4)	2/101 (2.0)	RR 1.19 ^a	0.17 to 8.26, 0.86 ^a
Piccirillo ¹³⁹	12	0/16 (0)	0/15 (0)		
Pinter ¹⁴⁰	6	1/36 (2.8)	1/36 (2.8)	RR 1.00 ^a	0.07 to 15.38, 1.00 ^a
RAFT ¹⁴¹	mean 40 (SD 20)	186/894 (20.8)	236/904 (26.1)	HR 0.75	0.62 to 0.91, 0.003
RethinQ ¹⁴³	6	5/87 (5.7)	1/85 (1.2)	RR 4.89 ^a	0.58 to 40.95, 0.14 ^a
RHYTHM ICD ¹⁴⁵	6	9/83 (10.8)	3/43 (7.0)	RR 1.55 ^a	0.44 to 5.44, 0.49 ^a

^a Calculated by reviewer.

Figure 19: All-cause mortality



4.4.2.2 Total cardiac deaths

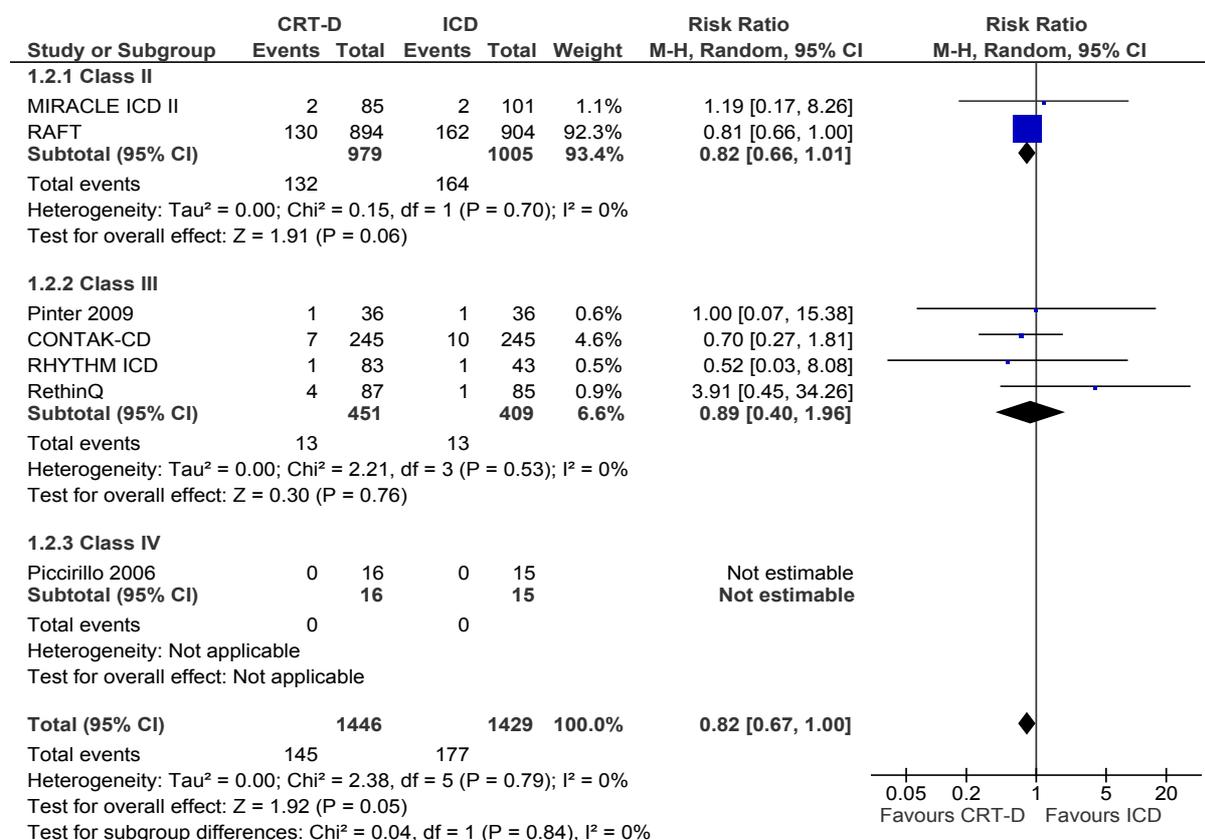
Seven trials reported data on total cardiac deaths, although only one of these compared events between groups statistically (see Table 58). RAFT¹⁴¹ found that CRT-D was associated with a statistically significant reduction in cardiac deaths (CRT-D 14.5% vs ICD 17.9%, HR 0.76, 95% CI 0.60 to 0.96, p=0.02). When these trials were combined in a meta-analysis (random effects) the overall risk ratio was 0.82 (95% CI 0.67 to 1.00, p=0.05) in favour of CRT-D (see Figure 20). There was no statistically significant heterogeneity (Chi² 2.38, df 5, I² 0%). Again these results were strongly influenced by the large RAFT study,¹⁴¹ and when this was omitted from the analysis there was little difference between the interventions [RR 0.92 (95% CI 0.44 to 1.92, p=0.83)].

Table 58: Total cardiac deaths

Study	Follow-up, months	CRT-D n/N (%)	ICD n/N (%)	Effect	95% CI, p value
CONTAK-CD ¹²⁸	3-6	7/245 (2.9)	10/245 (4.1)	RR 0.70 ^a	0.27, 1.81 ^a
MIRACLE ICD II ¹³⁸	6	2/85 (2.4)	2/101 (2.0)	RR 1.19 ^a	0.17, 8.26 ^a
Piccirillo ¹³⁹	12	0/16 (0)	0/15 (0)		
Pinter ¹⁴⁰	6	1/36 (2.8)	1/36 (2.8)	RR 1.00 ^a	0.07, 15.38 ^a
RAFT ¹⁴¹	mean 40 (SD 20)	130/894 (14.5)	162/904 (17.9)	HR 0.76	0.60 to 0.96, 0.02
RethinQ ¹⁴³	6	4/87 (4.6)	1/85 (1.2)	RR 3.91 ^a	0.45, 34.26 ^a
RHYTHM ICD ¹⁴⁵	6	1/83 (1.2)	1/43 (2.3)	RR 0.52 ^a	0.03, 8.08 ^a

^a Calculated by reviewer

Figure 20: Total cardiac deaths



4.4.2.3 Heart failure deaths

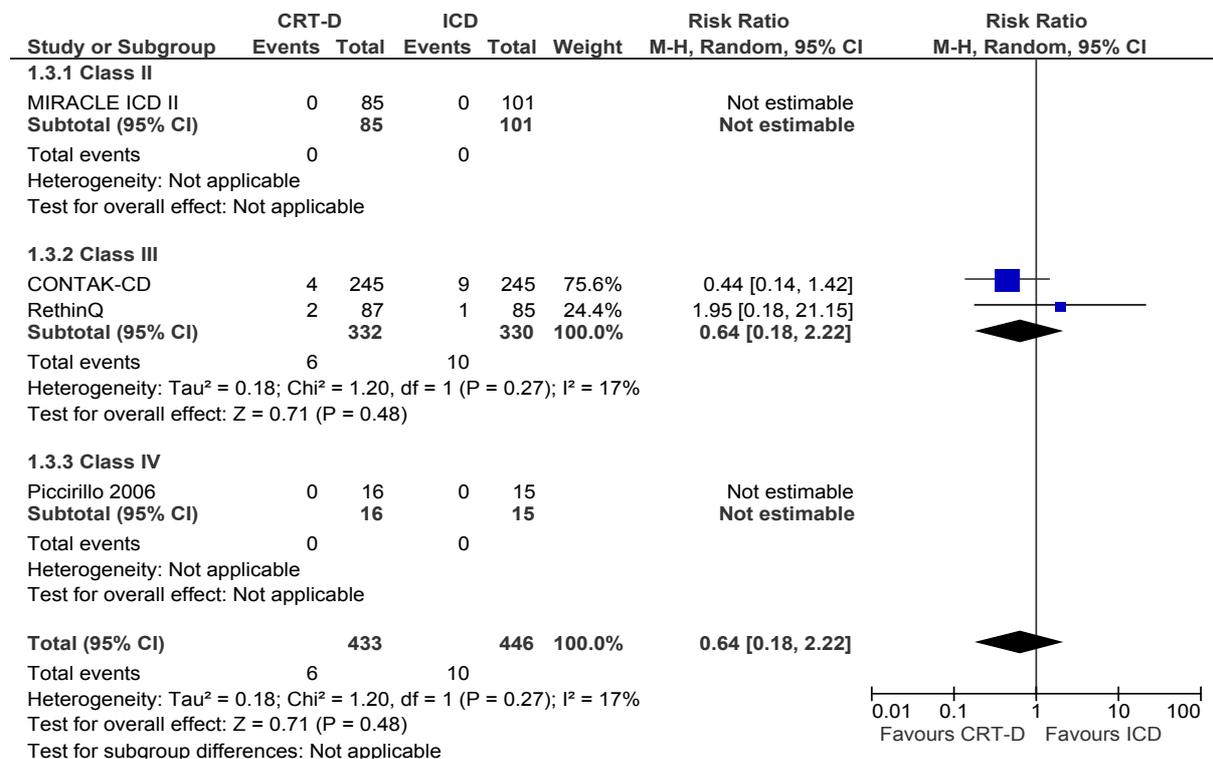
There were no deaths from heart failure in the MIRACLE ICD II¹³⁸ study of people with mild NYHA class II heart failure, or in the small Piccirillo study¹³⁹ of people with NYHA class IV or III. The CONTAK-CD study,¹²⁸ in which the majority of participants had NYHA Class III or II heart failure, reported deaths from heart failure in 1.6% and 3.7% of the CRT-D and ICD groups, respectively. Two (2.3%) people in the CRT-D group and one person (1.2%) in the ICD group of the RethinQ trial¹⁴³ died from heart failure (see Table 59). Combining these trials in a random effects meta-analysis gave an overall RR of 0.64 (95% CI 0.18 to 2.22, p=0.48) (Figure 21).

Table 59: Heart failure deaths

Study	Follow-up, months	CRT-D n/N (%)	ICD n/N (%)	Effect (RR)	95% CI, p value
CONTAK-CD ¹²⁸	3-6	4/245 (1.6)	9/245 (3.7)	0.44 ^a	0.14 to 1.42, 0.17 ^a
MIRACLE ICD II ¹³⁸	6	0/85 (0)	0/101 (0)		
Piccirillo ¹³⁹	12	0/16 (0)	0/15 (0)		
RethinQ ¹⁴³	6	2/87 (2.3)	1/85 (1.2)	1.95 ^a	0.18 to 21.15, 0.58 ^a

^a Calculated by reviewer.

Figure 21: Heart failure deaths



4.4.2.4 Sudden cardiac death

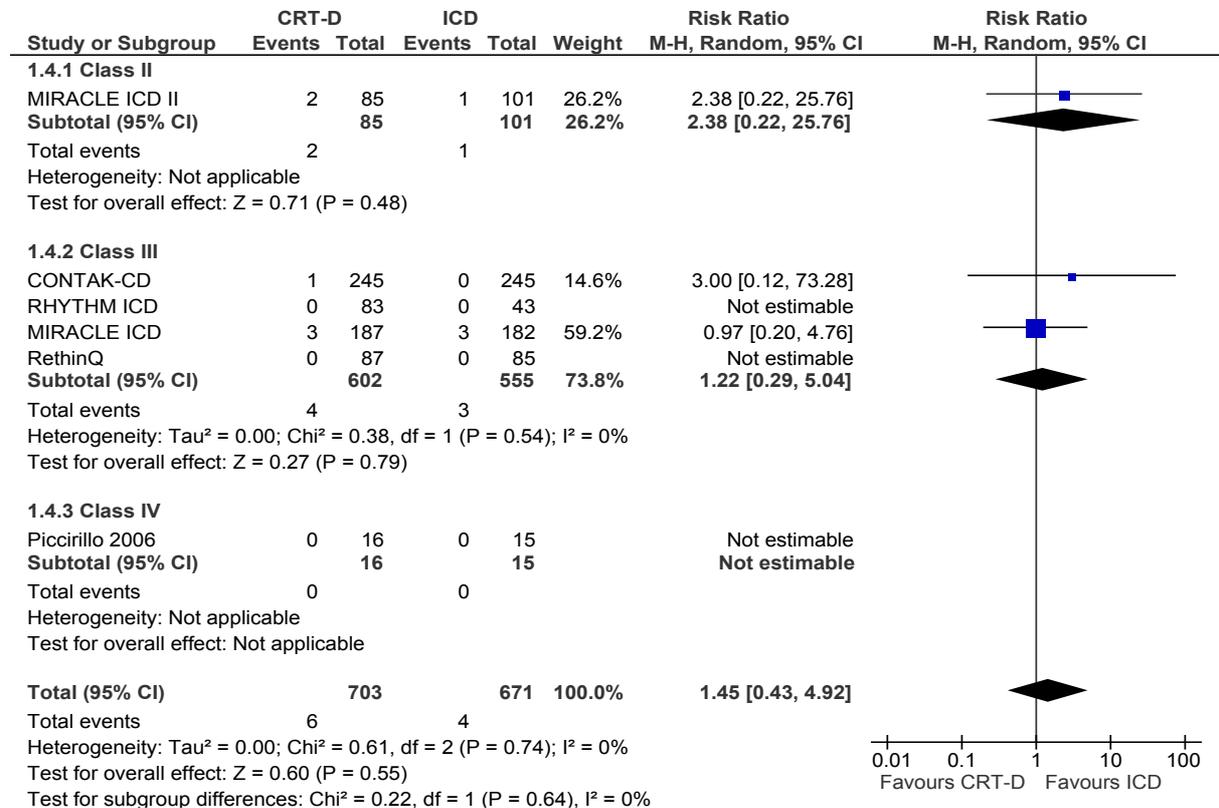
Six trials reported data on sudden cardiac death (Table 60). No sudden cardiac deaths occurred in either the small Piccirillo study,¹³⁹ RethinQ¹⁴³ or RHYTHM ICD.¹⁴⁵ Combining the other three trials (MIRACLE ICD II,¹³⁸ CONTAK-CD,¹³¹ MIRACLE ICD¹³⁷) in a meta-analysis gives an overall relative risk of 1.45 (95% CI 0.43 to 4.92, p=0.55), with no important statistical heterogeneity (Chi² 0.61, df 2, I² 0) (Figure 22).

Table 60: Sudden cardiac death

Study	Follow-up, months	CRT-D n/N (%)	ICD n/N (%)	Effect (RR)	95% CI, p value
CONTAK-CD ¹³¹	3-6	1/245 (0.4)	0/245 (0)	3.00	0.12 to 73.28, 0.5 ^a
MIRACLE ICD ¹³⁷	6	3/187 (1.6)	3/182 (1.7)	0.97	0.2 to 4.76, 0.97 ^a
MIRACLE ICD II ¹³⁸	6	2/85 (2.4)	1/101 (1.0)	2.38	0.22 to 25.76, 0.48 ^a
Piccirillo ¹³⁹	12	0/16 (0)	0/15 (0)		
RethinQ ¹⁴⁴	6	0/87 (0)	0/85 (0)		
RHYTHM ICD ¹⁴⁵	6	0/83 (0)	0/43 (0)		

^a Calculated by reviewer.

Figure 22 Sudden cardiac deaths



4.4.2.5 Other causes of death

Deaths due to non-cardiac causes were reported by CONTAK-CD¹³¹ (CRT-D 0.8%, ICD 1.2%) and RHYTHM ICD¹⁴⁵ (CRT-D 8.4%, ICD 4.7%). One (1.2%) death of unknown cause occurred in the CRT-D group of RethinQ.¹⁴³ No deaths due to non-cardiac causes occurred in the Piccirillo¹³⁹ or Pinter¹⁴⁰ trials (see Table 61).

Table 61: Other causes of death

Study	Follow-up, months	cause of death	CRT-D n/N (%)	ICD n/N (%)
CONTAK-CD ¹³¹	3-6	cardiac (not pump failure or arrhythmic)	2/245 (0.8)	1/245 (0.4)
		non-cardiac	2/245 (0.8)	3/245 (1.2)
		unknown	2/245 (0.8)	3/245 (1.2)
MIRACLE ICD II ¹³⁸	6	MI with cardiogenic shock	0/85 (0)	1/101 (1%)
Piccirillo ¹³⁹	12	non-cardiac	0/16 (0)	0/15 (0)
Pinter ¹⁴⁰	6	non-cardiac	0/36 (0)	0/36 (0)
RethinQ ¹⁴³	6	unknown	1/87 (1.2)	0/85 (0)
		unknown cardiac	1/87 (1.2)	0/85 (0)
RHYTHM ICD ¹⁴⁵	6	cardiac non-arrhythmic	1/83 (1.2)	1/43 (2.3)
		cardiac unknown	0/83 (0)	0/43 (0)
		non-cardiac	7/83 (8.4)	2/43 (4.7)
		unknown	1/83 (1.2)	0/43 (0)

4.4.2.6 Survival

No statistically significant difference in 6-month cumulative survival was found by MIRACLE ICD¹³⁷ (CRT-D 92.4% vs ICD 92.2%, p=0.96) or RethinQ¹⁴³ (CRT-D 94.2% vs ICD 98.8%, p=0.11), or in cumulative freedom from death caused by worsening heart failure (CRT-D 97.7% vs 98.9%, p=0.58, RethinQ¹⁴³) (Table 62). The probability of event-free survival at 5 years was 57.6% in the CRT-D group and 48.7% in the ICD group of the RAFT study,¹⁴¹ statistical significance was not reported.

Table 62: Survival

Study	Follow-up	CRT-D	ICD	p value
MIRACLE ICD ¹³⁷	6-month cumulative survival	92.4% (95% CI 87.5% to 95.4%)	92.2% (95% CI 87.2% to 95.3%)	0.96
RAFT ¹⁴¹	Probability of event-free survival at 5 years, %	57.6	48.7	
	5-year actuarial rate of death, %	28.6	34.6	
RethinQ ¹⁴³	Cumulative overall survival at 6 months, % (95 % CI),	94.2% (86.7 to 97.6)	98.8% (91.9 to 99.8)	0.11
	Cumulative freedom from death caused by worsening HF, % (95 % CI)	97.7% (91.1 to 99.4)	98.9% (91.9 to 99.8)	0.58

4.4.2.7 Hospitalisations related to heart failure

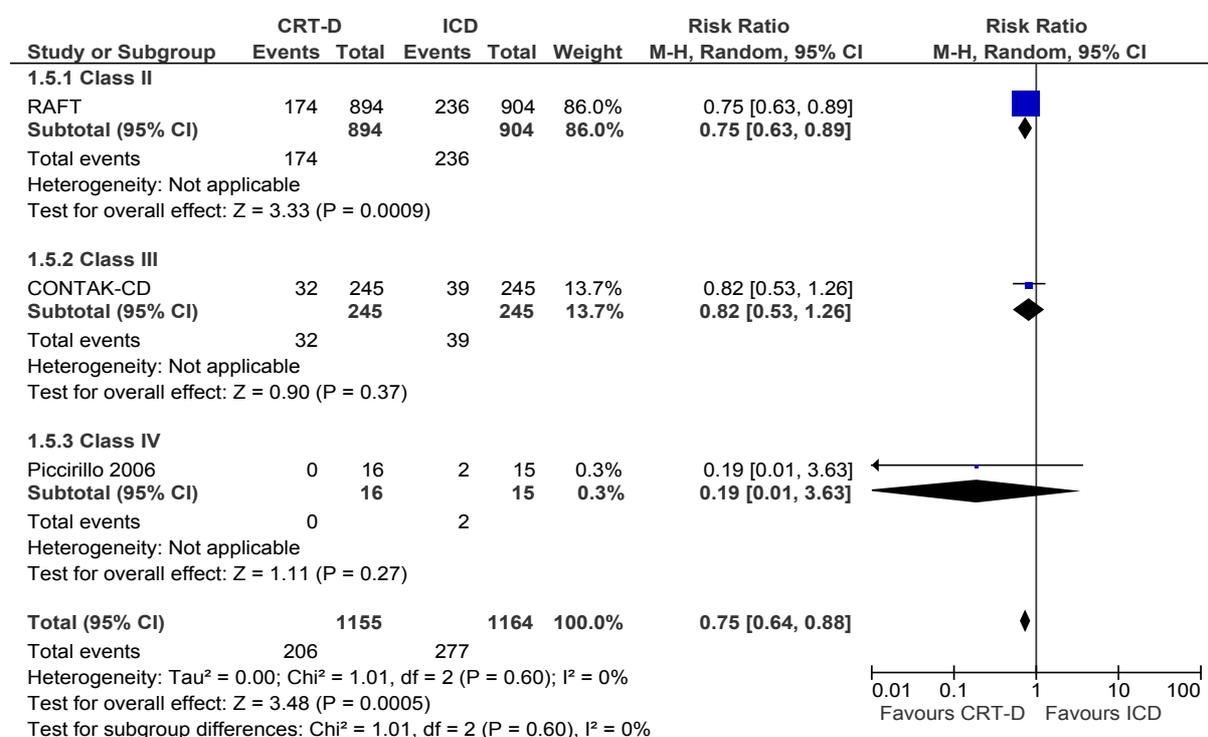
CONTAK-CD,¹²⁸ Piccirillo¹³⁹ and RAFT¹⁴¹ reported hospitalisations related to heart failure (Table 63); MIRACLE ICD,¹³⁷ Pinter¹⁴⁰ and RAFT¹⁴¹ reported all-cause hospitalisations (Appendix 7). The RAFT study¹⁴¹ found a statistically significant reduction in hospitalisations for heart failure in the CRT-D group (19.5% vs 26.1%, HR 0.68, 95% CI 0.56 to 0.83, $p<0.001$). CONTAK-CD¹²⁸ reported 13.1% of the CRT-D group were hospitalised due to heart failure, compared with 15.9% of the ICD group. Two people (13.3%) with ICDs and none of the CRT-D group were hospitalised due to heart failure in the small Piccirillo study.¹³⁹ When the studies were combined in a meta-analysis, CRT-D reduced the relative risk of heart failure hospitalisation by 25% compared with ICD (RR 0.75, 95% CI 0.64 to 0.88, $p=0.0005$, random effects model) (see Figure 23).

Table 63: Hospitalisation related to heart failure

Study	Outcome; follow-up, months	CRT-D n/N (%)	ICD n/N (%)	Effect	95% CI, p value
CONTAK-CD ¹²⁸	At least 1 HF hospitalisation, 6	32/245 (13.1)	39/245 (15.9)	RR 0.82 ^a	0.53 to 1.26, 0.37 ^a
Piccirillo ¹³⁹	Hospitalisations due to worsening HF, 12	0/16 (0)	2/15 (13.3)	RR 0.19 ^a	0.01 to 3.63, 0.27 ^a
RAFT ¹⁴¹	Hospitalisation for HF, mean 40 (SD 20)	174/894 (19.5)	236/904 (26.1)	HR 0.68	0.56 to 0.83, <0.001

^a Calculated by reviewer.

Figure 23: Heart failure hospitalisations



4.4.2.8 Arrhythmias

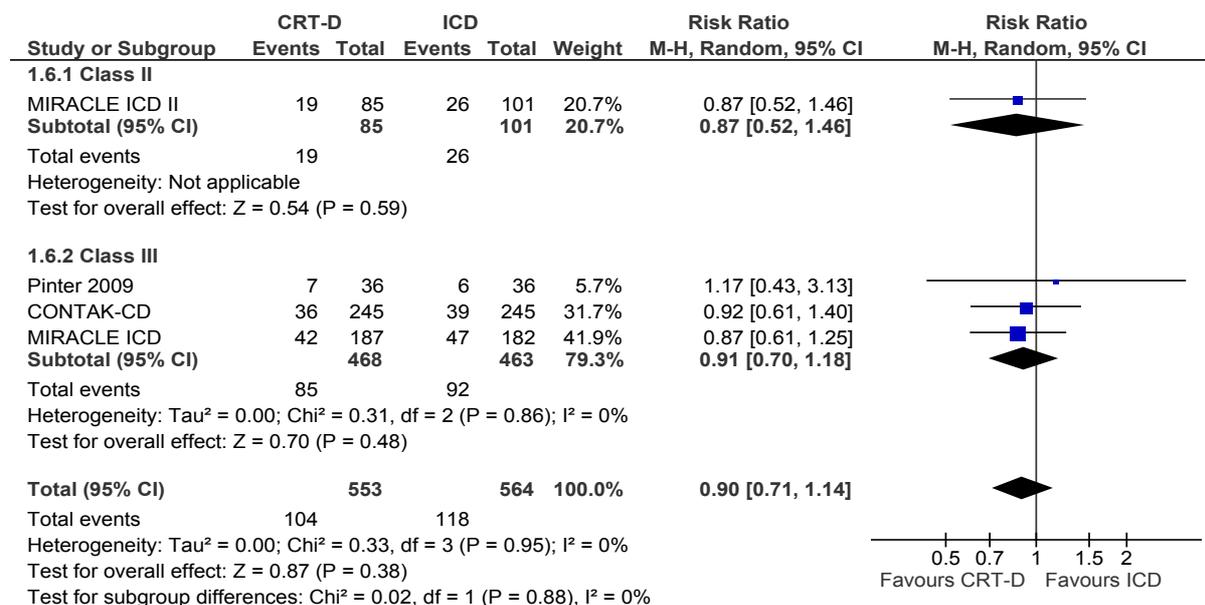
The number of participants experiencing at least one episode of ventricular tachycardia or ventricular fibrillation can be seen in Table 64. The proportions appear similar between groups. Random effects meta-analysis demonstrated no statistically significant difference in the number of people experiencing at least one arrhythmia (RR 0.90, 95% CI 0.71 to 1.14, p=0.38) (Figure 24).

Table 64: Arrhythmias

Study	Outcome; follow-up, months	CRT-D n/N (%)	ICD n/N (%)	Effect (RR)	95% CI, p value
CONTAK-CD ¹²⁸	≥1 VT/VF event, 6	36/245 (14.7)	39/245 (15.9)	0.92 ^a	0.61 to 1.40, 0.71 ^a
MIRACLE ICD ¹³⁷	≥1 spontaneous episode of VT or VF, 6	42/187 (22)	47/182 (26)	0.87 ^a	0.61 to 1.25, 0.45 ^a , 0.47 ^b
MIRACLE ICD II ¹³⁸	≥1 appropriately detected, spontaneous episode of VT or VF, 6	19/85 (22)	26/101 (26)	0.87 ^a	0.52 to 1.46, 0.59 ^a , 0.61 ^b
Pinter ¹⁴⁰	VT event requiring therapy from the device, n (%) patients; 6	7/36 (19.4)	6/36 (16.7)	1.17 ^a	0.43 to 3.13, 0.76 ^a , ns ^b

^a Calculated by reviewer. ^b Statistical analysis reported by trial.

Figure 24: Arrhythmias



4.4.2.9 NYHA class

Six of the eight trials reported change in NYHA class; three studies reported mean or median change and three reported the number of participants improved. MIRACLE ICD,¹³⁷ MIRACLE ICD II¹³⁸ and RHYTHM ICD¹⁴⁵ reported a statistically significant improvement in mean or median NYHA class among people with CRT-D compared with people with ICD (Table 65). Combining these studies in a random effects meta-analysis gives a mean difference of -0.19 (95% CI -0.34 to -0.05, p=0.008), although note that MIRACLE ICD¹³⁷ is not estimable (see Figure 25). A significantly greater proportion of the CRT-D group improved by one class or more in RethinQ¹⁴³ (54% vs 29%, p=0.006), and the majority (81% of participants) with CRT-D in the small Piccirillo study¹³⁹ had an improvement in NYHA class, compared with only 7% of those with ICD (see Table 65), however there is some uncertainty surrounding these data due to discrepancy in reporting by the paper (see Appendix 10). In CONTAK-CD¹²⁸ there was no statistically significant difference in the number of people with improvement in NYHA class. Substantial heterogeneity was evident when these studies were combined in a random effects meta-analysis (Chi² 8.57, df 2, I² 77%) and although the direction of effect favoured CRT-D, this was not statistically significant (RR 1.81, 95% CI 0.91 to 3.60), p=0.09) (see Figure 26).

Table 65: NYHA class

Study	Outcome; follow-up, months	CRT-D n/N (%)	ICD n/N (%)	p value
CONTAK-CD ¹²⁸	Improved 2 classes, 6	12 ^a /109 (11)	2 ^a /116 (2)	0.1
	Improved 1 class	27 ^a /109 (25)	35 ^a /116 (30)	
	No change	56 ^a /109 (51)	59 ^a /116 (51)	
	Worsened	14 ^a /109 (13)	20 ^a /116 (17)	
MIRACLE ICD ¹³⁷	Change in NYHA class score, 6	n=165, median -1 (95% CI -1 to -1, SD 0)	n=162, median 0 (95% CI -1 to 0, SD 3.2)	0.007
MIRACLE ICD II ¹³⁸	Change in NYHA class, 6	n=82, mean -0.18 (SD 0.61)	n=98, mean 0.01 (SD 0.63)	0.05
Piccirillo ¹³⁹	Improved 2 classes ^b , 12	5/16 (31.3)	0/15 (0)	
	Improved 1 class ^b	8/16 (50.0)	1/15 (6.7)	
	No change ^b	3/16 (18.8)	11/15 (73.3)	
	Worsened ^b	0/16 (0)	3/15 (20.0)	
RethinQ ¹⁴³	Improved by 1 class or more, n (%); 6	41/76 (54)	23/80 (29)	0.006
	No change, n (%)	31/76 (41)	51/80 (64)	
	Worsened, n (%)	4/76 (5)	6/80 (8)	
RHYTHM ICD ¹⁴⁵	Change in NYHA class, 6	n=83, mean -0.48 (SD 0.65)	n=43, mean -0.28 (SD 0.63)	0.048

^a Numerator calculated by reviewer. ^b Calculated by reviewer from information in text of paper, note that text does not correspond with table in paper.

Figure 25: Change in NYHA class

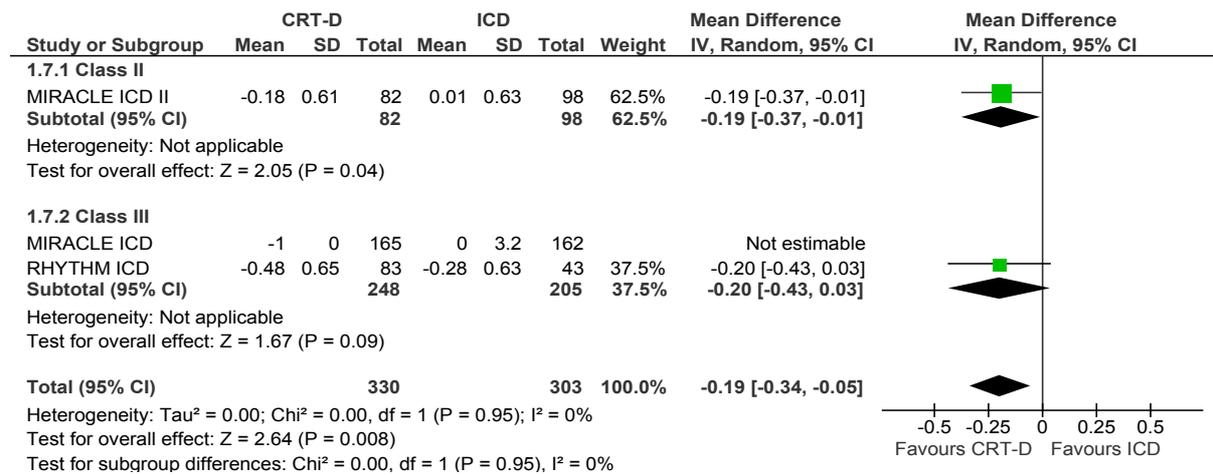
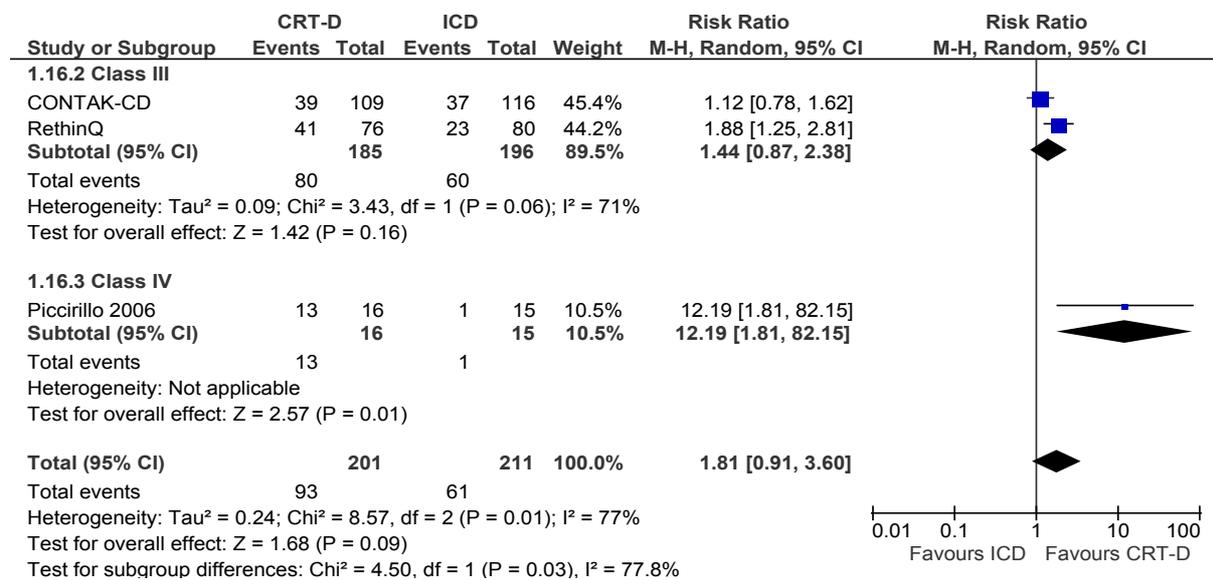


Figure 26: Proportion of people with improvement in NYHA class



4.4.2.10 Worsening heart failure

MADIT-CRT¹³² reported a statistically significant reduction in the number of people experiencing a non-fatal heart failure event among those with CRT-D compared with ICD (13.9% vs 22.8%, HR 0.59, 95% CI 0.47 to 0.74, p<0.001). Fewer heart failure events requiring intravenous therapy occurred with CRT-D (24 events in 16.1% of patients) than with ICD (41 events in 22.3% of patients) in RethinQ.¹⁴³ Worsening heart failure (other than that defined by change in NYHA class, section 4.4.2.9) was not reported by the other trials.

4.4.2.11 Left ventricular ejection fraction

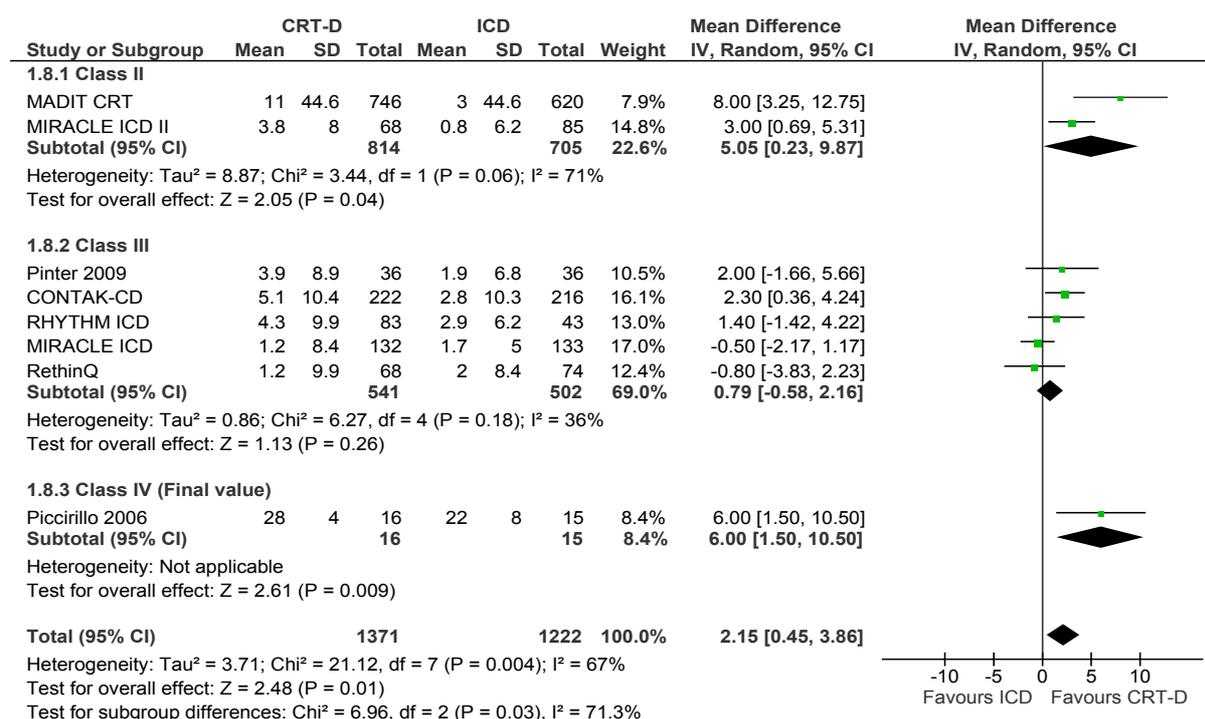
Three (CONTAK-CD,¹²⁸ MADIT-CRT,¹³² MIRACLE ICD II¹³⁸) of the eight trials reporting LVEF reported a statistically significant improvement in mean LVEF among people with CRT-D compared with ICD, whereas three (MIRACLE ICD¹³⁷, Pinter,¹⁴⁰ RethinQ¹⁴³) trials reported no statistically significant difference between the groups in change from baseline (Table 66). Piccirillo¹³⁹ and RHYTHM ICD¹⁴⁵ did not provide a statistical comparison. Combining the trials in a meta-analysis showed a statistically significant improvement in LVEF with CRT-D compared with ICD (mean difference 2.15, 95% CI 0.45 to 3.86, $p=0.01$) (Figure 27). There is substantial statistical heterogeneity (Chi^2 21.11, df 7, I^2 67%), however the direction of the effect is fairly consistent between studies.

Table 66: LVEF

Study	Outcome; follow-up, months	CRT-D	ICD	Effect	95% CI, p value
CONTAK-CD ¹²⁸	Change in LVEF %, 6	n=222, mean 5.1 (SE 0.7) (SD 10.4) ^a	n=216, mean 2.8 (SE 0.7) (SD 10.3) ^a	MD 2.30 ^b	0.36 to 4.24, 0.02 ^{b, c}
MADIT-CRT ¹³²	Change in LVEF %, average 2.4 yrs	n=746, mean 11 (SD 44.6) ^a	n=620, mean 3 (SD 44.6) ^a	MD 8.00 ^b	3.25 to 12.57, 0.001 ^{b, d}
MIRACLE ICD ¹³⁷	Change in LVEF %, 6	n=132, median 1.2 (95% CI 1.2 to 4.1) (SD 8.4) ^a	n=133, median 1.7 (95% CI 0.7 to 2.4) (SD 5.0) ^a	MD -0.50 ^b	-2.17 to 1.17, 0.56 ^{b, e}
MIRACLE ICD II ¹³⁸	change in LVEF, 6	n=68, mean 3.8 (SD 8.0)	n=85, mean 0.8 (SD 6.2)	MD 3.00 ^b	0.69 to 5.31, 0.01 ^{b, f}
Piccirillo ¹³⁹	LVEF % at 12 months	n= 16, mean 28 (4)	n=15, mean 22 (8)	MD 6.00 ^b	1.50 to 10.50, 0.009 ^b
Pinter ¹⁴⁰	change in LVEF %, 6 - measured by MUGA - measured by echocardiogram	n=36, mean 1.7 (SD 5.4) n=36, mean 3.9 (SD 8.9)	n=36, mean 0.6 (SD 6.8) n=36, mean 1.9 (SD 6.8)	MD 2.00 ^b	ns ^c -1.66 to 5.66, 0.28 ^{b, g}
RethinQ ¹⁴³	Change in LVEF %, (95 % CI)	n=68 median 1.2 (-0.4 to 4.4) (SD 9.9) ^a	n=74 median 2.0 (0.3 to 4.2) (SD 4.2) ^a	MD 0.80 ^b	3.83 to 2.23, 0.61 ^{b, h}
RHYTHM ICD ¹⁴⁵	Change in LVEF %, 6	n=83, mean 4.3 (SD 9.9)	n=43 mean 2.9 (SD 6.2)	MD 1.4 ^b	-1.42 to 4.22, 0.33 ^b

ns, not significant. ^a SD calculated by reviewer. ^b Calculated by reviewer. Statistical analysis reported by trial: ^c 0.020; ^d <0.001; ^e 0.12; ^f 0.02; ^g ns; ^h 0.83.

Figure 27: Change in LVEF



4.4.2.12 Exercise capacity

Exercise capacity was reported by six of the eight trials, six studies measuring distance walked in 6 minutes, two trials measuring exercise duration, with five trials measuring peak VO₂, and one trial reporting proportion of participants with an increase of at least 1.0 ml/kg body weight/minute in peak oxygen consumption (see Table 67). CONTAK-CD¹²⁸ found improvements in both peak VO₂ and distance walked in 6 minutes that were statistically significantly greater with CRT-D compared with ICD. MIRACLE ICD¹³⁷ and RHYTHM ICD¹⁴⁵ found statistically significant improvements in peak VO₂, but not distance walked in 6 minutes; MIRACLE ICD¹³⁷ also found significant improvements in exercise duration in favour of CRT-D. MIRACLE ICD II¹³⁸ (mild heart failure) found no statistically significant differences in change in peak VO₂ or exercise duration, but found a significant improvement in ventilatory response to exercise with CRT-D versus ICD. RethinQ¹⁴³ found no statistically significant differences in distance walked in 6 minutes, or proportion of participants with an increase of at least 1.0 ml/kg body weight/minute in peak VO₂. There was no statistically significant difference in change in 6 minute-walk distance in the Pinter study.¹⁴⁰

Meta-analysis of these trials demonstrated that the change from baseline in peak VO₂ (MD 0.75, 95% CI 0.23 to 1.27, p=0.005) (Figure 28) and distance walked in 6 minutes (MD 14.5 m, 95% CI 2.9 to 26.1, p=0.01) (Figure 29) was statistically significantly greater with CRT-D than with ICD. There was little statistical heterogeneity in these studies, and although MIRACLE ICD¹³⁷ and RethinQ¹⁴³

report medians not means, the difference remains statistically significant when these studies are omitted.

Figure 28: Change in peak VO₂

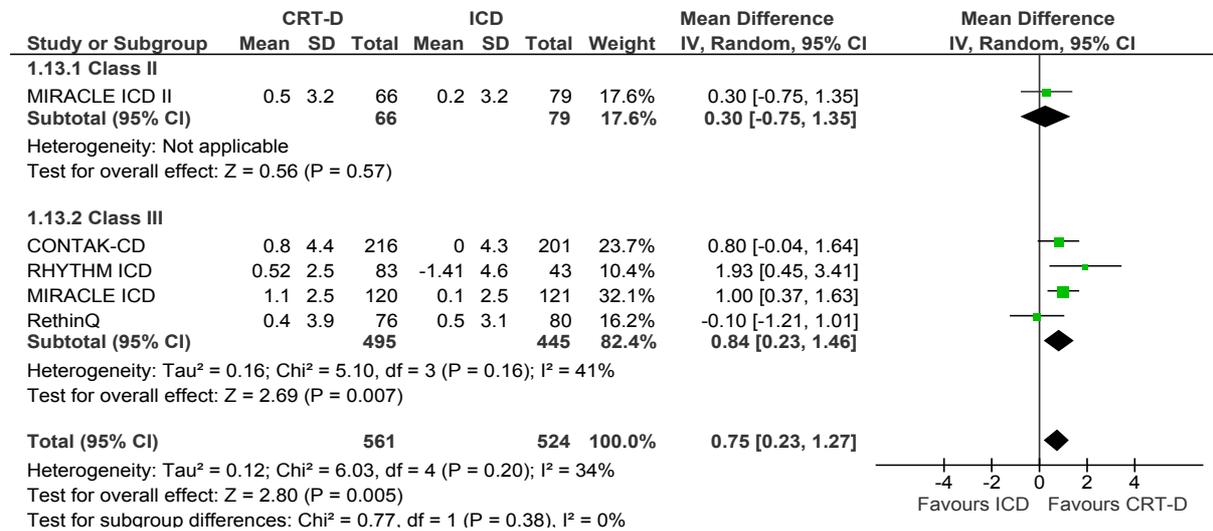


Figure 29: Change in 6-minute walk distance

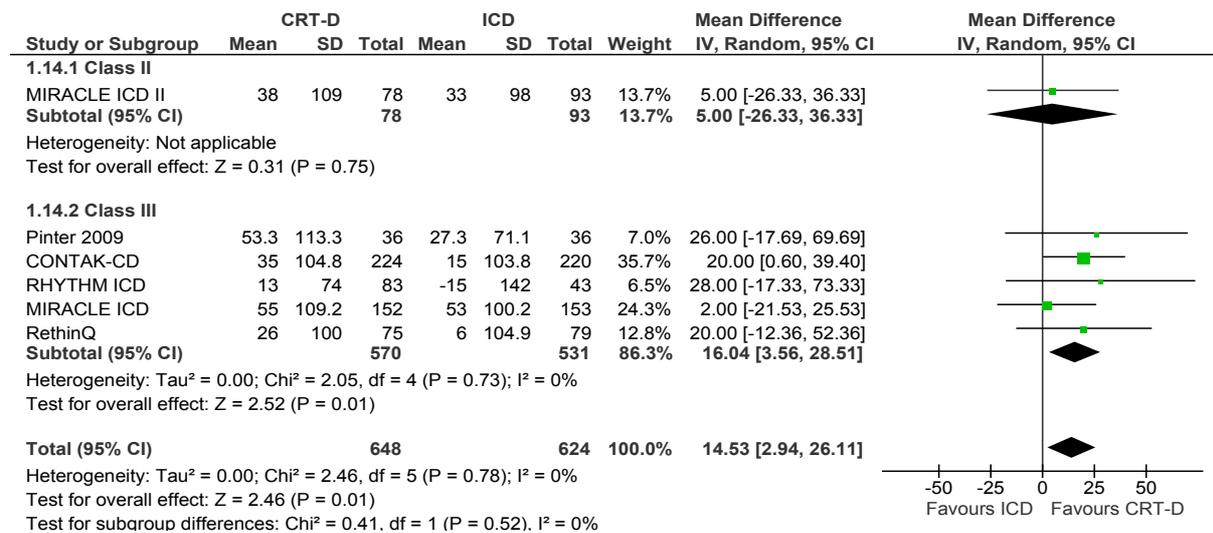


Table 67: Exercise capacity

Study	Outcome; follow-up, months	CRT-D	ICD	p value
CONTAK- CD ¹²⁸	Change in peak VO ₂ (ml/kg/min), 3-6	(n=216) mean 0.8 (SE 0.3) (SD 4.4) ^a	(n=201) mean 0.0 (SE 0.3) (SD 4.3) ^a	0.03
	Change in 6-minute walk (m), 3-6	(n=224) mean 35 (SE 7) (SD 104.8) ^a	(n=220) mean 15 (SE 7) (SD 103.8) ^a	0.043
MIRACLE ICD ¹³⁷	Change in 6-minute walk (m), 6	(n=152) median 55 (95% CI 44 to 79) (SD 109.2) ^a	(n=153) median 53 (95% CI 43 to 75) (SD 100.2) ^a	0.36
	Change in peak VO ₂ (ml/kg/min), 6	(n=120) median 1.1 (95% CI 0.7 to 1.6) (SD 2.5) ^a	(n=121) median 0.1 (95% CI -0.1 to 0.8) (SD 2.5) ^a	0.04
	Change in exercise duration (sec), 6	(n=120) median 55.5 (95% CI 30 to 79) (SD 135.5) ^a	(n=123) median -11 (95% CI -55 to 12) (SD 187.7) ^a	<0.001
MIRACLE ICD II ¹³⁸	Change in peak VO ₂ , 6	(n=66) mean 0.5 (SD 3.2)	(n=79) mean 0.2 (SD 3.2)	0.87
	Change in exercise duration (sec), 6	(n=66) mean 42 (SD 167)	(n=79) mean 37 (SD 186)	0.56
	Change in VE/VCO ₂ (mL/min), 6	(n=66) mean -1.8 (SD 6.2)	(n=78) mean 0.5 (SD 5.2)	0.01
	Change in 6-min walk distance (m), 6	(n=78) mean 38 (SD 109)	(n=93) mean 33 (SD 98)	0.59
Pinter ¹⁴⁰	Change in 6-min walk distance (m) 6 ^b	(n=36) mean 53.3 (SD 113.3)	(n=36) mean 27.3 (SD 71.1)	ns
RethinQ ¹⁴³	Change in peak VO ₂ , ml/kg/min, median (95 % CI)	(n=76) 0.4 (-0.6 to 1.2) (SD 3.9) ^a	(n=80) 0.5 (-0.3 to 1.1) (SD 3.1) ^a	
	Peak VO ₂ , increase ≥1.0 ml/kg/min, n (%)	(n=76) 35/76 (46)	(n=80) 33/80 (41)	0.63
	Change in 6-min walk, m, median (95 % CI)	(n=75) 26 (0 to 46) (SD 100) ^a	(n=79) 6 (-17 to 30) (SD 104.9) ^a	0.23
RHYTHM ICD ¹⁴⁵	Change in peak VO ₂ (ml/kg/min), 6	(n=83) mean 0.52 (SD 2.5)	(n=43) mean -1.41 (SD 4.6)	0.001
	Change in 6 minute walk distance, 6	(n=83) mean 13 (SD 74)	(n=43) mean -15 (SD 142)	0.07

ns, not significant; ^a SD calculated by reviewer. ^b Assumed values are mean (SD) but this is not specified in paper.

4.4.2.13 QoL

Six of the eight trials reported change in QoL at 6 months, assessed using the Minnesota Living with Heart Failure questionnaire (MLWHF) (see Table 68). An improvement in QoL score was seen with CRT-D when the trials were pooled (MD -6.9, 95% CI -10.4 to -3.4, $p=0.0001$) (Figure 30). Pinter¹⁴⁰ also reported Duke Activity Status Index, one item Global Visual Analogue Scale and SF-36. Comparisons of baseline to 6 month changes were statistically significant for the General Health component of the SF-36 only (-5.8 (SD 14.9) vs -5.8 (SD 13.6), $p=0.02$).

Figure 30: Change in MLWHF score

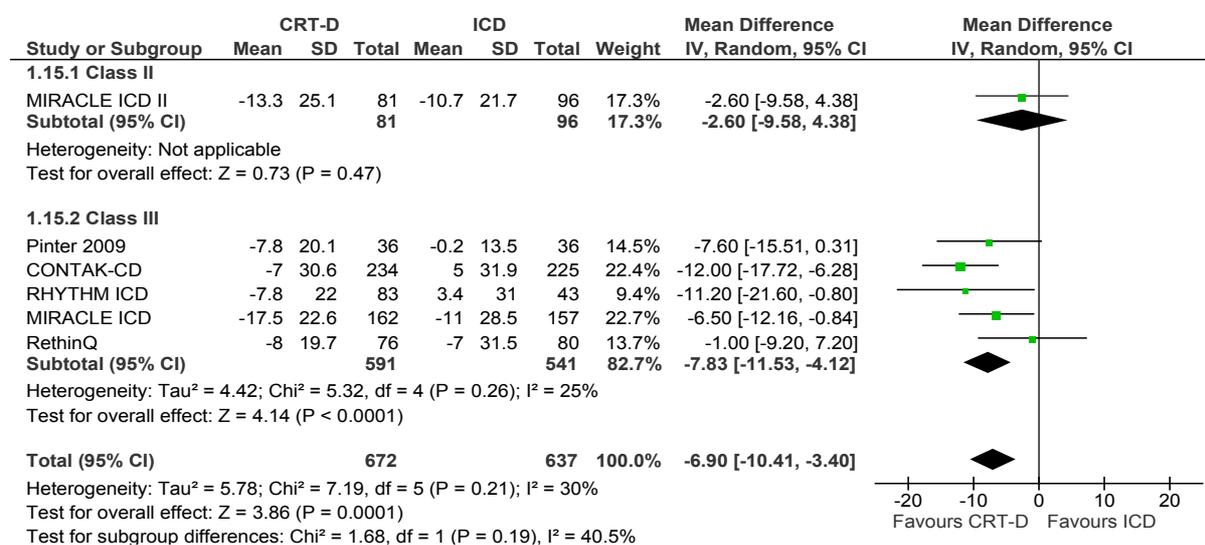


Table 68: Quality of Life

Study	Outcome; follow-up, months	CRT-D	ICD	p value
CONTAK-CD ¹²⁸	Change in MLWHF score, 6	(n=234) mean -7 (SE 2) (SD 30.6) ^a	(n=255) mean 5 (SE 2) (SD 31.9) ^a	0.39 ^b
MIRACLE ICD ¹³⁷	Change in MLWHF score, 6	(n=162) median -17.5 (95% CI -21 to -14) (SD 22.6) ^a	(n=157) median -11 (95% CI -16 to -7) (SD 28.5) ^a	0.02
MIRACLE ICD II ¹³⁸	Change in MLWHF score, 6	(n=81) mean -13.3 (SD 25.1)	(n=96) mean -10.7 (SD21.7)	0.49
Pinter ¹⁴⁰	Change in score, 6 ^c			
	Duke Activity Status Index	(n=36) mean 4.63 (SD 9.20)	(n=36) mean 1.08 (SD 7.02)	ns
	Global Visual Analogue Scale	(n=36) mean -0.07 (SD 2.22)	(n=36) mean -0.17 (SD 1.64)	ns
	MLWHF			
	- Total score	(n=36) mean -7.8 (SD 20.1)	(n=36) mean -0.2 (SD 13.5)	ns
	- Physical dimension	(n=36) mean -5.0 (SD 12.4)	(n=36) mean -0.6 (SD 7.9)	ns
	- Emotional dimension	(n=36) mean -1.3 (SD 5.0)	(n=36) mean 0.3 (SD 3.4)	ns
	SF 36, change to 6 months ^c			
	Physical functioning	(n=36) mean 11.2 (SD 24.2)	(n=36) mean 6.3 (SD 21.2)	ns
	Role physical	(n=36) mean 19.6 (SD 43.2)	(n=36) mean 21.6 (SD 38.1)	ns
	Bodily pain	(n=36) mean -3.3 (SD 16.6)	(n=36) mean -2.3 (SD 13.1)	ns
	General health	(n=36) mean -5.8 (SD 14.9)	(n=36) mean -5.8 (SD 13.6)	0.02
	Physical component score	(n=36) mean 1.4 (SD 6.4)	(n=36) mean 1.3 (SD 4.8)	ns
		Vitality	(n=36) mean 4.7 (SD 22.7)	(n=36) mean 2.6 (SD 15.7)
Social functioning		(n=36) mean 12.5 (SD 23.3)	(n=36) mean 5.4 (SD 32.6)	ns
Role emotional		(n=36) mean 29.5 (SD 48.4)	(n=36) mean 3.3 (SD 48.2)	ns

	Mental health	(n=36) mean 4.5 (SD 14.5)	(n=36) mean 0.1 (SD 21.8)	ns
	Mental component score	(n=36) mean 5.1 (SD 10.1)	(n=36) mean 0.5 (SD 12.4)	ns
RethinQ ¹⁴³	Change in MLWHF, median (95% CI), 6	(n=76) -8 (-10 to -1) (SD 19.7) ^a	(n=80) -7 (-11 to 3) (SD 31.5) ^a	0.91
RHYTHM ICD ¹⁴⁵	Change in MLWHF score, 6	(n=83) mean -7.8 (SD 22)	(n= 43) mean 3.4 (SD 31)	0.009

ns, not significant. MLWHF, Minnesota Living with heart Failure Questionnaire (more negative change scores indicate greater improvement).

^a SD calculated by reviewer. ^b Reported as not statistically significant in paper, but statistically significant in meta-analysis ($p < 0.0001$).¹²⁸ ^c Assumed values are mean (SD) but not always stated.

4.4.2.14 Adverse events

As described in section 4.4.1.1, three of the trials compared CRT-D and ICD devices (MADIT-CRT,¹³² Piccirillo¹³⁹ and RAFT¹⁴¹), whilst all participants in the six remaining trials^{128;137;138;140;143;145} were implanted with a device that could provide both CRT and ICD therapy (CRT-OFF in the comparator group). Differences in adverse events relating to the CRT-D device can therefore only be assessed in the former three trials, and of these only MADIT-CRT¹³² and RAFT¹⁴¹ provided adverse event data.

Reporting of adverse events by the included trials was limited and inconsistent. As can be seen in Table 69, in some of the trials the number of participants randomised differed from the number of people enrolled and had implantation attempted, as in six of the trials only people with successful implantations were randomised. However, adverse event data were reported for all participants who underwent implantation or attempted implantation by CONTAK-CD,¹²⁸ MADIT-CRT,¹³² MIRACLE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ RAFT¹⁴¹ and RHYTHM ICD.¹⁴⁵ MIRACLE ICD¹³⁷ and MIRACLE ICD II¹³⁸ also reported total complications for those with successful implants.

Five of the trials using the same device in all participants, i.e. CRT-ON versus CRT-OFF (CONTAK-CD,¹²⁸ MIRACLE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ RethinQ¹⁴³ and RHYTHM ICD¹⁴⁵) reported adverse events for both interventions combined (Table 70). MIRACLE ICD¹³⁷ also reported events separately for CRT-ON and CRT-OFF (see Table 71), as did MADIT-CRT¹³² and RAFT¹⁴¹ for CRT-D versus ICD devices. Adverse events were not reported by Pinter;¹⁴⁰ and Piccirillo¹³⁹ stated that there no major complications following implantation but provided no further information.

Between 83.3% and 99.4% of people undergoing an implantation attempt received an implanted device (see Table 69). Four of these studies (MIRACLE ICD,¹³⁷ MIRACLE ICD II,¹³⁸ Pinter,¹⁴⁰ RHYTHM ICD¹⁴⁵) clearly described the implantations as successful (83.3% to 91%) (Table 69).

Perioperative deaths occurred in between 0.1% (MADIT-CRT¹³²) to 2.4% (RHYTHM ICD¹⁴⁵) of participants (Table 70, Table 71), although it is not clear whether the time period of reporting is consistent between studies. Lead-related complications with CRT-D were experienced by around 7% of participants in three trials,^{141;143;145} and the overall lead-related adverse event rate was 14.5% in CONTAK-CD.¹²⁸ MIRACLE ICD¹³⁷ and MIRACLE ICD II¹³⁸ reported the proportion of complications that were related to the LV lead before hospital discharge, with 23% of 159 complications and 34% of 56 complications, respectively. Four per cent of people with a CRT-D in MADIT-CRT¹³² had the LV lead repositioned during the first 30 days.

The RAFT trial¹⁴¹ compared adverse events statistically between CRT-D and ICD devices (Table 71). Device or implantation related complications within 30 days of implantation was significantly higher in the CRT-D group than the ICD group (13.3% vs 6.8%, $p < 0.001$), as was device-related hospitalisation (20% vs 12.2%, HR 1.68, 95% CI 1.32 to 2.13, $p < 0.001$), lead-dislodgement requiring intervention (6.9% vs 2.2%) and coronary sinus dissection (1.2% vs 0). After the first 30 days, MADIT-CRT¹³² reported 4.5 (with CRT-D) and 5.2 (with ICD) serious device-related adverse events per 100 device-months.

Table 69: Flow of participants through studies

Number	CONTAK CD ¹²⁸	MADIT- CRT ¹³²	MIRACLE ICD ¹³⁷	MIRACLE ICD II ¹³⁸	Piccirillo ¹³⁹	Pinter ¹⁴⁰	RAFT ¹⁴¹	RethinQ ¹⁴³	RHYTHM ICD ¹⁴⁵
Enrolled	581	1820	429	222			1798	250	205
Attempted implant	567	Unclear ^a	429	210		90	Unclear ^b	250 ^c	205
Implanted	501/567 (88.4%)	1790/1820 (98.4%) ^d	379/429 (88.3%) ^e	191/210 (91%) ^e		75/90 (83.3%) ^e	1787/1798 (99.4%) ^f	Unclear ^c	182/205 (88.8%) ^e
Randomised	490	1820	369	186	31	72	1798	172	179
Only successful implants randomised?	yes	no	yes	yes	unclear	yes	no	yes	yes
Efficacy analysis	490	1820	369	186	31	72	1798	156	126

Shaded squares show reporting of adverse event data. ^a States 30/1820 patients did not receive a device, but not clear whether implantation was attempted in these patients. ^b reasons for non-implantation given as declined to participate, death, lack of venous access – unclear if the latter two were before/during implantation attempt. ^c States 4/250 (1.6%) did not undergo successful implantation, but unclear whether successful implantation occurred in the remaining 246/250 patients (2 died and 3 withdrew before baseline evaluation at 14 days after successful implantation, and 69 did not meet enrolment criteria and did not undergo randomisation). ^d overall implantation of device achieved in 1790/1820, 1736/1820 (95.4%) received the assigned device. ^e Described in paper as successful implants. ^f Left ventricular lead was successfully implanted in 841 of 888 (94.7%) attempted implants in CRT-D group.

Table 70: Adverse events reported for study population

Study	Adverse events	n/N (%)
CONTAK CD ^{128;131} Attempted implants n=567	Operative mortality	12/567 (2.1%) 95% CI 0.9 to 3.3
	Overall lead-related adverse event rate	75/517 ^a (14.5%) (95% CI 11.5 to 17.5)
	Severe device-related events	7/567 (1.2%)
	Device-related complications (occurring in >1% of patients): infections	7/517 ^a (1.4%)
MIRACLE ICD ¹³⁷ Attempted implants n=429	Experienced complication from implant to hospital discharge	120/429 (28%) 159 complications
	- complication related to LV lead	37/159 (23% of complications) - included 15 coronary sinus dissections - 4 cardiac perforations
	- HF decompensation	6/429 (received i.v. medication)
	- heart block	3/429 (required bradycardia pacing support)
	- muscle stimulation	4/429 (required either lead repositioning or replacement)
	- pericardial effusion	2/429 (treated with a pericardiocentesis)
	- pericarditis	1/429 (received intravenous medication)
	- hemo/pneumothorax	3/429 (placement of chest tube)
	- VT and VF	5/429 (3 received external defibrillation, 2 i.v. medications)
	- elevated pacing thresholds or loss of capture	7/429 (6 received lead repositioning, 1 set screw tightened in connector block)
Died within 30 days of latest implant attempt	5/429 (1.2%)	
Successful implants n=379	From hospital discharge to the 6- month follow-up, total complications	175/379 (46%) 398 complications
MIRACLE ICD II ¹³⁸ Attempted Implants n=210	Died (before randomisation)	1/210
	From implant to hospital discharge	46/210 (22%) 56 complications
	- complications related to placement of LV lead	19/56 (34% of complications) (including 3 coronary sinus dissections, 3 cardiac perforations, 5 lead dislodgements)
	Failed initial implant attempt ^b	23/210

Successful implants n=191 ^b	From hospital discharge to 6 months	66/191 (35%) 109 complications
	- complications related to LV lead	19/109 (17%) (including 11 lead dislodgements, 1 cardiac perforation, 3 diaphragmatic muscle stimulation, 4 elevated pacing thresholds)
RethinQ ¹⁴³ Randomised patients n=172	Lead dislodgement	13/172 (7.6)
	- involving left ventricular lead	5/172 (2.9)
	Infection	6/172 (3.5)
	Bleeding or hematoma	2/172 (1.2)
	Loss of pacemaker-lead capture	2/172 (1.2)
	Phrenic-nerve stimulation	3/172 (1.7)
	Deep venous thrombosis	3/172 (1.7)
	Pneumothorax	2/172 (1.2)
	Pericarditis	2/172 (1.2)
	Coronary sinus perforation	1/172 (0.6)
RHYTHM ICD ¹⁴⁵ Enrolled patients n=205 average 12.1 (3.4) patient months follow-up ¹⁴⁵	Death (before randomisation)	2/205 (1.0%)
	Total complications (adverse events requiring invasive intervention)	21 (10.2), 29 events
	- coronary sinus perforation/dissection	2 (1.0), 2 events
	- diaphragmatic/phrenic nerve stimulation	3 (1.5), 3 events
	- lead dislodgement or migration	8 (3.9), 9 events
	- bleeding/hematoma	6 (2.9), 6 events
	- blood clot/ thrombosis	1 (0.5), 1 event
	- high defibrillation/cardioversion requirements	2 (1.0), 2 events
	- infection	1 (0.5), 1 event
	- noise on EGM post shock (non-SJM RV lead)	1 (0.5), 1 event
	- pneumothorax	2 (1.0), 2 events
	- retained foreign body (surgical sponge)	1 (0.5), 1 event
	- elevated pacing threshold - LV lead	1 (0.5), 1 event
	Total observations (adverse events managed without invasive	57 (27.8), 68 events

	intervention)	
	- asystolic episode during LV lead placement	1 (0.5), 1 event
	- bleeding/hematoma	10 (4.9), 10 events
	- blood clot/ thrombosis	2 (1.0), 2 events
	- coronary sinus perforation/dissection	6 (2.9), 6 events
	- diaphragmatic/phrenic nerve stimulation - LV lead	10 (4.9), 10 events
	- diaphragmatic/phrenic nerve stimulation - RV lead	2 (1.0), 2 events
	- elevated pacing thresholds - LV lead	10 (4.9), 10 events
	- elevated pacing thresholds - RV lead	2 (1.0), 2 events
	- heart block at implant	2 (1.0), 2 events
	- high defibrillation/cardioversion requirements	1 (0.5), 1 event
	- hypotension requiring ventilator support	1 (0.5), 1 event
	- inappropriate therapy for SVT	10 (4.9), 13 events
	- infection	3 (1.5), 3 events
	- possible pulmonary embolism	1 (0.5), 1 event
	- T-Wave sensing	2 (1.0), 3 events
	- pocket inflammation/seroma	1 (0.5), 1 event
	LV lead-related complications at 6 months	11/155 (7.1) patients, 13 complications
	Epic HF system-related complications at 6 months	13/182 (7.1) patients, 16 complications
	Total adverse events (29 complications and 68 observations)	70 patients, 97 events
average 15.1 (4.1) patient months of follow-up	Total complications ^c	22 (10.7), 31 events
	- lead dislodgement or migration	9 (4.4), 10 events
	- infection	2 (1.0), 2 events
	Total observations ^c	59 (28.8), 76 events
	- diaphragmatic/phrenic nerve stimulation - LV lead	14 (6.8), 14 events
	- elevated pacing thresholds - LV lead	12 (5.9), 12 events
	- inappropriate therapy for SVT	11 (5.4), 14 events

	- infection	4 (2.0), 4 events
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^a 517 patients who had an attempted implant procedure with EASYTRAK leads, 448 with successful EASYTRAK lead implant. ^b States 191/210 (91%) patients were successfully implanted, but also states 23/210 failed initial implant (210-23=187); there were also 4 patients with LV lead dislodgements that were not corrected and were therefore not randomised. ^c Only those observations with added data detailed here.¹⁴⁶

Table 71: Adverse events reported by intervention

Study	Adverse event	CRT-D, n/N (%)	ICD, n/N (%)	Effect	95% CI, p value
MADIT-CRT ¹³² Enrolled and randomised n=1820 CRT-D n=1089 ICD n=731	Death in hospital after device implantation	1/1089 (pulmonary embolus)			
	Serious adverse events within 30 days of implantation				
	- pneumothorax	1.7%	0.8%		
	- infection	1.1%	0.7%		
	- pocket haematoma requiring evacuation	3.3%	2.5%		
	Coronary venous dissection with pericardial effusion during CRT-ICD implantation	5/1089 (0.5)	n/a		
	Left ventricular coronary-vein lead repositioned during 1 st 30 days	44/1089 (4.0)			
	Frequency of serious device-related adverse events during long-term follow-up after the 1 st 30 days	4.5 per 100 device-months	5.2 per 100 device-months		
Removal of device	14/1089 (1.3)	5/731 (0.7)			
MIRACLE ICD ¹³⁷ Successful implant and randomised n=369 CRT-D n=187 CRT-off n=182	Complications after hospital discharge to 6-months:	CRT-ON, n/N (%)	CRT- OFF, n/N (%)		
	LV lead related complication	20 (11%) 21 events	13 (7%) 14 events		
	ICD system related	9 (5%) 9 events	13 (8%) 14 events		
	Procedure related	10 (5%) 10 events	11 (6%) 13 events		
	HF decompensation	36 (19%) 63 events	40 (22%) 71 events		
	Other	45 (24%) 81 events	44 (24%) 74 events		
	Total	88 (47%) 184 events	80 (44%) 186 events		

RAFT ¹⁴¹		CRT-D, n/N (%)	ICD, n/N (%)		
Implanted n=1787 CRT-D n=888 ICD n=899	Death from worsening HF within 24hrs after implantation		1/899 (0.1)		
	Device-related hospitalisation	179/888 (20%)	110/899 (12.2)	HR 1.68	1.32 to 2.13, <0.001
	AEs at 30 days after implantation ^a	124/888 (14.0)	58/899 (6.5)		<0.001
	Hemothorax or pneumothorax	11/888 (1.2%)	8/899 (0.9%)		0.47
	Device-pocket hematoma requiring intervention	14/888 (1.6%)	11/899 (1.2%)		0.53
	Device-pocket infection requiring intervention	21/888 (2.4%)	16/899 (1.8%)		0.39
	Lead dislodgement requiring intervention	61/888 (6.9%)	20/899 (2.2%)		0.0001
	Device-pocket problems requiring revision	4/888 (0.5%)	1/899 (0.1%)		0.22
	Coronary sinus dissection	11/888 (1.2%)	0/899 (0)		0.0004
	Tamponade	2/888 (0.23)	2/899 (0.22)		1

^a Also reports device or implantation related complications within 30 days of implantation, CRT-D 118/888 (13.3%), ICD 61/899 (6.8%), p<0.001 - not clear what this includes and how it differs from 'adverse events' at 30 days.

4.4.2.15 Subgroup analyses reported by included RCTs

Three trials reported pre-specified subgroup analysis.

MADIT-CRT¹³² presented pre-specified stratified analysis according to ischemic or non-ischemic cardiomyopathy classification. A similar benefit from CRT-D was found in people with ischemic or non-ischemic cardiomyopathy (Table 72). Subgroup analysis of risk of death or heart failure according to selected clinical characteristics found that CRT-D was associated with a greater benefit in people with QRS duration 150 ms or more than in those with a QRS duration of less than 150 ms ($p=0.001$ for interaction), and with a greater benefit in women than in men ($p=0.01$ for interaction). There were no statistically significant interactions for the other subgroups (age, NYHA class, LVEF, LVEDV and LVESV) (Table 72). Additional analysis stratified by men and women reported in a secondary publication is presented in Table 73 and shows women achieved significantly better results from CRT-D than men.

RAFT¹⁴¹ reported analysis on 11 pre-specified subgroups (Table 74) and presented outcomes separately for NYHA class II and III subgroups (Table 75). CRT-D and ICD were associated with a similar reduction for the composite primary outcome of death or hospitalisation for heart failure ($p=0.91$ for interaction), death from any cause and hospitalisation for heart failure for NYHA class II and III. A statistically significant interaction was found between treatment and QRS duration ($p=0.003$), where CRT-D was more effective in people with intrinsic QRS duration of ≥ 150 ms (HR 0.59, 95% CI 0.48 to 0.73) than in those with an intrinsic QRS duration of < 150 ms (HR 0.99, 95% CI 0.77 to 1.27, $p = 0.002$ for interaction) or those with a paced QRS duration of ≥ 200 ms (HR 1.07, 95% CI 0.63 to 1.84, $p = 0.03$ for interaction). A statistically significant interaction ($p = 0.046$) between treatment and QRS morphologic type was also found, where CRT-D was more effective in people with LBBB than in those with nonspecific intraventricular conduction delay ($p = 0.046$ for interaction).

RethinQ¹⁴³ presented prespecified stratified analysis according to QRS interval (≥ 120 ms or < 120 ms) and cardiomyopathy classification (ischemic or non-ischemic). A statistically significant improvement in the proportion of people with an increase of at least 1 ml/kg body weight/min in peak oxygen consumption was found with CRT-D for people with QRS ≥ 120 ms (58.9% vs 19.7%, $p=0.02$), but not for those with QRS < 120 (42.2% vs 51.2%, $p=0.45$). There was a statistically significant improvement in the proportion with improvement in NYHA class with CRT-D for both QRS ≥ 120 ms (70.7% vs 28.0%, $p=0.01$) and < 120 ms (49.4 vs 29.3%, $p=0.04$) subgroups. There was no statistically significant difference between CRT-D and ICD in QoL or distance walked in 6 minutes for either QRS interval subgroup. Analysis stratified by ischemic or non-ischemic cardiomyopathy

classification reflected the results for the whole group for peak oxygen consumption, NYHA class and QoL. However, a statistically significant difference between CRT-D and ICD in change in distance walked in 6 minutes was found for those with non-ischemic cardiomyopathy (55.0 m vs 2.5 m, $p=0.01$), but not for those with ischemic cardiomyopathy (4.2 m vs 5.8 m, $p=0.57$).

Table 72: MADIT-CRT¹³² subgroups

Subgroups	CRT-ICD	ICD only	Effect	95% CI, p value
Patients with ischemic cardio-myopathy (NYHA class I or II)	n=598	n=401		
Death from any cause or non-fatal heart failure event, n/N (%)	122/598 (20.4%)	117/401 (29.2%)	HR 0.67	0.52 to 0.88, 0.003
- heart failure events only, n/N (%)	96/598 (16.1%)	105/401 (26.2%)	HR 0.58	0.44 to 0.78, <0.001
Death at any time, n/N (%)	53/598 (8.9)	35/401 (8.7)	HR 1.06	0.68 to 1.64, 0.80
Patients with nonischemic cardio-myopathy (NYHA class I or II)	n=491	n=330		
Death from any cause or non-fatal heart failure event, n (%)	65 (13.2%)	68 (20.6%)	HR 0.62	0.44 to 0.89, 0.01
- heart failure events only, n(%)	55 (11.2%)	62 (18.8%)	HR 0.59	0.41 to 0.87, 0.01
Death at any time, n (%)	21 (4.3%)	18 (5.5%)	HR 0.87	0.44 to 1.70, 0.68
Risk of death or heart failure according to selected clinical characteristics	No. of events/No. of patients		Effect	95% CI, p value for interaction
Age				
< 65 years	142/852		HR 0.80 ^a	
≥ 65 years	230/968		HR 0.60 ^a	
Sex				
male	294/1367		HR 0.76	0.59 to 0.97
female	78/453		HR 0.37	0.22 to 0.61, 0.01
NYHA class				
Ischaemic I	53/265		HR 0.76 ^a	
Ischaemic II	186/734		HR 0.62 ^a	
Nonischaemic II	133/821		HR 0.60 ^a	
QRS duration				

<150ms	147/645	HR 1.06	0.74 to 1.52
≥150ms	225/1175	HR 0.48	0.37 to 0.64, 0.001
LVEF			
≤25%	101/646	HR 0.70 ^a	
>25%	271/1174	HR 0.60 ^a	
LVEDV			
≤240ml	184/828	HR 0.70 ^a	
> 240ml	184/969	HR 0.62 ^a	
LVESV			
≤170ml	190/835	HR 0.66 ^a	
> 170ml	178/962	HR 0.70 ^a	
All patients	372/1820	HR 0.66	

^a Hazard ratios estimated from figure by reviewer.

Table 73: MADIT-CRT¹⁵² outcomes by gender

Outcome	Women, n=453		Men, n=1,367		P value of interaction
	CRT-D	ICD	CRT-D	ICD	
Heart failure or death (primary end point)	29/275 (11%)	51/178 (29%)	159/814 (20%)	137/553 (25%)	<0.01
	CRT-D:ICD HR 0.31 (95% CI 0.19 to 0.50), p<0.001		CRT-D:ICD HR 0.72 (95% CI 0.57 to 0.92), p<0.01		
Heart failure only	n=73 events CRT-D:ICD HR 0.30 (95% CI 0.18 to 0.50), p<0.001		n=249 events CRT-D:ICD HR 0.65 (95% CI 0.50 to 0.84), p=0.001		<0.01
Death at any time	n=20 events CRT-D:ICD HR 0.28 (95% CI 0.10 to 0.79), p=0.02		n=107 events CRT-D:ICD HR 1.05 (95% CI 0.70 to 1.57), p=0.83		<0.03

Table 74 RAFT¹⁴¹ subgroup analyses

Subgroup	HR	(95% CI) P value of interaction
Age: <65 yrs vs ≥ 65		0.75
Gender: male vs female		0.09
NYHA class: II vs III		0.91
Underlying heart disease: ischemic vs non-ischemic		0.90
QRS duration: intrinsic QRS <150ms vs intrinsic QRS ≥150m vs paced QRS ≥200ms	0.99 (0.77 to 1.27) 0.59 (0.48 to 0.73) 1.07 (0.63 to 1.84)	0.003, ^a 0.002, ^b 0.003 ^c
LVEF: <20% vs ≥20%,		0.05
QRS morphologic features: RBBB vs LBBB vs NIVCD vs paced		0.046
Atrial rhythm: permanent atrial fibrillations or flutter vs sinus or atrial paced		0.14
Diabetes: yes vs no		0.22
Hypertension: yes vs no		0.84
Estimated GFR (ml/min/1.73m ²): <60 vs ≥60		0.70

NIVCD = nonspecific intraventricular conduction delay. ^a Interaction between treatment and QRS duration. ^b More effective in those with intrinsic QRS duration of ≥150msec (HR, 0.59; 95% CI, 0.48 to 0.73) than in those with an intrinsic QRS duration of <150msec (HR, 0.99; 95% CI, 0.77 to 1.27; p = 0.002 for interaction). ^c More effective in those with intrinsic QRS duration of ≥150msec (HR, 0.59; 95% CI, 0.48 to 0.73) than in those with a paced QRS duration of ≥200msec (HR, 1.07; 95% CI, 0.63 to 1.84; p = 0.03 for interaction).

Table 75: RAFT¹⁴¹ NYHA subgroups

NYHA Class	CRT-D,	ICD	Effect	95% CI, p value
NYHA class II	n=708	n=730		
Primary outcome: death or hospitalisation for heart failure	193/708 (27.3)	253/730 (21.1)	HR 0.73	0.61 to 0.88, 0.001
Secondary outcomes: Death from any cause	110/708 (15.5)	154/730 (21.1)	HR 0.71	0.56 to 0.91, 0.006
Death from cardiovascular cause	74/708 (10.5)	100/730 (13.7)	HR 0.73	0.54 to 0.99, 0.04
Hospitalisation for heart failure	115/708 (16.2)	159/730 (21.8)	HR 0.70	0.55 to 0.89, 0.003
NYHA class III	n=186	n=174		
Primary outcome: death or hospitalisation for heart failure	104/186 (55.9)	111/174 (63.8)	HR 0.76	0.58 to 0.99, 0.04
Secondary outcomes: Death from any cause	76/186 (40.9)	82/174 (47.1)	HR 0.79	0.58 to 1.08, 0.14
Death from cardiovascular cause	56/186 (30.1)	62/174 (35.6)	HR 0.77	0.54 to 1.10, 0.15
Hospitalisation for heart failure	59/186 (31.7)	77/174 (44.3)	HR 0.63	0.45 to 0.88, 0.006

Table 76: RethinQ¹⁴³ subgroup analyses

QRS interval at 6 months^a	CRT-D ON + OPT, QRS ≥120, n=17 QRS <120, n=59	ICD+OPT, QRS ≥120, n=25 QRS <120, n=55	p value
Peak oxygen consumption, increase of ≥1 ml/kg/min			
QRS ≥120	58.9	19.7	0.02
QRS <120	42.2	51.2	0.45
NYHA class, proportion of patients improved by ≥ 1 class			
QRS ≥120	70.7	28.0	0.01
QRS <120	49.4	29.3	0.04
QoL, median change, %			
QRS ≥120	0	-3.7	0.24
QRS <120	-8.9	-7.0	0.63
6-min walk distance, median change, m			
QRS ≥120	0.0	-19.1	0.86
QRS <120	33.7	10.3	0.31
Cardiomyopathy classification at 6 months^a	CRT-D ON + OPT, Ischemic, n=40 Non-ischemic, n=36	ICD+OPT, Ischemic, n=41 Non-ischemic, n=39	p value
Peak oxygen consumption, increase of ≥1 ml/kg/min			
Ischemic	40.0	44.2	0.82
Non-ischemic	52.6	38.4	0.25
NYHA class, proportion of patients improved by ≥ 1 class			
Ischemic	55.3	29.5	0.02
Non-ischemic	53.2	28.4	0.04
QoL, median change, %			
Ischemic	-5.9	-3.6	0.68
Non-ischemic	-10.6	-6.5	0.60
6-min walk distance, median change, m			

Ischemic	4.2	5.8	0.57
Non-ischemic	55.0	2.5	0.01

^a All values estimated by reviewer using Engauge software, p values extracted from paper.

4.4.3 Summary of clinical effectiveness: people with both conditions

- Nine RCTs were included comparing CRT-D with ICD in people both at risk of sudden cardiac death due to ventricular arrhythmias and with heart failure as a result of LVSD and cardiac dyssynchrony.
- No RCTs comparing CRT-D with OPT or with CRT-P were identified for this population.
- The risk of bias was low in some of the trials, but unclear in others due to inadequate reporting.
- Length of follow-up was 6 months in five trials, one year in two trials, and an average of 2.4 years and 3.3 years in the remaining trials. Sample size ranged from 31 to 1820 participants.
- The trials differed in their eligibility criteria for heart failure; the majority of participants were in NYHA class II in three trials, NYHA class III in four trials, described as ‘mild to moderate’ in one trial, and NYHA class IV in one trial. One trial differed from the others in the criteria used to define cardiac dyssynchrony, recruiting people with a narrow QRS interval (<130 ms) and evidence of mechanical dyssynchrony on echocardiography. Trials were similar in other key characteristics. LVEF ranged from 21% to 26%.
- Meta-analysis found that CRT-D reduced the risk of all-cause mortality (8 RCTs, RR 0.84, 95% CI 0.73 to 0.96, p=0.01) and total cardiac deaths (6 RCTs, RR 0.82, 95% CI 0.67 to 1.00, p=0.05). These results were strongly influenced by the large RAFT trial, which included people with mild to moderate heart failure despite OPT, LVEF ≤30% from ischemic or nonischemic causes, a wide QRS interval, and planned ICD implantation for indicated primary or secondary prevention of sudden cardiac death.
- Fewer trials reported heart failure deaths or sudden cardiac deaths separately, and zero heart failure or sudden cardiac deaths occurred in some of these trials. Combining three RCTs in a meta-analysis found little difference in sudden cardiac death between CRT-D and ICD (RR 1.45, 95% CI 0.43 to 4.92, p=0.55).
- The RAFT trial found a statistically significant reduction in heart failure hospitalisations with CRT-D. Two small trials (CONTAK-CD and Piccirillo) found no significant difference. Combining these trials in a meta-analysis demonstrated that CRT-D reduced the relative risk of hospitalisation by 25% compared with ICD (RR 0.75, 95% CI 0.64 to 0.88, p=0.0005).
- Meta-analysis of four trials found no statistically significant difference in the proportion of people experiencing at least one episode of ventricular tachycardia or ventricular fibrillation (RR 0.90, 95% CI 0.71 to 1.14, p=0.38).

- An improvement in NYHA class was found with CRT-D among two trials reporting mean or median change (MD -0.19, 95% CI -0.34 to -0.05, $p=0.008$). Results were more heterogeneous among the three trials reporting the proportion of people improved by one or more NYHA class; two trials found a statistically significant improvement with CRT-D but one trial found no difference (meta-analysis RR 1.81, 95% CI 0.91 to 3.60, $p=0.09$).
- There was substantial statistical heterogeneity in LVEF among trials, although the direction of effect was fairly consistent. Meta-analysis found a significant improvement in LVEF with CRT-D compared with ICD (8 RCTs, MD 2.15, 95% CI 0.45 to 3.86, $p=0.01$).
- There was a greater improvement in exercise capacity, as demonstrated by change from baseline in peak VO_2 (5 RCTs, MD 0.75, 95% CI 0.23 to 1.27, $p=0.005$) and 6 MWT (6 RCTs, MD 14.5 m, 95% CI 2.9 to 26.1, $p=0.01$), with CRT-D than with ICD.
- An improvement in QoL (MLWHFQ) score was seen with CRT-D when six trials were pooled in a meta-analysis (MD -6.9, 95% CI -10.4 to -3.4, $p=0.0001$). One trial, Pinter,¹⁴⁰ reporting other measures of QoL (Duke Activity Status Index, one item Global Visual Analogue Scale and SF-36) found comparisons of baseline to 6 month changes were statistically significant for the General Health component of the SF-36 only.
- Reporting of adverse events was inconsistent between the trials. The large RAFT trial found that device or implantation related complications within 30 days of implantation was significantly higher in the CRT-D group than the ICD group (13.3% vs 6.8%, $p<0.001$), as was device-related hospitalisation (20% vs 12.2%, HR 1.68, 95% CI 1.32 to 2.13, $p<0.001$).
- Three trials reported prespecified subgroup analysis. Two trials reported that CRT-D was associated with a greater benefit in people with QRS duration 150 ms or more than in those with a QRS duration of less than 150 ms, and the third trial found significant improvements in the proportion of people with an improvement in peak oxygen uptake in those with $QRS \geq 120$ ms but not for those with $QRS < 120$ ms. CRT-D was associated with greater benefit in women than in men (one trial) and in people with LBBB than in those with nonspecific intraventricular conduction delay (one trial). One trial found a statistically significant improvement with CRT-D distance walked in 6 minutes for those with non-ischemic cardiomyopathy (55.0 m vs 2.5 m, $p=0.01$) but not for those with ischemic cardiomyopathy (4.2 m vs 5.8 m, $p=0.57$). Other evaluated subgroups showed no statistically significant effects.

4.5 Summary of SHTAC peer review of clinical effectiveness in the ABHI joint submission

A joint report on behalf of Biotronik UK, Boston Scientific, Medtronic UK, Sorin Group and St Jude Medical was submitted by the Association of British Healthcare Industries (ABHI) to NICE. The clinical effectiveness evidence presented in this manufacturers' submission (MS) has been briefly appraised (Appendix 11). The MS also presented individual patient level data (IPD) network meta-analysis (NMA) (section 4.5.1) and an economic model (section 5.3).

A systematic review of clinical effectiveness was undertaken in the MS. Details of the searches were reported and the search strategies were supplied. Details and results of studies included in the systematic review were tabulated. Risk of bias was assessed, although no narrative discussion of risk of bias was provided.

The inclusion criteria for the MS systematic review differed from the NICE scope, and the results were not presented according to the population groups defined in the NICE scope. As a result of this, the MS and SHTAC systematic reviews differ in the evidence included (Appendix 11).

The MS does not explicitly report their conclusions from the systematic review of clinical effectiveness in the main body of the submission. The executive summary states 'there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF' (MS p4), however there is no comment regarding the comparative effectiveness of the interventions for each of the populations defined in the NICE scope. Further conclusions are presented in the MS based on the IPD NMA, which is discussed below.

4.5.1 Individual patient level data network meta-analysis: a critical appraisal

The joint submission from the manufacturers presents an IPD NMA using meta-regression to assess the effectiveness of ICDs, CRT-P and CRT-D on the different sub-groups of people who have heart failure. The intention was for the IPD NMA to inform the cost-effectiveness model produced on behalf of the manufacturers. As such, it focuses on the outcomes of all-cause mortality, all cause hospitalisation and health related quality of life (HRQoL). In undertaking the IPD NMA, the MS recognises the heterogeneous nature of patients with heart failure and the likelihood that the interventions may have differing effects. It also changes the focus of the assessment from an evaluation of the effectiveness of the devices for specific sub-groups of patients as identified in the scope for the NICE appraisal, to trying to establish which sub-groups of patients the different devices appear to benefit. Inevitably these may not be the same groups. With limited published evidence on

the effectiveness of devices in different patient sub-groups with heart failure, the availability of IPD from the manufacturers makes a NMA meta-regression possible and justified.

This section of the assessment report presents a critical appraisal of the IPD NMA using a structured approach (Appendix 11). It provides an assessment of the appropriateness of the methods used and of the results and conclusions presented.

4.5.1.1 Methods

Network of evidence

The MS undertook a systematic review of clinical effectiveness, which included a comprehensive and transparent search strategy, criteria and reasons for study selection, extraction of baseline data on patient characteristics and study outcomes, quality assessment of studies and the process followed to complete these stages. The studies identified in the systematic review provided the basis for developing the network of evidence for the IPD NMA. However, the IPD NMA included only a subset of those identified in the systematic review for which the manufacturers' provided IPD (13 of 22 trials; 95% of patients from the evidence network). Also, the evidence network excluded seven trials identified in the SHTAC assessment report (DINAMIT,⁹⁷ IRIS,⁹⁹ CABG Patch,⁷⁷ AVID,⁷³ CASH,⁸³ CIDS,⁸⁶ DEBUT⁹¹). The extent of the evidence base for the NMA varied for the different outcomes assessed, with 13 trials (n=12,638) for all-cause mortality, 11 trials for all-cause hospitalisation (n=uncertain as it refers to studies not included in the NMA) and 3 trials (n=4,432) for HRQoL. The MS outlines reasons for excluding specific studies from the overall evidence network, the approach taken to allocating trials to different comparisons and the basis for handling data (i.e. separating or aggregating trial arms or phases) from the trials. The effects of a more limited evidence base and the manipulation of data are discussed. For all-cause mortality, NMA were produced to compare outcomes using aggregate data from all trials in the network with that from the trials included in the IPD only, finding no significant differences. Similar comparisons were not produced for the other outcomes.

Issues concerning differences in the 13 IPD trials were also considered. The effects of length of follow-up, trial cross-over, missing data and data handling were discussed in the MS, particularly with relation to all-cause mortality. Length of follow-up was limited to that specified in trials protocol (██████████) to limit the effects of trial cross-over at longest follow-up (██████████). Missing data for the covariables appeared limited (██████████), with data imputed through multiple imputations where necessary (details provided in MS Appendix 6). The covariables used to capture baseline risk and treatment effect modifiers in the NMA were outlined for

the different outcomes assessed, with the rationale for their inclusion and for any data manipulation (i.e. continuous to categorical) discussed.

Statistical Analysis

The IPD NMA adopted a multivariate approach through meta-regression to assess the effects of the different interventions on heart failure patients for the outcomes of all-cause mortality, all-cause hospitalisation and HRQoL, taking into account the impact of different patient characteristics. Although different types of regression were used for analysing the three outcomes, all analyses followed a similar two stage approach. First, a baseline rate was estimated for each outcome independent of the treatment effects of the devices. This used the pooled data from the relevant IPD trials for all patients randomised to OPT (i.e. all IPD trials assessing the specific outcome irrespective of the device assessed), which was the comparator treatment for the appraisal. Second, device specific treatment effects were estimated using all available data from the relevant IPD trials (i.e. trials focusing on the specific outcome for all the interventions compared). In both stages of the analyses, patient characteristics were included as covariables to incorporate baseline risk and treatment effect modifiers. This allowed sub-group specific treatment effects to be estimated and the opportunity to identify groups of patients for whom the treatment provided significant benefit. In using a NMA approach all interventions included can be compared relative to each other, where direct and indirect evidence is available. This is important in the current assessment, where direct evidence may be limited (e.g. CRT-D versus CRT-P and CRT-D versus OPT). However, it is important to note that the findings of NMA may be affected by limitations in the network of evidence, whether direct or indirect evidence, as will be evident from the appraisal of the NMA.

For the analysis of all-cause mortality, a parametric survival analysis was undertaken to generate estimates of baseline mortality for all patients randomised to OPT (n=3477). Several parametric distributions were used (i.e. exponential, Gompertz, log-logistic, log-normal and Weibull) in models both with and without covariables (i.e. patient characteristics) to ascertain which provided the most realistic predictions of survival. It also allowed effects of covariables to be considered and, where necessary, the approach to their inclusion altered (e.g. age as a time-dependent covariable). The MS states that these were assessed through visual comparisons of the fitted and Kaplan Meier survival curves within trial follow-up, visual review of the extrapolations and of the shape of the instantaneous hazard over time, Akaike Information Criteria (AIC), Cox Snell residuals, tests of acceptability of the proportional hazards assumption or accelerated failure time assumption, comparison against external data and review by clinical experts. Although these methods appear appropriate, the MS only presents the AIC statistics, a Kaplan Meier plot for the Weibull model (distribution selected for the analyses) showing risk quintiles and an assessment of the proportional hazards assumption. As such, it is not possible to comment with certainty whether the approach was suitable. IPD NMA using meta-

regression were undertaken to estimate the relative treatment effects (i.e. hazard ratios) of the different devices compared with each other and with OPT, taking account of factors that may influence their effectiveness (i.e. covariables). An initial set of NMA excluding the covariables were conducted at the aggregate level (i.e. trial). This allowed a comparison of the unadjusted efficacy estimates from the NMA with those produced by pairwise meta-analyses from aggregate trial data and with the individual trial estimates. This allowed an assessment of whether the IPD NMA appeared representative or whether differences existed that required further examination. It also provided an opportunity to assess the type of analyses that should be undertaken (i.e. fixed versus random effects). Although the MS reports that caterpillar plots, Brooks Gelman-Rubin statistics, autocorrelation and deviance information criteria (DIC) were assessed, only the DIC are reported. A second set of analyses, incorporating the covariables from the IPD, were estimated using fixed-effects models. These analyses used the Cox proportional hazards approach and were stratified by study to allow the baseline hazard for each study to be independent. A rationale for using fixed effects models and for the selection of covariables is presented and appeared appropriate. The MS states that proportional hazards tests and Schoenfeld residual-based tests were used to assess the models, however these are not reported.

The analysis of all-cause hospitalisation focused on the expected number of events per month and the expected number of days per month spent in hospital (excluding events in the 60 days post randomisation as these were accounted for separately in the MS economic model). The analysis used negative binomial regression (NBRM) to estimate both the baseline hospitalisation rate for patients on OPT and the effect of the different treatments on hospitalisation rates. The modelling approach was decided through a comparison with Poisson regression using measures of goodness of fit (i.e. Bayesian Information Criteria (BIC), AIC and two times log-likelihood score (2LL)) and the covariates incorporated into the analyses through a stepwise process (included at a significance level of $p=0.05$). Limited data availability meant that some categorical variables were pooled (e.g. NYHA) and for some sub-groups estimates were either not calculated or were considered unreliable. In such cases, adjustments were made and justifications provided. Although limited information on the specific elements of the process is provided, comparisons are made with previous evaluations where available. It is evident from the analysis that it is likely that the limited evidence base affects the results and although adjustments are made, uncertainty remains.

HRQoL was assessed using EQ-5D. UK age and gender specific utilities¹⁵³ were adjusted using disease and treatment specific decrements/increments estimated from the three IPD trials reporting EQ-5D and were varied over time. Baseline HRQoL taking account of disease severity was estimated using the NBRM, following a similar procedure to that for all-cause hospitalisation (justification for approach is provided). Prior to the analysis the raw data had been transformed as it appeared skewed

Derived values were checked against population norms and trial specific values to ascertain whether clinically plausible, reflecting the uncertainties resulting from the limited IPD available. The impact of treatment on HRQoL was estimated through the mean difference from the baseline to first follow-up (assumed as 180 days). With only three studies in the evidence network (n=3736), observations were limited for ICDs and CRT-D and were skewed by NYHA groups. This weakened evidence network affected the regression analysis, producing counter-intuitive results. Exploratory analysis using the Minnesota Living with Heart Failure Questionnaire (MLWHF) data at 6 months, the MS systematic review of clinical effectiveness, and a correction for a placebo effect were used to adjust the estimates for use in the MS cost-effectiveness model. Duration of benefit was estimated through comparing the mean device value with that for OPT and judging when no further difference occurred. Justification is provided for the decisions made.

Although it is not possible to provide a detailed critique of each stage in the three analyses (given the partial reporting of the exploratory and confirmatory analyses undertaken) or to replicate the NMA as the IPD remains unpublished, the steps taken seem appropriate and the results presented appear reasonable given the note of caution provided in the MS throughout all three analyses.

4.5.1.2 Results

All-cause mortality

The baseline Weibull survival model for patients randomised to OPT was shown, through Kaplan Meier curves, to differentiate between patients with varying risk profiles and demonstrate the heterogeneity in the IPD population. Predicted survival rates were reported to vary [REDACTED]. The baseline risk model was used in the MS cost-effectiveness model for their baseline survival curve (see MS Table 37, p121). Covariables included in the model with a statistically significant effect were age, gender, ischaemic aetiology, LVEF, NYHA class (NYHA I/II, NYHA III/IV) and QRS duration (<120ms, ≥120ms).

Exploratory NMA models without the covariables were fitted for the different comparisons of the interventions using the trials identified in the evidence network (13 trials, 12,638 patients). These showed limited difference in the hazard ratios for fixed and random-effects models and for IPD compared to aggregate data for all trials in the network and for the pairwise meta-analyses. As such, it was considered appropriate to use IPD for the NMA and to use fixed-effects models. The fixed-effects IPD NMA without the covariables estimated the hazard ratios compared to OPT [REDACTED] for CRT-D, [REDACTED] for CRT-P and [REDACTED]

██████████ for ICDs. Hazard ratios were presented for CRT-D compared with CRT-P ██████████ ██████████) and for CRT-D compared with ICD ██████████. The MS states that proportional hazards tests showed that the benefits were maintained over time (global p-value for device terms ██████████).

Univariate analyses and multivariate stepwise selection procedures were used to explore the covariables for inclusion in the final NMA model as treatment effect modifiers. Rationales were provided for the covariables included for the different comparisons made. The final NMA model was used in the cost-effectiveness model presented in the MS (see MS Table 39, p 132). The final NMA model was used to show the predicted treatment effect for different subgroups, presented as hazard ratios with confidence intervals (assumed to be 95% confidence intervals, although not stated in the MS) (Table 77). Importantly the MS warns that the analysis presented is ‘inherently more uncertain than the analysis without covariables’ and that ‘caution should be taken not to over-interpret individual subgroups since anomalies may arise as a result of patient level characteristics not accounted for’ (MS p130). This is particularly important in relating the broad conclusions made to the results presented in the MS. The analyses highlighted that age, gender, QRS duration and LBBB pattern were significant predictors of benefit from the different devices.

It is evident from the Forest plots presented in the MS (Figure 19, p133-4) and from hazard ratios presented in Table 77 below, that for the majority of sub-groups the devices provide some benefit on all-cause mortality compared to OPT (49 of 52 comparisons). However, the benefit provided by the device is rarely statistically significant (14 of 52 comparisons show significant benefit; 4 of 52 comparisons borderline significance) and, as indicated in the MS, should be considered with some caution. Despite this, it is possible to highlight the main findings for the different sub-groups where the benefit is statistically significant or on the margins of statistical significance. ICDs provided a statistically significant benefit compared to OPT for males aged <60 years irrespective of QRS duration or LBBB status and were marginally insignificant for both males ≥ 60 years and females aged <60 years with a QRS ≥ 120 to <150ms and without LBBB. CRT-D benefitted a wider group of patients when compared to OPT. Benefits that were statistically significant or on the margins of statistical significance were reported for males and females of all ages with a QRS ≥ 150 ms and for females of all ages with a QRS ≥ 120 to <150ms. In contrast, CRT-P only had a statistically significant effect for females aged ≥ 60 years with a QRS of ≥ 150 ms with LBBB.

Table 77 Hazard ratios (95% confidence intervals) for all-cause mortality from NMA with covariables for the comparisons between the different devices and OPT

Non-LBBB					
QRS	Device	Sex and Age Groups			
		Male <60yrs	Male ≥60yrs	Female <60yrs	Female ≥60yrs
<120	ICD				
≥120 to <150	ICD				
	CRT-D				
	CRT-P				
≥150	ICD				
	CRT-D				
	CRT-P				
LBBB					
QRS	Device	Sex and Age Groups			
		Male <60yrs	Male ≥60yrs	Female <60yrs	Female ≥60yrs
≥120 to <150	ICD				
	CRT-D				
	CRT-P				
≥150	ICD				
	CRT-D				
	CRT-P				

Source: MS, Figure 19, p133-134

All-cause Hospitalisation

The baseline regression model (see MS Table 40, p139) for patients randomised to OPT produced monthly probabilities of hospitalisation for the different sub-groups (Table 78). These were used for the baseline assessment. Where data allowed, treatment effects were estimated through a process similar to a fixed-effects NMA (MS, Table 42, p142) and are presented in Table 79. Limited data meant that estimates could not be provided for some groups (i.e. ICD NYHA IV and CRT-P NYHA I/II) and are thought unreliable for others (i.e. CRT-D NYHA III and IV). Alternative values have been put forward in the MS with justifications (Table 79), which appear reasonable. The effects of the devices on all-cause hospitalisations were translated into monthly transition probabilities (see Table 80 to Table 82), which were used in the economic model presented in the MS.

Table 78 Baseline monthly probability of hospitalisation by covariate pattern (patient receiving OPT)

	NYHA I/II	NYHA III	NYHA IV
Non-Ischaemic aetiology			
QRS <120ms	████	████	████
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████
Ischaemic aetiology			
QRS <120ms	████	████	████
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████

Source: MS, Table 41, p140. Assumed starting age 66 years.

Table 79 All cause hospitalisation treatment effects (i) derived from the NMA and (ii) used in the MS economic model (events per month)

	Derived value	Value used in model	Justification
ICD			
NYHA I/II	████	████	Results from IPD analysis clinically plausible
NYHA III	████	████	Results from IPD analysis clinically plausible
NYHA IV	██	██	Device not assessed in this patient group
CRT-P			
NYHA I/II	██	██	Device not assessed in this patient group
NYHA III	████	████	Results from IPD analysis clinically plausible
NYHA IV	████	████	Results from IPD analysis clinically plausible
CRT-D			
NYHA I/II	████	████	Results from IPD analysis clinically plausible
NYHA III	████	████	Results from IPD analysis not clinically plausible. Assumed same as CRT-P value given common component (CRT)
NYHA IV	████	████	Results from IPD analysis not clinically plausible. Assumed same as CRT-P value given common component (CRT)

Source: MS, Tables 43 and 44, p142-143.

Table 80 Monthly all cause hospitalisation transition probabilities (ICD, events per month)

	NYHA I/II	NYHA III	NYHA IV
Non-ischaemic aetiology			
QRS <120ms	████	████	N/A
QRS 120-149ms	████	████	N/A
QRS ≥150ms	████	████	N/A
Ischaemic aetiology			
QRS <120ms	████	████	N/A
QRS 120-149ms	████	████	N/A
QRS ≥150ms	████	████	N/A

Source: MS, Tables 45, p144.

Table 81 Monthly all cause hospitalisation transition probabilities (CRT-P, events per month)

	NYHA I/II	NYHA III	NYHA IV
Non-ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS 120-149ms	N/A	████	████
QRS ≥150ms	N/A	████	████
Ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS 120-149ms	N/A	████	████
QRS ≥150ms	N/A	████	████

Source: MS, Tables 46, p144.

Table 82 Monthly all cause hospitalisation transition probabilities (CRT-D, events per month)

	NYHA I/II	NYHA III	NYHA IV
Non-ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████
Ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████

Source: MS, Tables 47, p145.

Table 84 Treatment specific utility increments by device and NYHA group from the IPD analysis and adjusted values for use in the MS economic model

	IPD analysis		Economic model	Justification for value used in economic model
	N	Utility value (mean, SE) ^b	Utility value ^c	
NYHA I/II				
OPT	█	█	█	No clinical reason why person already on OPT would have a change in utility.
ICD	█	█	█	Value derived from IPD analysis █. Systematic review suggests ICDs have a positive impact.
CRT-P	█	█	█	Cost effectiveness results not generated for this treatment option.
CRT-D	█	█	█	Value derived from IPD analysis █. Systematic review and MLWHF suggests CRT-Ds have a positive impact.
NYHA III				
OPT	█	█	█	No clinical reason why person already on OPT would have a change in utility.
ICD	█	█	█	Results from IPD analysis not significantly different from zero. Literature review suggests ICDs have no benefit in this group.
CRT-P	█	█	█	Value derived from IPD analysis █. Literature review and MLWHF analysis suggests CRT-P has a benefit in this group.
CRT-D	█	█	█	Assumed same as CRT-P as not thought clinically different. IPD results derived from small patient numbers. Literature review and MLWHF analysis suggests CRT-D has a benefit in this group
NYHA IV				
OPT	█	█	█	No clinical reason why person already on OPT would have a change in utility.
ICD	█	█	█	Cost effectiveness results not generated for this treatment option

CRT-P	■	■	■	Not enough information available. Assumed same as for NYHA III. Analysis of MLWHF data supports this assumption.
CRT-D	■	■	■	Not enough information available. Assumed same as for NYHA III. Analysis of MLWHF data supports this assumption.

^aSignificant at 95% confidence level; ^b Mean changes from baseline in EQ-5D at 6 months; ^c all utility values for the economic model have the value for OPT NYHA class III from the IPD analysis deducted to remove any placebo effect.

Source: MS, Tables 56 and 58, p155 and 157.

4.5.1.3 Discussion

The MS presented an IPD NMA using meta-regression to assess the effectiveness of ICDs, CRT-P and CRT-D on different sub-groups of people with heart failure. As part of the NMA, the MS used a systematic review to identify the network of evidence for which IPD was available. It provided an outline of the methods used in the systematic review and in the different stages of the NMA. The effects of different decisions were discussed and comparisons made, though analyses used to underpin many decisions were not presented. Limitations in the underlying IPD and uncertainties in the analyses were outlined, with the MS suggesting caution when interpreting and using the results. Importantly, the IPD NMA presented by the MS did not take account of the sub-groups identified by the scope for the NICE appraisal. Instead it looked for sub-groups of heart failure patients for whom the different devices appeared to have some benefit. Although challenging in terms of developing guidance, it reflects the opinion of part of the clinical community. Given the lack of published evidence on sub-groups of heart failure patients, the IPD NMA provides a useful source of evidence. However it should be used cautiously given the uncertainties in the methods used in the NMA, the limitations in the evidence base (weak and imbalanced data), the assumptions used and the adjustments made to some counter-intuitive results, and possibility that some of the findings may be the result of chance.

All-cause Mortality

Fixed-effects IPD NMA without covariables showed that CRT-D, CRT-P and ICDs provided a statistically significant benefit compared to OPT on all-cause mortality. Comparison of CRT-D with both CRT-P and ICD showed statistically significant benefit for CRT-D. These results appeared appropriate when compared with original trial results and the pairwise meta-analyses undertaken in the SHTAC assessment report and the MS. When including covariates to identify sub-groups that benefitted from the different devices, the outcomes were less clear and the MS advises that results should be interpreted with caution. It was evident that all the devices appeared beneficial compared to

OPT, however rarely were differences statistically significant. CRT-D appeared to have a statistically significant benefit for people of all ages with a QRS ≥ 150 and for women of all ages with a QRS ≥ 120 to < 150 . Although CRT-D showed benefit for men of all ages, its effects were marginally insignificant. ICDs appeared to have a statistically significant benefit for males aged < 60 years at all QRS levels and for men aged ≥ 60 years with a QRS ≥ 120 to < 150 and non-LBBB. CRT-P only showed statistically significant benefit for women with a QRS ≥ 150 and LBBB.

All-Cause Hospitalisations

Estimates of the effects of the different devices on all-cause hospitalisations showed that all were beneficial. ICDs reduced hospitalisations in people in NYHA groups I to III [REDACTED] and CRT-P in NYHA groups III to IV [REDACTED]. Estimates for CRT-D suggested a constant effect for all NYHA groups [REDACTED] and so were adjusted in the MS to reflect those of CRT-P.

HRQoL

Baseline estimates of HRQoL using EQ-5D from the IPD showed that patients in NYHA I/II had similar values to the population norms, while patients in NYHA III and IV had values that were progressively lower. Treatment estimates showed counter-intuitive results, reflecting the limited IPD available. As a consequence, adjustments were made that assumed that CRT-P and CRT-D had the same effect on EQ-5D values and ICDs had an effect on NYHA I/II only. Benefits were thought to last for a fixed period of [REDACTED].

5 ECONOMIC ANALYSIS

The aim of this section is to assess the cost effectiveness of:

- ICD in addition to OPT for the treatment of people who are at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT;
- CRT-P or CRT-D in addition to OPT for the treatment of people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT;
- CRT-D in addition to OPT for the treatment of people with both conditions.

The economic analysis comprises:

- a systematic review of the literature on the cost-effectiveness of ICDs for people at risk of SCD and CRT for people with heart failure;
- a systematic review of studies of the health related quality of life (HRQoL) of people at risk of SCD or with heart failure
- a review of the manufacturers' submission to NICE;
- an independent economic model and cost-effectiveness evaluation (the SHTAC model).

5.1 Systematic review of existing cost-effectiveness evidence

A systematic review of the literature was conducted to summarise the existing evidence on the cost-effectiveness of ICDs for treatment of arrhythmia and CRT for treatment of heart failure. The quality of the included publications was assessed and those of relevance to the UK are discussed in greater detail in terms of the methodology used and the potential generalizability of their results.

The methods and inclusion criteria considered for this review of economic evaluations are presented in Section 3 and details of the search strategy are documented in Appendix 3. Given the volume of studies meeting the inclusion criteria, data extraction was undertaken as follows: for studies included in previous assessments, data extraction was derived from these reports and checked against original publications; for newly identified evidence, data extraction was undertaken in the normal manner directly from original publications.

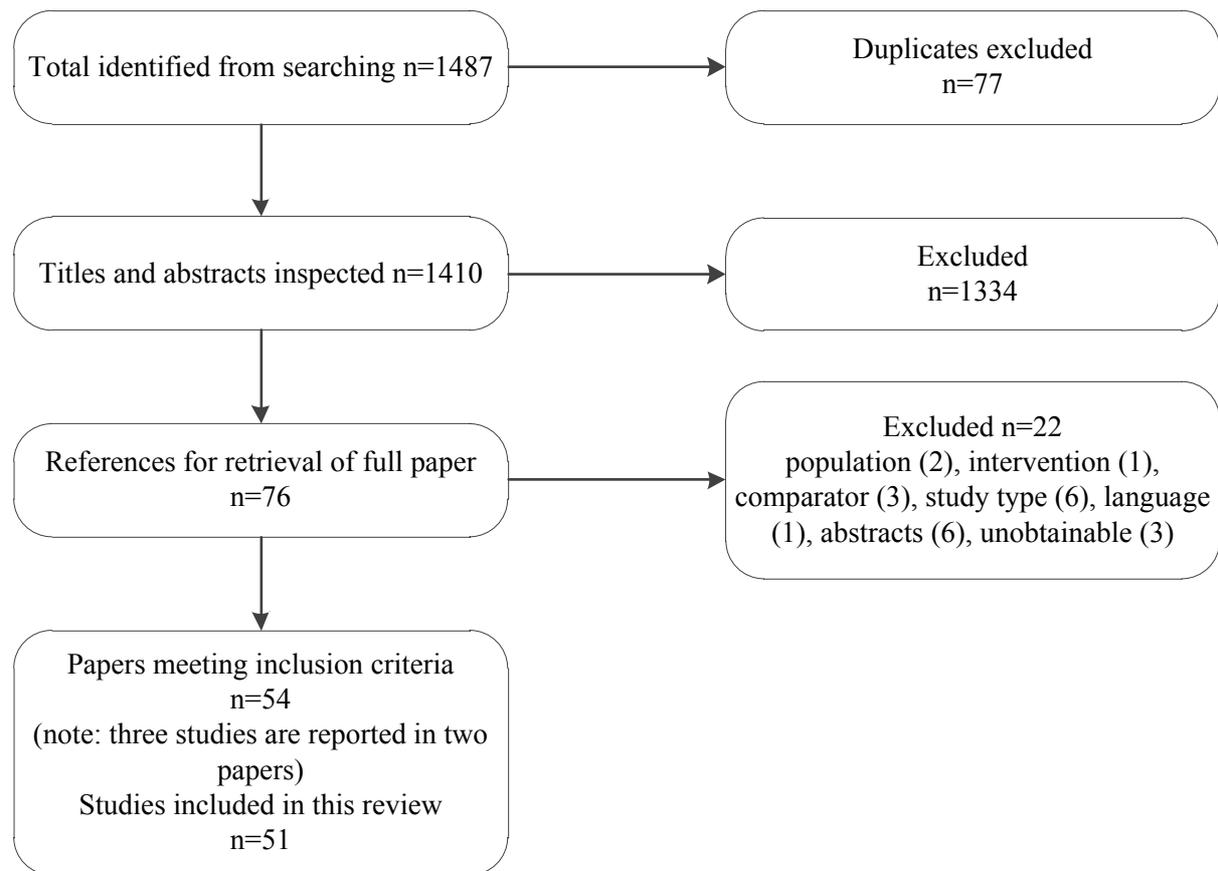
5.1.1 Quantity and quality of research available

The searches conducted identified 1410 studies that potentially met the inclusion criteria set out in section 3.2. From screening titles and abstracts, 1334 publications were excluded and 76 retrieved for full screening. Twenty two retrieved studies did not meet the inclusion criteria:

- 6 found not to be full economic evaluations
- 6 abstracts (five from 2010 and 2011 and one study treated as an abstract, which did not report sufficient details for inclusion)
- 3 references were unobtainable and thus did not provide sufficient details for inclusion
- 3 had a different comparator from that specified in the research protocol
- 2 had a different population
- 1 had a different intervention
- 1 was non-English language

A list of relevant excluded studies can be seen in Appendix 12. Fifty four papers met the inclusion criteria. Three studies were each reported in two publications. Thus, 51 separate economic evaluations were included in this review. A flow chart of the identification of the included studies is given below (Figure 31).

Figure 31: Flow chart of identification of studies for inclusion in the review of cost effectiveness



The included economic evaluations were categorised according to the type of the interventions assessed. Thirty six^{42;66;150;154-186} of the included studies assessed ICDs and 17^{43;155;172;187-200} economic evaluations assessed CRT. Two of these studies included both ICD and CRT (Bertoldi and colleagues¹⁵⁵ and MSAC¹⁷²); details of these two studies have been included within both the ICD and CRT sections. A summary of study characteristics and study quality are shown in Table 85 and Table 86 for ICD, and in Table 87 and Table 88 for CRT.

5.1.2 Economic evaluations of ICDs

Most of the economic evaluations identified in the systematic review were for the use of ICDs in patients at increased risk of SCD. Table 85 below provides an overview of these studies.

Nineteen economic evaluations were conducted in the USA,^{154;157-159;162;165-170;176;177;179-182;184;186} five in Canada,^{161;163;171;183;185} three in the UK,^{42;66;175} with three elsewhere in Europe,^{160;164;174} two in Brazil^{155;178} and one each in Australia¹⁷² and Japan.¹⁵⁰ Two studies were conducted in two countries (one in UK and France¹⁵⁶ and one in Germany and USA¹⁷³). The study type was predominately cost utility analysis (n = 21^{42;150;155;157-160;162-165;170;174;176-182;185}) and cost effectiveness analysis (n =

13^{66;154;166-169;171-173;175;183;184}1820}) with two cost benefit analyses.^{156;161} Most studies used a Markov model (n = 23^{42;150;155;157-160;162-164;166-168;171;174;176-182;185}) and five studies used a trial-based analysis^{169;170;173;183;186} with the remaining studies using a variety of methods. Most studies (n = 24) used a long term time horizon of more than 20 years,^{42;150;154;155;157-160;162;164-166;168;172;174-182;185} six studies had a short time horizon of less than seven years duration^{66;156;161;167;169;173} and six studies had a medium time horizon between 8 and 19 years duration.^{163;170;171;183;184;186} Fourteen studies were based upon a single trial^{66;154;156;157;161;164;169-171;173;174;180;183;186} with the MADIT II¹⁰³ (6 studies^{154;157;164;171;180;186}) and SCD-HeFT¹⁰⁷ (4 studies^{156;161;170;174}) the most commonly used. Ten studies used more than one trial, either through meta-analysis, systematic review or from different trial populations,^{42;150;155;160;163;172;176;177;181;182} eleven studies used other sources of evidence to model the intervention effect^{158;162;165-168;175;178;179;184;185} and one study did not state the source of data.¹⁵⁹ Almost half of studies (15 studies) reported that ICDs were cost effective,^{150;154-156;160;161;166-170;172;175;180;185} with an additional six finding ICD cost effective for high risk groups,^{158;165;173;176;177;181} according to study definitions. Nine studies did not find ICD cost effective^{42;157;159;162;163;174;178;183;186} and six studies were unclear whether ICD was cost effective.^{66;164;171;179;182;184}

The judgements of the methodological quality of the studies concerning ICDs are summarised in Table 86. The studies vary in their quality and relevance to the UK NHS. As mentioned above, many studies were conducted in countries outside the UK, and it is unclear how generalisable their results are to the UK NHS. Generally, the later studies have been of higher quality. Earlier studies were less likely to include QALYs, with long term life horizons and include all relevant costs and consequences.

Five studies^{42;155;160;178;182} were considered to be of high methodological quality by meeting all or all but one ('Setting comparable to the UK') recognised criteria.^{38;68} Of these, only one study was conducted for a UK setting and perspective, and is considered of most relevance (Buxton and colleagues⁴²). However, it should be noted that this study, published in 2006, used data from patients mostly implanted before 2002 and therefore may not be generalisable to current practice. We describe this study in more detail in the following section

Table 85: Summary of characteristics of economic evaluations of ICD versus OPT

First Author Publication date	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
Al-Khatib <i>et al.</i> , 2005 ¹⁵⁴	USA	Adults with a history of MI and an LVEF $\leq 30\%$	Survival	MADIT II	Cost-effective (\$50,500/LYG)
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Brazil	HF NYHA II, III or IV, EF $\leq 35\%$.	Markov	Meta-analysis of trials	Marginally cost-effective (\$32,663/QALY)
Buxton <i>et al.</i> , 2006 ⁴²	UK	Secondary prevention patients at risk of SCD with previous CA or VT	Markov	Observational data and CIDS	Not cost effective (£76,139/QALY)
Caro <i>et al.</i> , 2007 ¹⁵⁶	UK and France	HF NYHA II or II, LV dysfunction $\leq 35\%$	DES	SCD-HeFT	Cost effective (Cost benefit ratio 0.17 UK)
Chan <i>et al.</i> , 2006 ¹⁵⁷	USA	Ischemic heart disease and LVEF $\leq 30\%$.	Markov	MADIT II	Not cost-effective in all MADIT II patients (\$55,800/QALY); risk-stratification with MTWA improves cost-effectiveness (\$48,800/QALY)
Chan <i>et al.</i> , 2009 ¹⁵⁸	USA	Cardiomyopathy (EF $\leq 35\%$) and no prior VA	Markov	Prospective cohort	Cost effective for high risk groups (\$70,881/QALY)
Chen and Hay, 2004 ¹⁵⁹	USA	Newly diagnosed HF NYHA II or III	Markov	Not stated	Not cost effective (\$97,863/QALY)
Cowie <i>et al.</i> , 2009 ¹⁶⁰	Belgium	LVEF $\leq 35\%$. HF NYHA II or III, or prior MI.	Markov	AMIOVIRT, CAT, DEFINITE, MADIT I, MADIT II, SCD-HeFT	Cost-effective (€29,530/QALY)
Deniz <i>et al.</i> , 2009 ¹⁶¹	Canada	HF NYHA II or II, LV dysfunction $\leq 35\%$	DES	SCD-HeFT	Cost effective (Cost benefit ratio of 0.05)
Feingold <i>et al.</i> , 2010 ¹⁶²	USA	Children (10-15 years old) with dilated cardiomyopathy and HF	Markov	Paediatric cardiology prospective studies	Not cost effective (\$281,622/QALY)
Fillion <i>et al.</i> , 2009 ¹⁶³	Canada	Severe LV dysfunction at risk of SCD	Markov	Meta-analysis of trials	Not cost effective (\$108,900/QALY)
Gandjour <i>et al.</i> , 2011 ¹⁶⁴	Germany	EF $\leq 30\%$ or < 1 month after MI	Markov	MADIT II	Unclear (€44,736/QALY)

First Author Publication date	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
Goldenberg <i>et al.</i> , 2005 ¹⁶⁵	USA	Inherited cardiac disorders with high risk of SCD, patients aged 10 to 75 years	Survival	Several sources	Cost-effective in selected high-risk patients with inherited cardiac disorders due to gained productivity over lifetime (\$3,328 - 600,000/QALY)
Kupersmith <i>et al.</i> , 1995 ¹⁶⁷	USA	High risk patients with VT/VF with ICD implant from 1980-1987	Markov	Retrospective study with historical controls	Cost-effective (Epicardial ICD \$31,100/LYG; Endocardial ICD \$25,700/LYG)
Kuppermann <i>et al.</i> , 1990 ¹⁶⁶	USA	CA survivors, not associated with MI, and persistent VT/VF	Decision tree + Markov	Several ICD case series	Cost effective (\$15,600 - \$29,600/LYG)
Larsen <i>et al.</i> , 1992 ¹⁶⁸	USA	Patients with sustained VT/VF	Markov	Case series of ICD patients	Cost effective (\$29,244/LYG)
Larsen <i>et al.</i> , 2002 ¹⁶⁹	USA	EF \leq 40%. Sustained VT or resuscitated from CA	Trial	AVID	Moderately cost-effective (\$66,677/LYG)
Mark <i>et al.</i> , 2006 ¹⁷⁰	USA	HF NYHA II or III, LV dysfunction \leq 35%	Trial	SCD-HeFT	Cost effective (\$41,530/QALY)
McGregor and Chen, 2004 ¹⁷¹	Canada	Adults with a history of MI and an LVEF \leq 30%	Markov	MADIT II	Unclear (\$47,458/LYG)
MSAC, 2006 ¹⁷²	Australia	Adults with a history of MI and an LVEF \leq 30%; or HF NYHA II or III, LV dysfunction \leq 35%	Decision tree	SCD-HeFT, COMPANION	Cost-effective in patients with moderate to severe symptoms of CHF (ICD \$39,885/LYG)
Mushlin <i>et al.</i> , 1998 ¹⁷³	Germany and USA	Adults with a history of MI and an LVEF \leq 30%	Trial	MADIT	Cost-effective in selected high-risk patients (\$27,000/LYG)
Neyt <i>et al.</i> , 2008 ¹⁷⁴	Belgium	HF NYHA II or II, LV dysfunction \leq 35%	Markov	SCD-HeFT	Not cost effective (€132,100/QALY)
O'Brien <i>et al.</i> , 1992 ¹⁷⁵	UK	Patients at high risk of SCD	Simple calculation model	ICD case series	Cost-effective (£15,400/LYG)

First Author Publication date	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
Owens <i>et al.</i> , 1997 ¹⁷⁶	USA	CA survivors at high risk of SCD	Markov	CASH, MADIT	Cost effective for high risk groups (\$74,400/QALY)
Owens <i>et al.</i> , 2002 ¹⁷⁷	USA	Patients at risk of SCD (trial characteristics)	Markov	MADIT, AVID, CIDS, CASH, MUSTT, CABG-PATCH	Cost effective in high risk groups (\$54,700/QALY)
Parkes <i>et al.</i> , 2000 ⁶⁶	UK	Patients at risk of SCD from arrhythmia.	Survival calculation	AVID	Unclear (£40,500 – 87,000/LYG)
Ribeiro <i>et al.</i> , 2010 ^{178,201}	Brazil	HF NYHA II and III, LVEF ≤ 35%	Markov	Several sources; scenario with MADIT I	Not cost effective (R\$ 68,318/QALY)
Sanders <i>et al.</i> , 2001 ¹⁷⁹	USA	Patients with MI who did not have sustained VA	Markov	Range of ICD efficacies evaluated	Unclear (\$71,800/QALY - \$557,900/QALY for moderate efficacy and EF < 0.3 to EF > 0.4).
Sanders <i>et al.</i> , 2004 ¹⁸⁰	USA	Adults with a history of MI and an LVEF <30%	Markov	MADIT II	Cost-effective (\$50,900/QALY)
Sanders <i>et al.</i> , 2005 ¹⁸¹	USA	Patients at risk of SCD (trial characteristics)	Markov	MADIT, CABG Patch, MUSTT, MADIT II, DEFINITE, DINAMIT, COMPANION, SCD-HeFT	Cost-effective in selected high-risk patients (\$34,000-70,200/QALY)
Sanders <i>et al.</i> , 2010 ¹⁸²	USA	Patients with LV dysfunction.	Markov	MADIT, MADIT II, DEFINITE, MUSTT, SCD-HeFT	Unclear, varies widely among trials (\$37,031 - \$\$138,458/QALY)
Sheldon <i>et al.</i> , 2001 ¹⁸³ & O'Brien <i>et al.</i> , 2001 ²⁰²	Canada	Secondary prevention patients at risk of SCD with previous CA or VT	Trial	CIDS	Not cost-effective but more attractive in patients with at least 2 risk factors for SCD (Can\$213,543/LYG; Can\$65,195/LYG)
Wang <i>et al.</i> , 2008 ¹⁵⁰	Japan	Brugada syndrome with abnormal hearts	Markov	Several trials including DEBUT	Cost-effective (\$14,667/QALY)
Weiss <i>et al.</i> , 2002 ¹⁸⁴	USA	VT or VF	Retrospective cohort study		Unclear (\$78,400/LYG)

First Author Publication date	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
You <i>et al.</i> , 2007 ¹⁸⁵	Canada	Hypertrophic cardiomyopathy at risk of SCD (no previous CA)	Markov	ICD registries and cohort studies	Cost-effective (\$19,400/QALY)
Zwanziger <i>et al.</i> , 2006 ¹⁸⁶	USA	Adults with a history of MI and an LVEF ≤30%	Trial	MADIT II	Not cost-effective for trial 3.5 years time horizon (\$235,000/LYG)

HF – heart failure; MTWA Microvolt T-wave alternants; NYHA – New York Heart Association; LV – Left ventricular; EF ejection fraction; VT – ventricular tachycardia; VF – ventricular fibrillation; SCD – sudden cardiac death; CA – cardiac arrest; MI - myocardial infarction;

Table 86: Summary of the quality of economic evaluations on ICD

	Decision problem relevant to the UK	Setting comparable to the UK	Appropriate methodology	Relevant costs and consequences	Data inputs justified	QALYs measured	Appropriate time horizon	Discounting	Incremental analysis	Sensitivity analysis
Al-Khatib <i>et al.</i> , 2005 ¹⁵⁴	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Buxton <i>et al.</i> , 2006 ⁴²	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Caro <i>et al.</i> , 2007 ¹⁵⁶	Y	Y	Y	?	Y	N	N	Y	Y	Y
Chan <i>et al.</i> , 2006 ¹⁵⁷	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Chan <i>et al.</i> , 2009 ¹⁵⁸	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Chen and Hay, 2004 ¹⁵⁹	Y	N	Y	?	?	Y	Y	Y	Y	Y
Cowie <i>et al.</i> , 2009 ¹⁶⁰	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Deniz <i>et al.</i> , 2009 ¹⁶¹	Y	N	Y	?	Y	N	N	Y	Y	Y
Feingold <i>et al.</i> , 2010 ¹⁶²	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Fillion <i>et al.</i> , 2009 ¹⁶³	Y	N	Y	?	Y	Y	?	Y	Y	Y
Gandjour <i>et al.</i> , 2011 ¹⁶⁴	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Goldenberg <i>et al.</i> , 2005 ¹⁶⁵	Y	N	?	?	N	Y	Y	Y	Y	Y
Kupersmith <i>et al.</i> , 1995 ¹⁶⁷	Y	N	Y	?	Y	N	Y	Y	Y	Y
Kuppermann <i>et al.</i> , 1990 ¹⁶⁶	Y	N	Y	N	N	N	N	Y	N	Y
Larsen <i>et al.</i> , 1992 ¹⁶⁸	Y	N	Y	?	Y	N	Y	Y	Y	Y
Larsen <i>et al.</i> , 2002 ¹⁶⁹	Y	N	Y	?	Y	N	?	Y	Y	Y
Mark <i>et al.</i> , 2006 ¹⁷⁰	Y	N	Y	?	Y	Y	?	Y	Y	Y
McGregor and Chen, 2004 ¹⁷¹	Y	N	?	?	Y	N	?	Y	Y	Y
MSAC, 2006 ¹⁷²	Y	N	Y	Y	Y	N	Y	N	Y	Y

	Decision problem relevant to the UK	Setting comparable to the UK	Appropriate methodology	Relevant costs and consequences	Data inputs justified	QALYs measured	Appropriate time horizon	Discounting	Incremental analysis	Sensitivity analysis
Mushlin <i>et al.</i> , 1998 ¹⁷³	Y	N	Y	N	?	N	?	Y	Y	Y
Neyt <i>et al.</i> , 2008 ¹⁷⁴	Y	N	Y	?	Y	Y	Y	Y	Y	Y
O'Brien <i>et al.</i> , 1992 ¹⁷⁵	Y	Y	Y	N	?	N	Y	Y	N	Y
Owens <i>et al.</i> , 1997 ¹⁷⁶	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Owens <i>et al.</i> , 2002 ¹⁷⁷	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Parkes <i>et al.</i> , 2000 ⁶⁶	Y	Y	?	N	Y	Y	N	N	Y	Y
Ribeiro <i>et al.</i> , 2010 ^{178;201}	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Sanders <i>et al.</i> , 2001 ¹⁷⁹	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Sanders <i>et al.</i> , 2004 ¹⁸⁰	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Sanders <i>et al.</i> , 2005 ¹⁸¹	Y	N	Y	?	N	Y	Y	Y	Y	Y
Sanders <i>et al.</i> , 2010 ¹⁸²	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Sheldon <i>et al.</i> , 2001 ¹⁸³ & O'Brien <i>et al.</i> , 2001 ²⁰²	Y	N	Y	N	Y	N	?	Y	Y	Y
Wang <i>et al.</i> , 2008 ¹⁵⁰	Y	N	Y	?	N	Y	Y	Y	Y	Y
Weiss <i>et al.</i> , 2002 ¹⁸⁴	Y	N	Y	?	N	N	?	Y	Y	N
You <i>et al.</i> , 2007 ¹⁸⁵	Y	N	Y	?	?	Y	Y	Y	Y	Y
Zwanziger <i>et al.</i> , 2006 ¹⁸⁶	Y	N	Y	?	Y	N	?	Y	Y	Y

5.1.2.1 Buxton and colleagues⁴²

Buxton and colleagues⁴² developed a Markov model to estimate the cost effectiveness of ICDs compared with anti-arrhythmic drug treatment in the UK in secondary prevention patients at risk of SCD (see Appendix 13 for data extraction). The economic evaluation was part of a wider study of the clinical characteristics, survival, quality of life and costs of ICD patients in the UK. The model combined patient data from two major UK implanting centres with data from three published RCTs (CIDS,⁸⁶ CASH,⁸³ and AVID⁷³). The Markov model had daily cycles and eight states: out of hospital (well); in hospital: arrhythmic, other cardiac, other non-cardiac, ICD maintenance, ICD replacement, amiodarone problems; death.

UK specific survival and admission rates were estimated from the UK sampled observational data for ICD patients, with data from the Canadian ICD trial (CIDS)⁸⁶ being used to estimate the relative survival and admission rates between ICD and amiodarone patients. The review of clinical characteristics included 535 UK patients implanted between 1991 and 2002. Mean actuarial survival at 1, 3 and 5 years was 92%, 86% and 71% respectively.

A cross sectional survey collected HRQoL data using various QoL measures, including EQ-5D, on a sample of 229 patients. The levels of most of the HRQoL measures were lower in the cohort than for a UK general population. There was no evidence of a change in QoL with time from implantation although length of follow-up is not clear. Patients who had suffered ICD shocks had significantly poorer HRQoL. Most patients nevertheless expressed a high level of satisfaction with ICD therapy. Based on the HRQoL data, the model base case assumes a constant utility value of 0.75 for all patients. Sensitivity analyses used utility estimates of 0.75 for ICD patients with 0.65 for patients receiving AAD, and 0.83 for ICD patients with 0.8 for patients receiving AAD.

Buxton and colleagues⁴² collected resource and cost data for 211 patients from Papworth NHS Trust and 167 patients from Liverpool NHS Trust. In addition to the costs of the implantation, post discharge costs (tests, medications and follow-up consultation) and costs of additional hospitalisations were also calculated. The mean initial costs of implantation showed little variation between centres or between earlier and more recent implants, and the model assumed a cost of £16,402 for the ICD device (with leads) and an implantation cost of £23,608 (device cost, implant cost, associated tests and hospital stay).

Buxton and colleagues⁴² concluded that the benefit from ICD may not be sufficient to make the technology cost effective in the UK. The mean ICER for an average UK patient over a 20 year time horizon was £76,139 per QALY gained. Cost effectiveness was most favourable for men aged over 70

years with an LVEF below 35%. Patients with below 35% had an ICER of £72,000 per QALY over 20 years. Extrapolating over the lifetime of the patients with low LVEF gave an ICER of £48,372 per QALY. Reduction of the cost of implant/replacement and improvements in reliability of ICDs (repair/replacement of 3% per patient-year instead of base case 6%) would reduce the ICER to £35,500 per QALY.

As noted above, the Buxton study⁴² used costs and resources associated with patients implanted between 1991 and 2002 which may not reflect current practice and could mean that the ICERs reported are no longer appropriate. The other high quality studies, all published since the Buxton study⁴² for slightly different populations and for different settings, present a range of conclusions about the cost-effectiveness of ICDs from not cost-effective,¹⁷⁸ uncertainty about whether cost-effective,¹⁸² marginally cost-effective¹⁵⁵ to cost-effective.¹⁶⁰

5.1.3 Economic evaluations of CRT

Seventeen economic evaluations of the use of CRT concern patients with heart failure. Table 87 provides an overview of these studies.^{43;155;172;187-200} Four studies were conducted in the UK,^{43;189;190;198} with six conducted elsewhere in Europe.^{187;188;191;193;196;199} There were two studies in Australia,^{172;195} two in USA,^{192;197} and one each in Canada,¹⁹⁴ Brazil¹⁵⁵ and Argentina.²⁰⁰ The study type was mostly cost utility analysis (n = 16) with one cost effectiveness analysis.¹⁷² Most studies used a Markov model (n = 11^{43;155;187;188;193;194;196-200}) with six studies using other methodology^{172;190-192;195} including one trial-based analysis.¹⁸⁹ Twelve studies used a long term time horizon of more than 20 years^{43;155;172;188;189;191;194-198;200} and five studies had a short time horizon of less than eight years duration.^{187;190;192;193;199} Eight studies were based upon a single trial, with the CARE-HF (5^{188-191;198}) and COMPANION (3^{172;192;196}) the most commonly used. Five studies used more than one trial, either through meta-analysis, systematic review or from different trial populations^{155;194;195;197;200} and four studies used other sources of evidence to model the intervention effect.^{43;132;193;199} The majority of studies (15) reported that CRT was cost effective.^{43;155;172;187-193;195;196;198-200} Two studies (conducted in USA¹⁹⁷ and Canada¹⁹⁴) in patients with NYHA Class III and prolonged QRS duration, were uncertain whether CRT was cost effective.

The judgements of the methodological quality of the studies concerning CRTs are summarised in Table 88. The studies vary in their quality and relevance to the UK NHS. As mentioned above, some studies are conducted in countries outside the UK, and it is unclear how generalisable their results are to the UK NHS. The studies have been conducted in the last ten years and generally are fairly high quality. However, some studies have used a short time horizon, and some have not included justification for the selection of effectiveness data sources or details of all costs and consequences. For one study the focus was patients with mild heart failure which may limit relevance to the UK.

Table 87: Summary of characteristics of economic evaluations of CRT versus OPT

Study	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
<i>CRT-P vs OPT</i>					
Banz, 2005 ¹⁸⁷	Germany	Patients with HF	Markov	Several publications and expert opinion	Cost-effective (€36,600/QALY)
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Brazil	HF NYHA II, III or IV, EF ≤35%	Markov	Meta-analyses	Cost-effective (Int \$15,723/QALY)
Blomstrom <i>et al.</i> , 2008 ¹⁹¹	Denmark, Finland, Sweden	HF NYHA III or IV, LVEF <35%	Survival	CARE-HF	Cost-effective (Denmark €4,759/QALY; Finland €3,571/QALY; Sweden €6,493/QALY)
Bond <i>et al.</i> , 2009 ²⁰³ Fox <i>et al.</i> , 2007 ⁴³	UK	HF NYHA III or IV, LVEF <35%, QRS > 120ms	Markov	Systematic review and other published sourced	Cost-effective (£16,738/QALY)
Callejo <i>et al.</i> , 2010 ¹⁸⁸	Spain	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective (€28,612/QALY)
Calvert <i>et al.</i> , 2005 ¹⁸⁹	UK	HF NYHA III or IV, LVEF <35%	Trial-based	CARE-HF	Cost-effective (€19,319/QALY)
Caro <i>et al.</i> , 2006 ¹⁹⁰	UK	HF NYHA III or IV, LVEF <35%	DES	CARE-HF	Cost effective (£15,247/QALY)
Feldman <i>et al.</i> , 2005 ¹⁹²	USA	HF NYHA III or IV, LVEF ≤35%, QRS > 120ms	Survival	COMPANION	Cost-effective (\$19,600/QALY)
Heerey <i>et al.</i> , 2006 ¹⁹³	Ireland	HF NYHA III or IV and QRS interval of > 130 ms	Markov	Retrospective cohort study	Cost-effective (Dominant)
McAlister <i>et al.</i> , 2004 ¹⁹⁴	Canada	HF NYHA III and prolonged QRS duration	Markov	Systematic review (9 RCTs: MIRACLE, MIRACLE-ICD, PATH-CHF, COMPANION, MUSTIC-SR, MUSTIC-AF, Garrigue, CONTAK-CD, MIRACLE-ICD, MUSTIC-AF, RD-CHF)	Uncertain (\$90,700/QALY)
MSAC, 2006 ¹⁹⁵	Australia	HF NYHA III or IV, LVEF <35%	Decision tree	CARE-HF, MIRACLE	Cost-effective for patients with moderate to severe chronic HF (NYHA III and IV)
Neyt <i>et al.</i> , 2011 ¹⁹⁶	Belgium	HF NYHA III or IV, LVEF ≤35%, QRS > 120ms	Markov	COMPANION	Cost effective (€11,200/QALY)

Study	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
Nichol <i>et al.</i> , 2004 ¹⁹⁷	USA	HF NYHA III and prolonged QRS duration	Markov	MUSTIC-SR, MUSTICAF, Path-CHF, Contak-CD, Miracle, Miracle-ICD, COMPANION, Garrigue, RD-CHF	Uncertain (\$107,800/QALY)
Poggia <i>et al.</i> , 2012 ²⁰⁰	Argentina	HF NYHA I or II, LVEF \leq 40% QRS \geq 120ms	Markov	Meta-analysis of REVERSE, MADIT-CRT, RAFT	Cost-effective (Int \$34,185/QALY)
Yao <i>et al.</i> , 2007 ¹⁹⁸	UK	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective (€7,538/QALY)
<i>CRT-D vs OPT</i>					
Aidelsburger <i>et al.</i> , 2008 ¹⁹⁹	Germany	HF NYHA III or IV	Markov	COMPANION and Banz ¹⁸⁷	May be cost-effective for NYHA III and IV depending on device longevity (Cost/QALY)
Feldman <i>et al.</i> , 2005 ¹⁹²	USA	HF NYHA III or IV, LVEF \leq 35%, QRS > 120ms	Survival	COMPANION	Cost-effective (\$43,000/QALY)
MSAC, 2006 ¹⁷²	Australia	HF NYHA III or IV, LVEF \leq 35%, QRS > 120ms	Decision tree	COMPANION	Cost-effective for patients with CHF NYHA III or IV, sinus rhythm, LVEF \leq 35% and a QRS duration \geq 120ms despite OPT. (€22,944/LYG)
Yao <i>et al.</i> , 2007 ¹⁹⁸	UK	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective at WTP of €44,100/QALY
<i>CRT-D vs CRT-P</i>					
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Brazil	HF NYHA II, III or IV, EF \leq 35%.	Markov	Meta-analyses	Non cost-effective (Int \$84,345/QALY)
Bond <i>et al.</i> , 2009 ²⁰³ Fox <i>et al.</i> , 2007 ⁴³	UK	HF NYHA III or IV, LVEF <35%, QRS > 120ms	Markov	Systematic review and other published sourced	Non cost-effective (£40,160/QALY)
Callejo <i>et al.</i> , 2010 ¹⁸⁸	Spain	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Non cost-effective (€53,547/QALY)
Neyt <i>et al.</i> , 2011 ¹⁹⁶	Belgium	HF NYHA III or IV, LVEF \leq 35%, QRS > 120ms	Markov	COMPANION	Not cost effective (€57,000/QALY)
Yao <i>et al.</i> , 2007 ¹⁹⁸	UK	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective (€18,017/QALY)
<i>CRT-D vs ICD</i>					
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Brazil	HF NYHA II, III or IV, EF \leq 35%.	Markov	Meta-analyses	Marginally cost-effective (Int \$36,940/QALY)

HF – heart failure; Int \$ - International Dollars; LV – Left ventricular; EF ejection fraction; VT – ventricular tachycardia; VF – ventricular fibrillation

Six studies^{43;155;188;194;196;197} were considered to be of high methodological quality by meeting all or all but one ('Setting comparable to the UK') recognised criteria.^{38;68} Of these, one study, conducted for a UK setting, is considered of most relevance.⁴³ We describe this study in more detail in the following section.

5.1.3.1 Fox and colleagues,⁴³ Bond and colleagues²⁰³

Fox and colleagues⁴³ (also reported in Bond and colleagues²⁰³) developed a Markov model to compare CRT-P and CRT-D with OPT in patients with heart failure in the UK (see Appendix 13 for data extraction). The model followed a mixed age cohort of people (start age from 30 to 90 years) with HF (NYHA Class III and IV) due to LVSD (with LVEF $\leq 35\%$) and electrical dyssynchrony (QRS duration > 120 ms) over their lifetime. A cycle length of 4 weeks was used and a lifetime time horizon.

The model had the following health states: surgery (original implant, upgrade, routine maintenance), postoperative complication, stable with device, stable with OPT, infection (CRT, ICD related) hospitalised (HF, HF and heart transplant), death (sudden cardiac cause, HF, non-cardiac related). The baseline population mortality in the OPT arm was taken from the CARE-HF trial as this was a large UK based trial. The mortality benefit of CRT over time was calculated using the survival curve from the OPT group in CARE-HF with the pooled HR, estimated in their systematic review of the clinical effectiveness of cardiac resynchronisation in HF. The model used QoL estimates related to NYHA class (Class I 0.93 and Class II 0.78 from Kirsch and McGuire,²⁰⁴ Class III 0.61 and Class IV 0.44 from Calvert and colleagues²⁰⁵) and utility for hospitalisation with HF (0.57 from McAllister and colleagues¹⁹⁴). Patients were distributed across NYHA classes according to the data from the CARE-HF trial at baseline, 90 days and 18 months. The cost of the devices were obtained from a sample of 61 NHS 'buying units' (either individual health service Trusts or purchasing consortia of Trusts) during 2004 and 2005. Costing year and currency for the analysis were 2005 and GBP (£), except for drug costs which were 2006 and GBP (£).

Compared with OPT, the model base case analysis estimated that CRT-P conferred an additional 0.70 QALYs for an additional £11,630 per person, giving an estimated ICER of £16,735 per QALY gained for a mixed age cohort (range £14,630 – 20,333).^{43;203} CRT-D versus CRT-P conferred an additional 0.29 QALYs for an additional £11,689 per QALY, giving an ICER of £40,160 per QALY for a mixed age cohort (range £26,645 – 59,391). Sensitivity analyses showed that in comparison to CRT-P, CRT-D devices were most likely to be cost-effective when implanted in younger individuals and in those with a high risk of SCD. Of the other five high quality studies, the three studies^{155;188;196} with the patient group most comparable to that of Fox and colleagues⁴³ also found CRT-P cost-effective when

compared with OPT, whilst the remaining two studies were uncertain.^{194;197} Three of the other high quality studies^{155;188;196} also considered CRT-D compared with CRT-P and found it not cost-effective..

Table 88: Summary of the quality of economic evaluations on CRT

	Decision problem relevant to the UK	Setting comparable to the UK	Appropriate methodology	Relevant costs and consequences	Data inputs justified	QALYs measured	Appropriate time horizon	Discounting	Incremental analysis	Sensitivity analysis
<i>CRT-P vs OPT</i>										
Banz, 2005 ¹⁸⁷	Y	N	Y	Y	Y	Y	N	N	Y	Y
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Blomstrom <i>et al.</i> , 2008 ¹⁹¹	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Bond <i>et al.</i> , 2009 ²⁰³ Fox <i>et al.</i> , 2007 ⁴³	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Callejo <i>et al.</i> , 2010 ¹⁸⁸	Y	?	Y	Y	Y	Y	Y	Y	Y	Y
Calvert <i>et al.</i> , 2005 ¹⁸⁹	Y	Y	Y	?	Y	Y	Y	Y	Y	Y
Caro <i>et al.</i> , 2006 ¹⁹⁰	Y	Y	Y	?	Y	Y	?	Y	Y	Y
Feldman <i>et al.</i> , 2005 ¹⁹²	Y	N	Y	?	Y	Y	N	Y	Y	Y
Heerey <i>et al.</i> , 2006 ¹⁹³	Y	N	Y	Y	?	Y	N	Y	Y	Y
McAlister <i>et al.</i> , 2004 ¹⁹⁴	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
MSAC, 2006 ¹⁹⁵	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Neyt <i>et al.</i> , 2011 ¹⁹⁶	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Nichol <i>et al.</i> , 2004 ¹⁹⁷	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Poggia <i>et al.</i> , 2012 ²⁰⁰	?	N	Y	Y	Y	Y	Y	Y	Y	Y
Yao <i>et al.</i> , 2007 ¹⁹⁸	Y	Y	Y	?	?	Y	Y	Y	Y	Y
<i>CRT-D vs OPT</i>										
Aidelsburger <i>et al.</i> , 2008 ¹⁹⁹	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Feldman <i>et al.</i> , 2005 ¹⁹²	Y	N	Y	?	Y	Y	N	Y	Y	Y
MSAC, 2006 ¹⁷²	Y	N	Y	Y	Y	N	Y	N	Y	Y
Yao <i>et al.</i> , 2007 ¹⁹⁸	Y	Y	Y	?	?	Y	Y	Y	Y	Y

	Decision problem relevant to the UK	Setting comparable to the UK	Appropriate methodology	Relevant costs and consequences	Data inputs justified	QALYs measured	Appropriate time horizon	Discounting	Incremental analysis	Sensitivity analysis
<i>CRT-D vs CRT-P</i>										
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Bond <i>et al.</i> , 2009 ²⁰³ Fox <i>et al.</i> , 2007 ⁴³	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Callejo <i>et al.</i> , 2010 ¹⁸⁸	Y	?	Y	Y	Y	Y	Y	Y	Y	Y
Neyt <i>et al.</i> , 2011 ¹⁹⁶	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Yao <i>et al.</i> , 2007 ¹⁹⁸	Y	Y	Y	?	?	Y	Y	Y	Y	Y
<i>CRT-D vs ICD</i>										
Bertoldi <i>et al.</i> , 2011 ¹⁵⁵	Y	N	Y	Y	Y	Y	Y	Y	Y	Y

5.1.4 Summary of published economic evaluations

- A systematic review of the cost effectiveness of ICDs for the treatment of arrhythmia and CRT for treatment of heart failure identified 51 studies (36 studies of ICDs and 17 of CRT). Two studies included the cost effectiveness of both ICD and CRT.
- The evaluations were published between 1990 and 2012, and the majority were conducted in North America, but there were also several UK studies.
- Most of the evaluations employed state transition models to estimate long term outcomes extrapolated from short-term outcomes in the trials. Time horizons varied between 3 years to lifetime.
- Many of the studies were based upon a single trial, with MADIT II and SCD-HeFT the most common ICD trials and CARE-HF and COMPANION the most common CRT trials. There were also several evaluations that used results from systematic reviews and meta-analyses of different combinations of trials.
- Almost half the studies reported that ICDs were cost effective, whilst the others found ICDs only cost effective in high risk groups, not cost effective or were uncertain. Five studies^{42;155;160;178;182} were considered to be of high methodological quality and report different conclusions about cost-effectiveness. Of these, only one study was conducted for a UK setting and perspective, and is considered of most relevance.⁴² This study reported a mean ICER for an average UK secondary prevention patient over a 20 year time horizon of £76,139 per QALY gained and therefore concluded that the benefit from ICDs may not be sufficient to make the technology cost-effective as used currently (2006) in the UK. However, these results may not be applicable to current UK practice as some data used in the model came from patients implanted between 1990 and 2002 which is now out of date.
- Almost all studies reported that CRT was cost effective, with only two studies uncertain as to whether CRT was cost effective. Six studies^{43;155;188;194;196;197} were considered to be of high methodological quality, two of which were the studies reporting uncertainty about cost-effectiveness. One of the high quality studies⁴³ was conducted for a UK setting and is considered of most relevance to the UK NHS. This study estimated an ICER of £16,735 per QALY gained for CRT-P compared with OPT, and an ICER of £40,160 per QALY gained for CRT-D compared with CRT. The authors concluded that CRT-D is not cost-effective for LV dysfunction and that CRT alone is the most cost-effective option in the population of patients evaluated (NYHA class III and IV with LVEF \leq 35% and QRS duration $>$ 120 ms). CRT-D is more likely to be cost-effective in subgroups of younger patients or those with high risk of SCD who would qualify for CRT.

- Two of the included economic evaluations analysed both CRT and ICD neither of which was conducted in the UK.^{155;172} Both found ICD cost-effective versus OPT, one¹⁷² found CRT-D cost-effective compared with OPT and one found CRT-D marginally cost-effective compared with ICD.¹⁵⁵

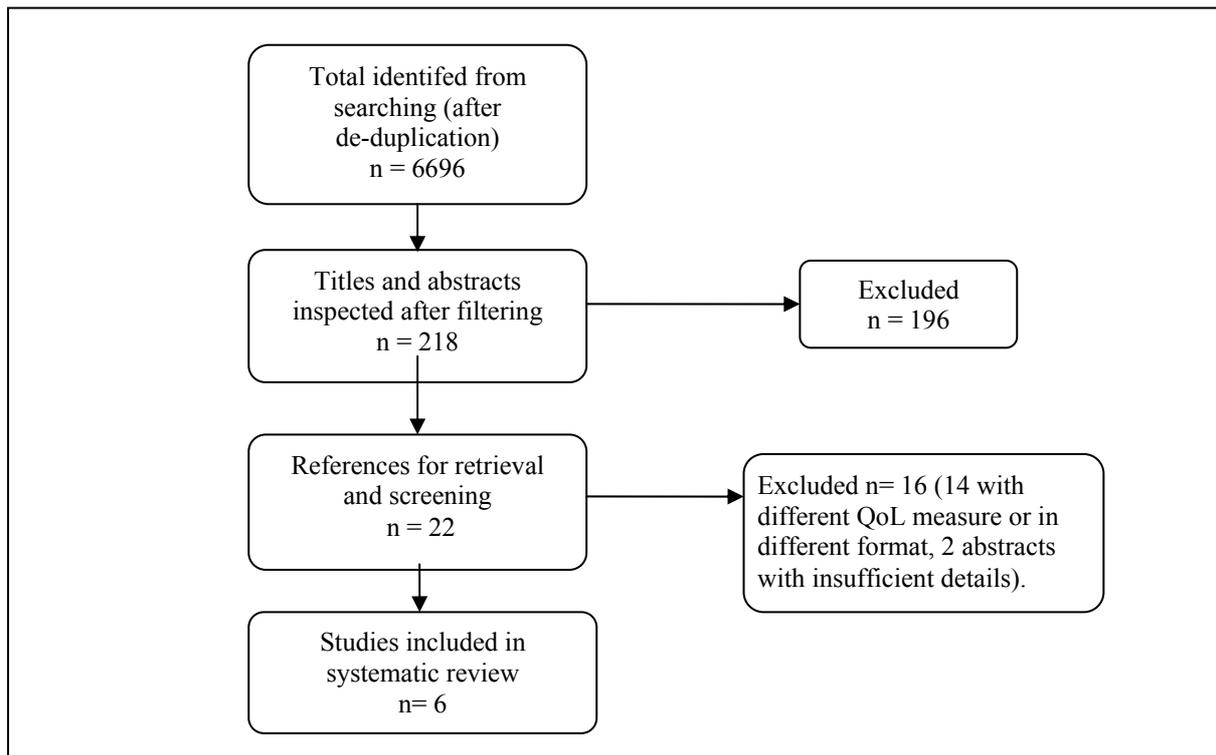
5.2 Systematic review of health-related quality of life studies

A systematic review was undertaken to assess the HRQoL of people eligible for ICD or CRT devices. The aims of the review were to provide data to populate the lifetime economic model with utilities to calculate QALYs, and to provide estimates of the HRQoL by NYHA class for those with heart failure.

For adults, the NICE preferred measure of HRQoL is the EQ-5D²⁰⁶ and this was used in the previous ICD and CRT TARs.^{42;43} We were interested in HRQoL data of similar or better quality than that used in previous studies and therefore filtered the results of our searches to studies using EQ-5D (Index not VAS). The search strategies used are described in Appendix 3. The inclusion and exclusion criteria for the review are shown in section 3.2.

The search strategy identified 6696 references which after filtering for EQ-5D resulted in 218 papers that were potentially relevant. Titles and abstracts were screened and the full text of 22 papers was retrieved for further inspection. After examining the retrieved papers, six studies met the inclusion criteria. A summary of the selection process and the reasons for exclusion are presented in Figure 32. Most studies were excluded because they did not use the EQ5D or did not report it in the required format. A list of the excluded studies is shown in Appendix 14.

Figure 32: Flow chart of identification of studies for inclusion in the review of HRQoL



HRQoL was assessed using EQ-5D in four studies of patients with heart failure^{205;207-209} and two studies^{42;210} of patients who had received an ICD (see Table 89). Three studies were cohort studies^{42;207;210} and three studies were observational analyses based on RCTs (EPHESUS5,²⁰⁸ CARE-HF²⁰⁵ and HeartMed RCT²⁰⁹).

Buxton and colleagues⁴² conducted a retrospective postal survey of patients who had received an ICD in the UK between 1991 and 2002, as part of a wider review of ICD therapy. Based upon the responses from 229 patients, they analysed the effect of time since implantation and age on HRQoL. Their analyses showed that there was no evidence that the time since implant changes HRQoL substantially over time with values similar at 1 year (0.78) and at more than six years (0.77). However, there are limitations with the type of study used (cross sectional survey) and results should be viewed with caution.

Groeneveld and colleagues²¹⁰ measured and compared HRQoL among primary and secondary prevention ICD recipients in USA. They recruited 120 patients undergoing clinical evaluation at the cardiac electro-physiology clinics who had previously received an ICD. The average duration since ICD implantation was 2 years. The authors found no differences between the EQ-5D of primary and secondary patients with health state utility values of 0.84 for both groups. They concluded that the quality of life in patients with ICDs was similar to that of similarly aged adults in the general

population. This study also had limitations in terms of methodology due to the convenience sampling technique used.

Calvert and colleagues²⁰⁵ investigated the HRQoL of 813 patients with chronic heart failure due to LVSD and dyssynchrony (NYHA class III or IV) in the CARE-HF RCT in the UK. CARE-HF was a trial to investigate the effects of CRT-P on the mortality and morbidity of patients already receiving optimal medical therapy. The baseline EQ-5D was collected for 740 patients primarily of NYHA class III (94%). The authors found that mean baseline health state utility value was 0.6 and that heart failure had an important impact on all aspects of quality of life which was independent of age. A limitation of the study was that patients were not a random sample of patients with heart failure but patients enrolled in a study receiving optimal medical therapy.

Eurich and colleagues²⁰⁷ compared several HRQoL measures for 298 people with heart failure. Patients were recruited across 14 medical centre outpatient departments in the United States and Canada. HRQoL was assessed at baseline and at six weeks. EQ-5D health state valuations were completed for both the UK and US population valuations. Mean EQ-5D (UK valuation) was 0.66 at baseline and 0.71 at six weeks for those with no change in NYHA status (70% patients). This was a cohort study which evaluated the random changes observed in heart failure patients in the outpatient setting with no specific intervention during the follow-up period.

Gohler and colleagues²⁰⁸ estimated utilities for NYHA classification and number of cardiovascular rehospitalisations for patients with chronic heart failure after acute myocardial infarction in the EPHEBUS RCT. The EPHEBUS trial was a multicentre RCT that investigated the effect of aldosterone antagonist eplerenone. HRQoL was investigated in a subset of 1395 patients at months 0, 3, 6, 12 and 18 using the EQ-5D. The health state utility values were weighted by the appropriate preference weight based on the subject's specific region of origin (USA 31%, Western Europe 52%, Latin America 14%). The study used univariate and multivariate linear regression analyses with independent variables for NYHA classification, number of CV hospitalisations between study intake and the follow-up time point, age, sex and cardiovascular morbidities. In univariate analyses, utilities associated with NYHA class were 0.85 for Class I, 0.77 for Class II, 0.67 for Class III and 0.53 for Class IV.

Table 89: Characteristics of included QoL studies

Details	Country	Study type	Study population	Patient characteristics	QoL instrument and methodology	Results
Buxton <i>et al.</i> , 2006 ⁴²	UK	Retrospective Cohort study	229 patients who had received an ICD	Mean age 60 years, 81% male. NYHA class	EQ-5D	Mean EQ-5D was reported by time since ICD implantation (up to ≥ 6 years) and ranged from 0.69 - 0.78.
Calvert <i>et al.</i> , 2005 ²⁰⁵	UK	CARE-HF RCT	813 patients with chronic heart failure due to left ventricular systolic dysfunction and dyssynchrony.	Mean age: 65 years. 74% male. NYHA: 94% Class III; 6% Class IV	EQ-5D using UK population preferences.	Mean EQ-5D: 0.60 (95% CI 0.58-0.62). NYHA class III 0.61 NYHA class IV 0.44.
Eurich <i>et al.</i> , 2006 ²⁰⁷	USA/Canada	Cohort study	298 patients with heart failure with left ventricular systolic dysfunction.	Mean age 60 years, Male 75%, NYHA 11% class I, 43% class II, 41% class III, 4% class IV.	EQ-5D with UK scoring at baseline and after 6 weeks.	Mean EQ-5D: 0.66 (SD +/- 0.26). Mean EQ-5D at 6 weeks: 0.71 (SD +/- 0.22) for those with no change in NYHA
Gohler <i>et al.</i> , 2009 ²⁰⁸	USA	EPHESUS RCT	1395 patients with chronic heart failure after acute myocardial infarction.	Mean age 64 years. Male 71%. Patient origin: US 31%, Europe 52%, Latin American 14%.	EQ-5D weighted by the appropriate preference weight based on the subject's origin.	Mean EQ-5D by NYHA class: I = 0.855 (95% CI 0.845 – 0.864), II = 0.771 (95% CI 0.761 – 0.781), III = 0.673 (95% CI 0.727 – 0.765), IV = 0.532 (0.480 – 0.584)
Groeneveld <i>et al.</i> , 2007 ²¹⁰	USA	Cohort study	Patients who had previously received ICD therapy for primary (n= 45) and secondary prevention (n = 75)	Mean age 60 years. Male 73%. Years since ICD implantation: 2.	EQ-5D	Median EQ-5D score: Primary prevention 0.84 (IQR 0.77,1) Secondary prevention.0.84 (0.78, 1)
Holland <i>et al.</i> , 2010 ²⁰⁹	UK	Cohort analysis within HeartMed RCT	293 patients with heart failure following emergency hospital admission.	Mean age 77 years. 64% male. SA NYHA*: 33% class I/II, 34% class III, 33% class IV.	EQ-5D using UK population preferences at baseline and 6 months follow-up.	Mean baseline EQ-5D for SA NYHA*: I/II 0.72 (SD 0.25), III 0.53 (SD 0.32) IV 0.47 (SD 0.35). Mean 6 month EQ-5D for SA NYHA*: I/II 0.6 (SD 0.25), III 0.38 (SD 0.32), IV 0.34 (SD 0.35).

* SA NYHA – self assigned New York Heart Association.

Holland and colleagues²⁰⁹ conducted a cohort analysis within the HeartMed RCT. A total of 293 adults with heart failure were included from three large district general hospitals in the UK after an emergency admission and followed over six months. The analysis aimed to test whether patients' self-assigned NYHA class at baseline predicted outcomes. Patients classified themselves into one of four self-assigned NYHA classes using a questionnaire that described their functional status. Mean baseline EQ-5D score was 0.72, 0.53 and 0.47 for self-assigned NYHA I/II, III and IV respectively, and mean six month EQ-5D score was 0.6, 0.38 and 0.34 respectively. The authors concluded that heart failure patients' own assessment of their NYHA class is a predictor of outcomes in heart failure, in the same way as clinician-assigned NYHA class; however the study was limited by there being no clinician assessment to compare with patients' own assessment.

Both studies in patients who had received an ICD had methodological limitations with a key one being the selection of participants, who were a small number of volunteers attending a single defibrillator clinic in the USA²¹⁰ and survey respondents at two centres in the UK.⁴² This may have biased results by not including patients representative of elsewhere with different experiences. However, in the absence of more rigorous information they supply some information of relevance. One study suggests that there is no difference between the EQ-5D score of primary and secondary prevention patients and that quality of life for ICD patients was similar to the general population of similar age²¹⁰ and the other shows no evidence that quality of life changes over time since implant.⁴²

Four cohort studies reported utility estimates for heart failure patients with two conducted in the UK^{42;209} and two in the USA.^{207;208} Patient characteristics were generally similar across studies in terms of sex and age, except one study²⁰⁹ where mean age was greater (77 years compared with 60 to 65 years). The severity of heart failure as measured by NYHA differed between the studies with the percentage of NYHA Class III participants ranging from 94%²⁰⁵ to 34%.²⁰⁹ Mean baseline EQ-5D scores were similar in the two studies that reported this (0.60²⁰⁵ and 0.66²⁰⁷). Three studies reported mean baseline EQ-5D score by NYHA class. Mean baseline EQ-5D score for NYHA Class III was 0.61,²⁰⁵ 0.63²⁰⁸ and 0.53 in the study where patients self-assigned NYHA Class.²⁰⁹ For NYHA Class IV mean baseline EQ-5D scores were 0.44,²⁰⁵ 0.53²⁰⁸ and 0.47.²⁰⁹ Overall results suggest that heart failure has a significant effect on HRQoL. One study reports random changes in utility after 6 weeks in patients with no change in NYHA Class²⁰⁷ and another which used self-assigned NYHA classification showed decreased EQ-5D scores in each NYHA class after 6 months.²⁰⁹

5.2.1 Summary of the health-related quality of life review

- The systematic review found six relevant HRQoL studies that measured EQ-5D in heart failure, stratified by NYHA class, or reported on patients who had previously received an ICD.

- Two studies were conducted in patients who had received an ICD; one in the UK of patients at two hospitals implanted between 1991 and 2002 who responded to a postal questionnaire and one of volunteers attending a defibrillator clinic in the USA.
- The UK ICD study reported that mean EQ-5D score did not change with time after implant (mean EQ-5D score ranged from 0.69 to 0.78 for years up to ≥ 6 years since implantation). The USA study reported no difference between EQ-5D score of primary and secondary prevention patients (median EQ-5D score 0.84) and that quality of life for ICD patients was similar to the general population.
- Four cohort studies reported EQ-5D scores in heart failure, two in the UK (one of which was based on the CARE-HF RCT) and two in the USA (one based on the EPHESUS RCT).
- Two studies reported similar mean baseline EQ-5D scores of 0.60 (UK RCT based study) and 0.66 (USA cohort study).
- Three studies reported mean baseline EQ-5D score by NYHA class. Mean baseline EQ-5D score for NYHA Class III was 0.61 and 0.53 (UK studies) and 0.63 (USA study). The lowest value was reported in the study where patients self-assigned NYHA class. Mean baseline EQ-5D score for NYHA Class IV was 0.44 and 0.47 (UK studies) and 0.53 (USA study).
- One USA study reports random changes in utility after 6 weeks in patients with no change in NYHA Class and one UK study (which used self-assigned NYHA classification) showed decreased EQ-5D scores in each NYHA class after 6 months.
- Overall results show decreased EQ-5D scores in heart failure compared with the general population particularly in NYHA Class III and IV.

5.3 Review of the manufacturers' submission

As described in section 4.5, one MS consisting of a written report and an electronic model supporting the reported cost effectiveness analyses was submitted to NICE. Further details on the submission and a discussion of the clinical data reviewed and presented can be found in section 4.5 and Appendix 11

The review of the economic assessment within the MS consists of a brief overview of the cost effectiveness analysis, including the approach taken to modelling disease progression and the effects of treatment, followed by a critical appraisal of the cost effectiveness analysis.

5.3.1 Review of the ABHI submission to NICE

A structured data extraction form was used to guide the review of the MS (Appendix 11), jointly submitted by the ABHI on behalf of Biotronik, Boston Scientific, Medtronic, Sorin and St Jude Medical. The submission includes a review of published clinical effectiveness studies of OPT, ICD,

CRT-P and CRT-D for the treatment of cardiac arrhythmias and heart failure, a network meta-analysis of individual patient data (IPD), and a report of an economic evaluation undertaken for the NICE MTA process.

The cost-effectiveness analysis (CEA) uses a survival-based model to estimate the relative cost-effectiveness of OPT, ICD, CRT-P and CRT-D (compared with each other) in 48 subgroups of patients. Individual patient data of 12,638 patients from 13 RCTs were used to inform the manufacturers' economic model. All individuals are adults with heart failure (HF), LVEF $\leq 35\%$, and/or at risk of SCD. This heterogeneous group of patients was split into 48 subgroups according to their NYHA class, QRS duration, Left Bundle Branch Block (LBBB) status and aetiology of heart disease, and cost-effectiveness results are reported for each subgroup.

The perspective adopted for the manufacturers' economic evaluation is that of the UK NHS and PSS. General UK population utilities were used at baseline to which disease-specific decrements were applied. The impact of each intervention on patients' HRQoL was incorporated as intervention-specific increments. These estimates were derived from published sources and IPD from the trials included in the manufacturers' systematic review of clinical effectiveness studies.

For each subgroup, cost-effectiveness results were presented per intervention as incremental cost per QALY relative to the intervention immediately less effective.

The interventions compared in the MS consist of those comprised in NICE's scope. However, not all of them were included as comparators for all patient subgroups in the MS, as no patients were identified for these combinations:

- ICD excluded for NYHA class IV
- CRT-P excluded for NYHA class I/II and QRS <120ms
- CRT-D excluded for QRS <120ms

Clinical advice indicated that these exclusions are reasonable.

5.3.2 Modelling approach

A cohort survival model was developed in Microsoft Excel with two states for alive and dead. Death is modelled via a series of covariate-based regression equations for baseline risk and treatment effect using long-term IPD. Based upon the numbers of patients alive, the model also estimates the numbers of patients hospitalised in each cycle. The model had monthly cycles and a lifetime time horizon. Costs and health benefits in the model were discounted at 3.5%.

The baseline probability of death is for patients who receive OPT but no device, based on a range of clinical covariates. These probabilities are used in combination with device-specific treatment effects, derived from the network meta-analyses. For the model baseline survival curve, a Weibull distribution was used with the parameters of the risk model shown in Appendix 11. A similar approach is taken to estimate the probability of all-cause hospitalisation. HRQoL utility is applied to patients in the model according to their treatment and clinical characteristics.

The model does not include short-term device related adverse events as the costing approach used to derive total implant costs covers additional costs such as short term adverse events.

Results were generated in a two stage process. In the first, cost and QALY estimates were derived for all relevant comparators in all 4,992 patient profiles (4 NYHA, 2 aetiology status (ischaemic/ non-ischaemic), 3 QRS categories, 4 LVEF categories, LBBB status (yes/no), 2 gender groups, 13 age categories). In the second stage, results were aggregated over LVEF and age and gender categories, reducing the subgroups to 48 subgroups, defined by NYHA class, QRS duration, LBBB status and aetiology.

5.3.3 Assumptions

The manufacturers' model makes the following additional assumptions:

- The effects of treatment on HRQoL diminish over time. The model assumes that the benefit observed at six months is maintained up to five years and thereafter begins to recede in a linear manner over the time period from five to ten years. After ten years, an individual with a device will have no additional HRQoL benefit over an identical person receiving OPT.
- HRQoL increments were assumed to be associated with device implantation.
- Reduction in all-cause hospitalisation varied according to the device implanted and the patient's NYHA class.

5.3.4 Estimation of effectiveness

The clinical effectiveness estimates were based upon a network meta-analysis of IPD from 13 clinical trials (12,638 patients, followed up for up to 7.5 years). The clinical trials were: CARE-HF, COMPANION, CONTAK-CD, DEFINITE, MADIT, MADIT II, MADIT-CRT, MIRACLE ICD, RAFT, RethinQ, REVERSE and SCD-HeFT. These trials were identified through a systematic review of the clinical effectiveness for all the interventions. A further nine trials were also identified in the review, but IPD were not available for these trials. See 4.5 and Appendix 11 for further discussion on the clinical effectiveness data included in the MS.

The NMA enabled the combination of trials that compared different sets of treatments within a single analysis, and to use available direct and indirect evidence to inform a comparison between possible treatments. The analysis assessed the outcomes of all-cause mortality, all-cause hospitalisation and HRQoL, using the results to inform the economic model developed as part of the MS. A critique of the IPD NMA is presented in section 5.3.10.

The IPD NMA showed that ICDS, CRT-D and CRT-P were significantly more effective than OPT for people with heart failure when assessed on all-cause mortality, with CRT-D also providing statistically significant benefit compared to ICDs and CRT-P. Analysis of those sub-groups that benefitted from the different interventions when compared to OPT was less clear. CRT-D had a statistically significant benefit for all people with a $QRS \geq 150$ ms and all women with a $QRS \geq 120$ to < 150 ms and a marginally insignificant effect for all men $QRS \geq 120$ to < 150 ms. ICDs had a significant benefit for men aged < 60 years and for men aged ≥ 60 years with a $QRS \geq 120$ to < 150 ms and non-LBB. CRT-P had a significant benefit for women with $QRS \geq 150$ and LBBB. The network meta-analysis found CRT-D to have the strongest effect on all-cause mortality [REDACTED]. Treatment effects for the individual devices were also statistically significant [REDACTED].

All devices reduced all-cause hospitalisations compared to OPT, with rates decreasing for NYHA groups I to III from ICDs [REDACTED], for NYHA groups III [REDACTED] and IV [REDACTED] from CRT-P and for all NYHA groups from CRT-D [REDACTED]. HRQoL was assessed using EQ-5D, showing counter-intuitive results for the effects of treatment. Adjustments were made assuming that CRT-P and CRT-D would have the same effects and ICDs only having an effect on NYHA groups I and II. Benefits were thought to last for [REDACTED] years.

UK device longevity estimates were derived from NHS data of the Central Cardiac Audit Database (CCAD) on all implants with verified life status from 2000 to 2011 (~ 40,000 implants). The MS consider that the device longevity estimates represent the best currently available as it contained a large number of implants from which data were available and the CCAD is run by the NHS Information Centre. Device specific median survival estimates were obtained by fitting Weibull curves to the data. The Weibull curve was chosen since it is commonly used to model such data and the MS considered it a good fit (both in terms of within-data accuracy and long term predictive plausibility). Median time to device failure in the model was 7.1 years for ICD, 10.4 years for CRT-P and 5.8 years for CRT-D. The methodology used by the manufacturers to estimate devices' longevity is commonly used; however, clinical advice indicated that these estimates seem to be overestimated.

5.3.5 Critical appraisal of the MS model

The ABHI MS was appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements⁶⁹ and the Philips and colleagues checklist.⁷⁰ Overall, the submission meets all the requirements for methodological quality and generalisability, except that it did not provide evidence that the economic model had been validated, and the model assumptions were not listed and justified. Table 90 provides a summary of the MS critical appraisal.

The model structure is consistent with the currently accepted theory of the heart failure and ventricular arrhythmia. The MS does not describe the sources of evidence used to develop and inform the model structure but provides a brief justification for its choice (related to the large amount of IPD being available). The MS also does not include a review of economic evaluations of the scoped interventions and comparators. Other structures could have been adopted, but the fundamental features of the condition and the impact of the interventions seem to be captured. Adverse effects of treatment, such as perioperative complications, were not explicitly incorporated in the model. The model was populated with data from the MS systematic review of clinical effectiveness studies. A monthly cycle length and a lifetime horizon were appropriately used, and Weibull models were used to extrapolate all-cause mortality beyond trial duration. There is no reference to the internal validation of the model in the MS. Overall, the model results make intuitive sense and the conclusions seem valid. In addition, the MS has compared their results with those from results generated in previous appraisals, and given reasons for the differences in results.

Table 90: Critical appraisal checklist of economic evaluation^a

	Item	MS	Comments
1	Is there a clear statement of the decision problem?	Yes	
2	Is the comparator routinely used in UK NHS?	Yes	
3	Is the patient group in the study similar to those of interest in UK NHS?	Yes	
4	Is the health care system comparable to UK?	Yes	
5	Is the setting comparable to the UK?	Yes	
6	Is the perspective of the model clearly stated?	Yes	
7	Is the study type appropriate?	Yes	
8	Is the modelling methodology appropriate?	Yes	
9	Is the model structure described and does it reflect the disease process?	Yes	
10	Are assumptions about model structure listed and justified?	No	
11	Are the data inputs for the model described and justified?	Yes	
12	Is the effectiveness of the intervention established based on a systematic review?	Yes	
13	Are health benefits measured in QALYs?	Yes	
14	Are health benefits measured using a standardised and validated generic instrument?	Yes	
15	Are the resource costs described and justified?	Yes	
16	Have the costs and outcomes been discounted?	Yes	
17	Has uncertainty been assessed?	Yes	Limited to few parameters
18	Has the model been validated?	?	Limited reporting of validation

Yes / No / ? (unclear). ^a Questions in this checklist based on Philips et al⁶⁹

5.3.6 Estimation of QALYs

The approach taken for HRQoL was i) to estimate UK specific age and gender population utilities, ii) derive a disease specific decrement using IPD EQ-5D data, and iii) derive treatment-specific increments associated with each device at first follow-up visit by NYHA class.

UK specific age and gender population utilities were taken from a study by Kind and colleagues¹⁵³ of 3,395 individuals resident in the UK. Disease specific decrements were taken from the CARE-HF, MADIT-CRT and RAFT trials. For the impact of treatment, the utility decrement was calculated as the difference between baseline and first follow-up period. The health state utility values used in the model are presented in the data extraction form in Appendix 11.

The health state utility values used are derived from the patient level EQ-5D data. The MS reports that some of the results were highly counter-intuitive given the nature of the underlying disease and the interventions, for example the results for CRT-D for NYHA III/IV showed a utility decrement, in contrast to those for CRT-P. The MS has dealt with these inconsistencies in the patient-level data by using several assumptions: CRT-D is assumed to have the same utility increment as for CRT-P for NYHA III/IV, ICD assumed to have [REDACTED] for NYHA III. ICD is associated with a utility increment of [REDACTED] in NYHA class I/II. CRT-D has a utility increment of [REDACTED] for NYHA-I/II, and [REDACTED] for NYHA III/IV. These values for ICD and CRT-P were derived from the IPD analysis after subtracting the OPT NYHA class III value ([REDACTED]). The values for CRT-P used were of similar magnitude to those reported in the CARE-HF study which gave a utility increment of 0.18 months after implantation compared to OPT patients.

In the model, the HRQoL benefit observed at six months is maintained up to five years and thereafter begins to recede in a linear manner over the time period five to ten years. After ten years, the model assumed that the individual with a CRT or ICD device will have no additional HRQoL benefit over an identical person receiving OPT.

The MS does not report a systematic review of HRQoL studies. A review of utility values used in previous economic evaluations is reported but no details of how these were obtained are provided. The MS approach differs from that of most previous models (including Buxton et al⁴² and Fox et al⁴³) where no benefit from the intervention was assumed. However, the device-specific increments used in the MS are similar to those used in some of the previous models (Feldman 2005,¹⁹² Neyt 2011,¹⁹⁶ Owens 2002¹⁷⁷). The impact of treatment-related adverse events (such as infection and perioperative complications) on HRQoL considered in previous models was not included in the MS.

5.3.7 Estimation of costs

The resource use accounted for in the MS included device-related costs, medication, and resources related to disease progression. IPD from the trials were used to estimate the mean number of all cause hospitalisation events per month and the mean number of days per month. The hospital costs were derived from the NHS Schedule of Reference Costs (SRC) and combined with the average mean length of stay. The heart failure hospitalisation event cost was £2,295 and the non HF hospitalisation event cost was £2,448.

Device costs were sourced from the average selling prices from the manufacturers via the ABHI. These prices are an aggregate across all sponsors (manufacturers) for ICD, CRT-P and CRT-D devices and leads sold in the UK to the NHS. The implantation costs were taken from the Healthcare

Resource Group tariff values. Device related infection costs were derived by inflating values in the previous TAR on CRT⁴³ to £3,139. Device costs, with implantation costs, were £15,248, £8,281 and £17,849 for ICD, CRT-P and CRT-D respectively. Further device costs are shown in Appendix 11.

The manufacturers assumed that an OPT regimen is taken by all patients for HF treatment, regardless of whether they receive a device in addition, and the drug cost allocated in any given month to each patient alive is based on their baseline NYHA class. The proportion of patients using a range of HF medications, by NYHA class was derived from a combination of the clinical studies identified in the systematic review and expert opinion. The recommended daily dose for each commonly used drug was sourced from the British National Formulary (BNF). The total cost of treatment per 1 month cycle was £14.28 for NYHA class I and between £22.13 and £22.30 for NYHA class II-IV.

Overall, the derivation of costs and assumptions presented in the MS seem appropriate and consistent with previous approaches. However, specific searches for resource use or cost studies in the UK are not reported in the MS, and the impact of changes to the values and assumptions used was not analysed in the MS. The estimates in the model seem to cover the relevant resource use, including complications, non-HF hospitalisations, and outpatient visits.

5.3.8 Cost-effectiveness results

The base case deterministic results are presented for 48 subgroups defined by NYHA class, QRS duration, LBBB status, and aetiology, but are not presented for the population as a whole or according to the population groups scoped by NICE, and it is unclear how these results could be aggregated.

The MS base case results can be found in the data extraction form (Appendix 11) and are summarised in Table 91. The MS provides limited reporting of the results and sensitivity analyses. Generally only the ICERs are presented for each of the base case results, rather than a more detailed breakdown of costs and QALYs, and incremental costs and QALYs between competing interventions. For the base case results, full aggregated results where total costs and QALYs are reported is only presented for subgroups of NYHA III class patients comparing CRT-D vs. OPT. Overall, the MS results show that for most subgroups there is at least one device with an ICER below £30,000/QALY, and that in some cases a different device might be cost-effective if a £20,000/QALY threshold is considered.

Table 91: Summary of the ABHI base case deterministic results

Heart failure severity	QRS duration	Results summary
NYHA class I/II	QRS duration < 120ms	The ICERs for ICD vs. OPT are below £25,200 per QALY gained.
	QRS duration 120-149ms	ICD is a cost-effective treatment option ^a (ICER < £17,000 / QALY) patients with no LBBB. For CRT-D all ICERs are below £25,000 per QALY gained in LBBB patients (£20,608 to £24,343)
	QRS duration ≥ 150ms	CRT-D is cost effective treatment ^a with an ICER of less than £28,000 per QALY for all options.
NYHA class III	QRS duration < 120ms	ICD vs. OPT generates ICERs below £30,000 per QALY
	QRS duration 120-149ms	CRT-P is cost-effective ^a . CRT-D generates ICERs between £23,900 and £27,400 per QALY gained relative to CRT-P.
	QRS duration ≥ 150ms	CRT-P is cost-effective vs. OPT (ICER < £20,000 per QALY). Compared with CRT-P, CRT-D generates ICERs below £30,000 per QALY gained. ICD is either dominated or extended dominated.
NYHA class IV	QRS duration < 120ms	No comparative analysis was possible in this patient group, as no patients were identified for this combination.
	QRS duration ≥120ms	For CRT-P compared with OPT, all ICERs are close to or below £20,000 per QALY gained. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

^a According to willingness to pay threshold of £20,000 - £30,000 per QALY gained.

The manufacturers conclude that in many cases, where there are small differences in cost-effectiveness between devices and high uncertainty as to which is the preferred device, NICE recommendations should allow for clinical flexibility.

The MS explores model uncertainty through deterministic and probabilistic sensitivity analyses, where most deterministic sensitivity analyses reported in the MS consist of scenario analyses. Not all forms of uncertainty were explored, only uncertainty associated with a few methodological assumptions. The MS does not report ranges used for the sensitivity analyses, only different scenarios tested, and does not identify the model parameters with greatest influence on the results. The MS does not report the assessment of uncertainty associated with resource use and cost parameters, and

structural assumptions have not been tested. For instance, a scenario of reduced device longevity was not analysed nor one assuming no HRQoL benefit from the interventions.

The following scenarios were tested in sensitivity analyses: removal of treatment effect tapering (mortality and HRQoL), use of alternative NYHA based IPD results, increase in device longevity. The base case assumed that treatment effects on mortality or HRQoL are not constant but diminish over time. When constant treatment effects for mortality and quality of life were explored, ICERs in all patient groups were lower than in the base case.

According to the MS, there may be a lower mortality treatment effect in patients with NYHA class IV compared to NYHA classes I/II/III for CRT-D. The economic model was run using the estimated all-cause mortality treatment effects based on the grouping of NYHA class IV vs. NYHA class I-III patients. This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups are lower than in the base case. Device longevity was investigated by increasing time to device failure by 10%. There were only minimal changes to the cost effectiveness results.

Probabilistic sensitivity analyses (PSA) were conducted for a few subgroups, selected to reflect the baseline characteristics of the MADIT-CRT trial, but no overall population analysis was performed. Due to the complexity of patient level heterogeneity, the MS reported that a full PSA would take several months to execute. Results were presented graphically for four subgroups of 65-year old, NYHA class II, ischemic, QRS >150ms, LVEF between 20 and 25% patients: male and female with and without LBBB. For these subgroups, CRT-D and OPT showed similar probability of being cost-effective around a threshold of £20,000/QALY. The manufacturers concluded that results suggested that the deterministic and probabilistic sensitivity analyses were broadly aligned.

The MS does not provide any details of the variables included in the PSA, such as mean values, distributions and variability of those variables. Credible intervals for mean ICERs of the most cost-effective intervention were not reported either. It is therefore not clear whether the methods of assessment of parameter uncertainty are appropriate and whether the estimates of variation in PSA are appropriate to reflect uncertainty in parameter estimates.

The MS has compared its cost effectiveness estimates to those produced in the previous appraisals for CRT in patients with NYHA class III/IV heart failure developed by Fox et al., and the review of ICDs in primary prevention. They found that the estimates from their model are markedly lower than were generated in the models developed for TA95 and TA120. They give the following reasons for the differences: real time reduction in production costs, increases in device longevity compared to those

used in previous models, better estimates of the impact of treatment on mortality and better understanding of the impact of treatment on HRQoL.

5.3.9 Summary of ABHI submission

- The ABHI submission was jointly submitted by the ABHI on behalf of five manufacturers.
- The submission includes a NMA of IPD from over 12,000 patients and 13 RCTs.
- The ABHI economic model is a survival model, based upon IPD data according to patient clinical characteristics.
- The model compared ICD vs. CRT-P vs. CRT-D vs. OPT.
- The model met all but two criteria for methodological quality.
- The cost-effectiveness results are presented in ABHI's submission for subgroups according to NYHA class, QRS duration, LBBB status and aetiology.
- The cost effectiveness results do not directly address questions posed in NICE's scope, as it is unclear how the subgroups selected relate to the groups scoped by NICE.
- Overall, ABHI's results show that for most subgroups there is at least 1 device with an ICER below £30,000 per QALY gained, and in some cases a different device might be below £20,000 per QALY gained.

5.3.10 Critique of the ABHI submission

The ABHI economic model is a cohort survival model with survival based upon a series of covariate-based regression equations. The model includes the costs and health related quality of life of associated events related to hospitalisation and device implantation. The general approach taken by the manufacturer seems reasonable, and the model structure is consistent with the current understanding of heart failure and ventricular arrhythmia. Generally, the model meets most criteria for methodological quality, although there is limited reporting in the MS on the sources of evidence used to develop and inform model structure, the assumptions used in the model have not been fully reported and explained and there is no evidence given for internal validation of the model in the MS.

The manufacturers' joint submission presented an individual patient level data (IPD) network meta-analysis (NMA) to assess the effectiveness of the different interventions on people with heart failure. It used meta-regression, allowing the effects of various patient characteristics on treatment outcomes to be assessed and any sub-groups who may benefit differently to be identified. The analysis assessed the outcomes of all-cause mortality, all-cause hospitalisation and HRQoL, using the results to inform the economic model developed as part of the MS. As an appraisal of the IPD NMA is presented in

section 4.5.1, this section provides a brief summary of the limitations and findings that are relevant to the economic model produced as part of the MS.

The data sources used to populate the model for effectiveness are based upon IPD data from over 12,000 patients and 13 RCTs are of high quality and as stated by the MS ‘represent the first analysis of its kind and magnitude’. Although the NMA appeared to follow established methods and had access to unpublished IPD, aspects of the reporting of the analysis and apparent limitations in the data meant there was uncertainty in the findings presented. Despite the IPD including 13 of the 22 trials (95% of patients) in the evidence network, data appeared limited given the co-variables included (i.e. number of variables and sub-categories) and the lack of data for specific outcomes assessed. As a consequence, the MS suggests that the analyses for all-cause mortality that includes treatment effect modifiers (i.e. sub-groups) should be interpreted cautiously and makes adjustments to counter-intuitive results in the analyses of all-cause hospitalisations and HRQoL. The methods used in the NMA are discussed; however the exploratory and confirmatory analyses used to decide upon the approach taken are not fully reported. Inevitably these may affect the results and, although some comparisons are made with other evidence, a degree of uncertainty remains. Importantly, the IPD NMA has a different focus from that identified in the scope for the NICE appraisal. Rather than assessing the effectiveness of the technologies in specific groups of patients, it tries to identify which patients the different technologies benefit. As these groups may not be the same, it is difficult to use the findings to address the original decision problem.

The assumptions over costing and resource use are similar to the approach used by Fox and colleagues⁴³ and are consistent with current clinical practice. However, specific searches for resource use or cost studies in the UK are not reported in the MS, and the impact of changes to the values and assumptions used was not analysed in the MS. The estimates in the model seem to cover the relevant resource use, including complications, non-HF hospitalisations, and outpatient visits. In addition the sources used appear reasonable. The UK device longevity estimates are based upon all available implant data from the CCAD and as stated by the manufacturer represent the best device longevity currently available.

The MS does not report a systematic review of HRQoL studies. A review of utility values used in previous economic evaluations is reported but no details of how these were obtained are provided. The MS approach differs from that of most previous models (including Buxton et al⁴² and Fox et al⁴³) where no benefit from the intervention was assumed. However, the approach appears reasonable and intuitive and the device-specific increments used in the MS are similar to those used in some of the previous models (Feldman 2005,¹⁹² Neyt 2011,¹⁹⁶ Owens 2002¹⁷⁷) and were of similar magnitude to those reported in the CARE-HF study.

The model presents results according to subgroups defined by the manufacturers (NYHA class, QRS duration, LBBB status and aetiology), and it is not clear how subgroups defined in the MS relate to the populations scoped by NICE. Furthermore, the results have not been aggregated across subgroups, and it is unclear how the results compare to previously developed economic models. Uncertainty is not comprehensively assessed in the MS as the sensitivity analyses presented are limited to few scenarios. The methodology used in the MS for PSA is not described in sufficient detail to determine whether joint parameter uncertainty was properly assessed.

5.4 Independent economic evaluation

5.4.1 Statement of the decision problem and perspective for the cost-effectiveness analysis

In accordance with the NICE scope,⁶⁴ we developed an economic model to estimate the cost effectiveness of:

- ICDs for people at risk of sudden cardiac death as a result of ventricular arrhythmias compared with standard care without ICD;
- CRT-P or CRT-D for people with heart failure as a result of LVSD and cardiac dyssynchrony compared with each other and with standard care without CRT;
- CRT-D for people with both conditions compared with CRT-P, ICD, and OPT.

The perspective of the analyses was that of the NHS and PSS. A 3.5% rate was used to discount future health gains and costs.

5.4.2 Strategies and comparators

The scope for the appraisal as defined by NICE⁶⁴ stated that the interventions to be considered are ICD for patients at risk of sudden cardiac death and CRT for patients with heart failure as a result of LVSD and cardiac dyssynchrony, alongside standard care (also referred to OPT).

The scoped population groups are eligible for different interventions and comparators, hence the cost-effectiveness analyses were performed specifically for each population group. The relevant comparisons for each population are as follows:

- For people at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT, ICD with OPT will be compared with standard care (OPT without ICD)

- For people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite OPT, CRT-P and CRT-D (both with OPT) will be compared with each other or with standard care (OPT without CRT);
- For people with both conditions described above, CRT-D with OPT will be compared with ICD with OPT, CRT-P with OPT or standard care (OPT alone).

5.4.3 Methods for economic analysis

5.4.3.1 Model type and rationale for model structure

All-cause mortality, SCD, heart failure mortality, and death from other causes were key outcomes in clinical trials reviewed in section 4. Secondary outcomes included hospitalisation due to heart failure, NYHA class, and quality of life. To estimate the impact of changes in these outcomes we required an appropriate model of disease progression and its effect on patient HRQoL. We conducted a systematic search of the literature to identify source material on the natural history, epidemiology and treatment of SCD and heart failure (Appendix 3). References identified by these searches, along with previous economic evaluations reviewed in section 5.1, informed the development of a Markov state transition model.

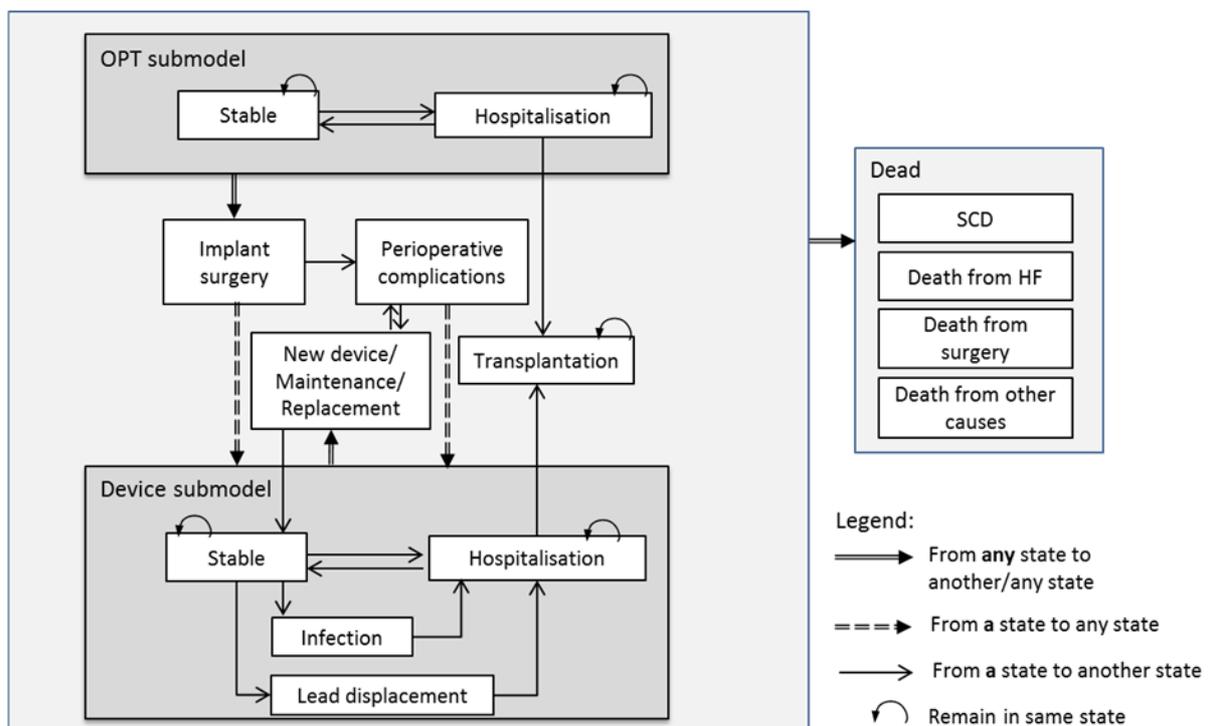
A Markov model developed in Microsoft Excel was used to simulate disease progression in a cohort of patients, who move between distinct health states over their lifetime. The probability of being in a given health state or moving to a different one (experiencing an event) is calculated repeatedly over monthly cycles. Disease progression varies according to the characteristics of the population group and the care pathway they follow. Each care pathway represents a distinct possible sequence of interventions. As patients are modelled moving between health states over a lifetime, the respective health outcomes and costs can be estimated for a given population following each care pathway. Utility values for the several health states modelled were used to estimate the benefit of each intervention in terms of quality-adjusted life years (QALYs).

The adaptation of the model developed by Fox and colleagues for TA120⁴³ was found appropriate for the analysis of the cost-effectiveness of ICD for the treatment of arrhythmias and CRT devices for the treatment of heart failure. For patients with heart failure as a result of LVSD and cardiac dyssynchrony considered as candidates for CRT, we based the pathways on those included in the model developed for TA120.⁴³ For patients at increased risk of SCD as a result of ventricular arrhythmias we adapted the pathways based on our review of previous models developed for this population and expert opinion.

Our model structure is similar to that of the model developed for TA120.⁴³ The key events modelled were hospitalisation due to HF or arrhythmia, transplant, surgical failure, death, peri-operative complications of implant procedure, routine device replacements, lead displacement, infections, and device upgrades.

Figure 33 provides a general schematic of the health states patients can experience and the possible transitions from one health state to another. Patients being managed with OPT enter the model in the stable health state of the OPT sub-model, whereas patients undergoing management with a device enter in the implant surgery state and will typically transition to stable in the device sub-model.

Figure 33: General schematic of the model



Patients in a stable health state (either with OPT or with a device) can remain stable, be hospitalised due to heart failure or arrhythmia, or may die from a variety of causes. In addition patients in a stable health state with a device may experience device-related adverse events (infection or lead displacement/ failure) or may require maintenance/ replacement of their current device. Patients who are hospitalised due to heart failure may be referred for heart transplantation. Patients in any of the live health states (stable, hospitalised, and transplanted) can die from arrhythmia (SCD), heart failure, or any other cause (cardiac or non-cardiac). Transitions among health states vary according to the population group and the treatment received.

5.4.3.2 Relevant patient populations

The baseline cohorts modelled for the economic analyses consist of the three population groups who were identified in the scope⁶⁴ developed by NICE for this assessment:

1. Patients at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT;
2. Patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT;
3. Patients with both conditions.

Baseline characteristics (age, sex and, where relevant, proportion in NYHA class) for the modelled cohorts were based on values reported for relevant clinical trials providing data to populate the model.

5.4.3.3 Treatment options to be evaluated

The three population groups described above were scoped as eligible for OPT, ICD and/or CRT devices. Different treatment strategies were modelled accordingly. Table 92 below presents the relevant comparisons for each group, as per the scope⁶⁴ developed by NICE for this assessment. For patients at increased risk of SCD as a result of ventricular arrhythmias despite OPT (Population 1), two treatment arms were compared: ICD with OPT and initial management with OPT alone. People with heart failure as a result of LVSD and cardiac dyssynchrony despite OPT (Population 2) were modelled receiving OPT alone, or CRT-P or CRT-D alongside OPT. Patients with both conditions (Population 3) who were implanted with a CRT-D were compared with patients receiving OPT alone, CRT-P with OPT, and ICD with OPT. In each case, a proportion of people receiving OPT alone can be referred for and receive a device.

Table 92: Treatment strategies being compared for each population group

Population	Comparisons	
	<i>Intervention</i>	<i>Comparator</i>
Population 1	ICD + OPT	OPT
Population 2	CRT-P + OPT	OPT
	CRT-D + OPT	OPT
	CRT-P + OPT	CRT-D + OPT
Population 3	CRT-D + OPT	OPT
	CRT-D + OPT	CRT-P + OPT
	CRT-D + OPT	ICD + OPT

NB: OPT strategies correspond to having patients initially treated with OPT and subsequently receiving devices as clinically necessary.

5.4.3.4 Treatment pathways

Population 1: patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT

Receiving ICD + OPT

Patients enter this arm of the model undergoing ICD implantation surgery. Patients undergoing surgery experience a risk of procedure-related death. Those who survive surgery and have a successful implantation can become stable with the device or be hospitalised due to heart failure, perioperative complications (including mechanical failures as well as operative complications such as haematoma or pneumothorax), lead displacement, infection, or battery failure. Patients who experience unsuccessful implantations are referred for re-implantation and are subject to the same risks of surgical failure and any complications, such as surgical complications, infection, or lead displacement, as those who attempt implantation for the first time.

Stable ICD patients can be hospitalised due to heart failure, severe arrhythmia, lead displacement, infection, or battery failure. ICD patients who are hospitalised may continue to be hospitalised, return to the stable with ICD state after treatment, or may be referred for heart transplantation (if hospitalised for heart failure). Stable ICD patients are also subject to periodic battery replacement. As with initial implant surgery, and re-implantation, these routine replacement procedures expose the patient to risk of procedure-related death, perioperative complications and unsuccessful implantation.

Receiving OPT

In this arm, patients enter the model in a stable health state where they are treated with OPT in order to prevent major ventricular arrhythmia. Stable OPT patients can remain stable, be hospitalised due to heart failure, or be hospitalised due to major arrhythmia and therefore referred for ICD implantation. Hospitalised patients can return to the stable health state after treatment, be referred for ICD implantation (if hospitalised for major arrhythmia), or be referred for transplantation (if hospitalised for heart failure). Patients referred for ICD implantation are assumed to follow the same pathway described above for the cohort who enters the model receiving ICD + OPT and to be subject to the same risk of events.

Model assumptions for Population 1

Being an adaptation of the economic model developed by Fox and colleagues for TA120,⁴³ our model relies on some of the assumptions underlying Fox and colleagues' model that were validated by clinical advice:

- Patients being managed with OPT alone who experience hospitalisation due to non-fatal arrhythmia are assumed to be referred to and undergo ICD implantation
- Patients with OPT hospitalised due to HF who experience a serious arrhythmic event are assumed to be implanted with an ICD and become stable with the device or be hospitalised due to HF, perioperative complications, lead displacement, or infection, in the following cycle.

For modelling simplicity and given the exceptional nature of some events, some assumptions underlying our model were incorporated following clinical advice:

- Patients with lead displacements are assumed to have no risk of surgical failure as these interventions do not require a new device.
- Unsuccessful implantations are assumed to have re-implantation attempted in the following cycle.
- Patients undergoing re-implantation are assumed to be subject to the same risks of events as those who attempt implantation for the first time.
- The model assumes no risk of return to management with OPT alone due to unsuccessful ICD implantation.

Population 2: patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT

Receiving OPT

Patients enter the model in a stable health state being treated with OPT in order to prevent heart failure. Stable OPT patients may remain stable or be hospitalised due to heart failure or severe arrhythmia. OPT patients who are hospitalised may return to the stable health state with OPT after treatment, be referred for CRT-P implantation, CRT-D implantation, or transplantation. Patients referred for CRT devices follow a similar pathway to those described below for patients entering the model undergoing CRT-P or CRT-D implantation.

Receiving CRT-P + OPT

Patients with heart failure enter the model undergoing CRT-P implantation surgery. They may experience procedure-related mortality or survive the implantation procedure. Patients who survive the procedure may have successful or unsuccessful implantation. Patients with a successful CRT-P implantation may experience perioperative complications, lead displacement, infection, and hospitalisation due to heart failure or severe arrhythmia – those who do not experience any of these events transition to the stable state with CRT- P alongside OPT. Patients who have unsuccessful CRT-

P implantations may return to the OPT stable health state or may be hospitalised due to heart failure or due to severe arrhythmia, and then progress onwards according to the pathway described above for patients receiving OPT alone.

Stable CRT-P patients may be hospitalised if they experience heart failure, lead displacement, infection, or battery failure. CRT-P patients who are hospitalised may return to stable with CRT-P after treatment, remain hospitalised, be referred for upgrade to CRT-D if they experience serious arrhythmia, or be referred for a heart transplant if they experience worsening heart failure.

Receiving CRT-D + OPT

Patients with heart failure enter the model undergoing CRT-D implantation surgery. Similar to patients who enter the model with CRT-P implantation surgery (described above), those who receive a CRT-D may die from surgery or survive the implantation procedure. Patients who survive with a successful CRT-D implantation may experience perioperative complications, lead displacement, infection, and hospitalisation due to heart failure or severe arrhythmia – those who do not experience any of these events transition to the stable state with CRT-D alongside OPT.

Patients who survive unsuccessful CRT-D implantations are assumed to undergo ICD implantations. These patients may die from ICD implantation surgery. Those who survive ICD implantation and have a successful implantation can become stable with the device or be hospitalised due to heart failure or severe arrhythmia, perioperative complications, lead displacement, infection, or battery failure. Those with unsuccessful ICD implantations are assumed to be managed with OPT alone and follow the pathway described above for Population 2 receiving OPT.

Patients who are stable with CRT-D alongside OPT can be hospitalised if they experience heart failure or severe arrhythmia, lead displacement, infection, or battery failure. CRT-D patients who are hospitalised may return to stable with CRT-D after treatment, remain hospitalised, or be referred for a heart transplant if they experience worsening heart failure.

Model assumptions for Population 2

Some of the assumptions underlying our model for Population 2 derive from the adaptation of the economic model developed by Fox and colleagues for TA120⁴³ following clinical validation:

- Patients with CRT-P who experience a serious arrhythmic event are assumed to be referred to CRT-D implantation
- Patients who survive unsuccessful CRT-P implantation are assumed to return to being managed with OPT alone

- Patients who are hospitalised due to HF and are referred to a device upgrade are assumed to be implanted and become stable with the device or be hospitalised due to HF, perioperative complications, lead displacement, or infection, in the following cycle.

Other assumptions were incorporated according to clinical advice:

- Patients who survive unsuccessful CRT-D implantation are assumed to undergo ICD implantations.
- For consistency with unsuccessful CRT-P implantation, patients who survive unsuccessful ICD implantation are assumed to return to being managed with OPT alone

Population 3: patients with both conditions

For Population 3, four cohorts were modelled receiving initially CRT-D + OPT, CRT-P + OPT, ICD + OPT, or OPT alone. All these strategies allow for subsequent device implants and upgrades.

Receiving CRT-D + OPT

Patients with both conditions enter the model undergoing CRT-D implantation surgery, following a pathway similar to that described for Population 2 receiving CRT-D + OPT above. Patients who survive unsuccessful CRT-D implantations are also assumed to undergo ICD implantations. However, patients with ICD who become hospitalised due to heart failure are referred for CRT-D re-implantation.

Receiving CRT-P + OPT

Patients with both conditions enter this arm of the model undergoing CRT-P implantation surgery and experience a similar pathway to that of Population 2 receiving CRT-P + OPT described above.

Receiving ICD + OPT

Patients enter this arm of the model undergoing ICD implantation surgery. Those who survive with successful ICD implantations can become stable with the device or be hospitalised due to heart failure, serious arrhythmic event, perioperative complications, lead displacement, infection, or battery failure. Those hospitalised for HF are upgraded for a CRT-D implant. Those with unsuccessful ICD implantations are assumed to be managed with OPT alone and follow the pathway described below for Population 3 receiving OPT.

Receiving OPT

Patients with both conditions enter the model being managed with OPT alone. These patients may remain stable with OPT or be hospitalised due to heart failure or severe arrhythmia. Patients

hospitalised for HF may return to the stable health state with OPT after treatment, be referred for CRT-P implantation, CRT-D implantation, or transplantation. OPT patients who are hospitalised due to serious arrhythmia are referred to CRT-D implant. Patients referred for CRT devices follow a similar pathway to those described above for Population 3 patients entering the model receiving CRT-P + OPT or CRT-D + OPT.

Model assumptions for Population 3

Some assumptions underlying the model by Fox and colleagues for TA120⁴³ validated by clinical advice were used in our model:

- Patients being managed with OPT alone who experience a serious arrhythmic event are assumed to be referred for CRT-D implantation
- Patients with CRT-P who experience a serious arrhythmia are assumed to be referred for CRT-D implantation
- Patients with an ICD who are hospitalised due to HF are assumed to be referred to a CRT-D.
- Patients who are hospitalised due to HF and are referred to a device upgrade are assumed to be implanted and become stable with the device or be hospitalised due to HF, perioperative complications, lead displacement, or infection, in the following cycle.

Clinical experts confirmed the reasonability of other assumptions conveyed in our model:

- Patients who survive unsuccessful CRT-D implantation are assumed to undergo ICD implantations.
- For consistency with unsuccessful CRT-P implantation, patients who survive unsuccessful ICD implantation are assumed to return to being managed with OPT alone.

Pathways common to all populations

For each population modelled, patients being managed with devices can be in hospital due to perioperative complications, lead displacement, routine device replacements, or infection. The pathways subsequent to each of these events are common to all populations and described below.

a) Perioperative complications

Patients with perioperative complications can become stable with the device or continue hospitalised due to heart failure, lead displacement, battery failure, or infection.

b) Heart failure

Patients hospitalised due to heart failure can return to the stable state with the device, continue hospitalised due to heart failure, experience a device-related infection or a lead displacement, or be

referred to a transplant. Concerning populations 2 and 3 exclusively, patients with a CRT-P hospitalised due to HF can be referred for an upgrade to CRT-D if they experience a major arrhythmia or need a routine device replacement.

c) Lead displacement

Patients experiencing lead displacement will undergo re-surgery to replace the lead(s) and are assumed to be subject to the same risks of surgical death, surgical failure and any complications as those of an initial implantation.

d) Routine device replacements

Patients will undergo re-surgery to replace the device due to battery failure. Devices are assumed to work for a fixed period and all patients stable with the device at the end of that period are assumed to have a new device fitted.

e) Infection

In order to treat a device-related infection, patients will undergo explantation of the device, treatment for the infection, and re-implantation of a new device. These patients are assumed to have the same risks of surgical death, surgical failure and any complications as those of an initial implantation.

Model assumptions common to all populations

As the models developed for each population follow a similar structure, the following assumptions are common to all of them:

- Patients in any health state in the model can die.
- Patients in health states involving a surgical procedure can also die from surgery.
- The probability of death post-transplant is assumed to be lower than that for the non-transplanted patients, except in the first cycle.
- Only patients who are hospitalised due to heart failure are assumed to be at risk of heart transplant.
- Patients referred to transplantation are assumed to remain in this health state until they die.
- Patients hospitalised due to HF while being managed with OPT are assumed to have a null probability of remaining hospitalised due to HF the following cycle.
- Patients hospitalised due to perioperative complications are assumed to have no risk of surgical death or surgical failure.
- All patients undergoing surgery (due to initial implantation, re-attempt of implantation, routine device replacement, or infection) are assumed to have the same risk of surgical failure.

5.4.3.5 Discounting

In accordance with current NICE guidance,⁶⁹ future costs and benefits were discounted at a rate of 3.5%. The impact of discounting using 0% and 6% rates were explored in sensitivity analysis.

5.4.3.6 Presentation of results for the base case analyses

We report the findings on the cost effectiveness of interventions based on analysis of cohorts of patients having the age and sex characteristics discussed earlier. For Population 1 (people at increased risk of SCD as a result of ventricular arrhythmias despite OPT) comparisons for ICD+OPT are made against OPT. For Population 2 (people with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT) comparisons for CRT-P+OPT are made against OPT and comparisons for CRT-D+OPT are made against CRT-P+OPT and OPT. For Population 3 (people with both conditions) comparisons for CRT-D+OPT are made against OPT, ICD+OPT and CRT-P+OPT.

Base case results are reported in terms of estimated costs and QALYs accrued for each intervention, as well as incremental costs and QALYs gained for each comparison.

5.4.3.7 Assessment of uncertainty

Deterministic sensitivity analysis is used to address particular areas of uncertainty in the model related to model structure, methodological assumptions, and parameters around which there is considerable uncertainty or which may be expected, a priori, to have disproportionate impact on study results. The purpose of this analysis is to identify clearly the impact of this uncertainty and to test the robustness of the cost-effectiveness results to variation in structural assumptions and parameter inputs.

Parameter uncertainty is addressed using PSA.²¹¹ Probability distributions are assigned to the point estimates used in the base case analysis and values from these distributions are sampled during the probabilistic analysis. The derivation of point estimates for state transitions, costs and health state utilities are described in section 5.4.4. Appendix 15 reports the variables included in the probabilistic sensitivity analysis, the form of distribution used for sampling and the parameters of the distribution.

5.4.4 Data Sources and Parameter Estimates

5.4.4.1 Population 1 - patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT

Effectiveness Data

Mortality and relative risks

Survival estimates over time for use in the model were derived from data reported for the relevant trials included in our systematic review. Three trials with the longest reported follow-up (AVID,⁷³ MADIT II¹⁰³ and SCD-HeFT¹⁰⁷) were included in this analysis. According to the evidence found in Section 4.2, patients who survived cardiac arrest or sustained ventricular tachycardia are likely to be those for whom ICDs have consistently shown benefit. Being the largest trial found for this population, AVID⁷³ results were used for our base case analysis of patients at increased risk of SCD due to ventricular arrhythmia. MADIT II¹⁰³ was the trial with largest number of patients with remote myocardial infarction and was considered representative of a relevant group who might benefit from ICD for primary prevention of SCD. Similarly, results from the SCD-HeFT¹⁰⁷ were used to inform a subgroup analysis of patients with mild-moderate heart failure with indication for an ICD. An additional subgroup analysis was conducted for patients with cardiomyopathy using as baseline the all-cause mortality reported for the SCD-HeFT¹⁰⁷ subgroup of patients with non-ischaemic congestive heart failure in the placebo arm.

Kaplan-Meier curves for overall survival for the OPT arm (the control groups) of the relevant trials were used to derive the baseline mortality risk of patients receiving OPT in the Population 1 model. Parametric models were fitted to these curves to derive approximate hazard functions and those showing better goodness-of-fit were used to estimate survival beyond trial follow-up. Hence, baseline time-dependent transition probabilities to the all-cause death health state for the model OPT arm were calculated from the estimated hazard functions.²¹¹ For patients receiving ICD + OPT, death transition probabilities were estimated by applying the RRs estimated for ICD + OPT in our systematic review of clinical effectiveness (Section 4.2.2.1) to the baseline transition probabilities of the OPT arm.

Weibull approximations were fitted to the Kaplan-Meier curve for overall survival of patients from the AVID trial,⁷³ the MADIT II trial,¹⁰³ and the SCD-HeFT trial.¹⁰⁷ Details of the regression analyses and comparison between the regression results and the observed survival in these trials are shown in Appendix 16. The Weibull distribution is defined according to two parameters: the scale parameter (λ)

and the shape parameter (γ). These parameters were fitted using linear regression of transformations of the Kaplan-Meier estimates (see Appendix 16 for further details). To do this, scanned images of the Kaplan-Meier curves were imported in Engauge software (Engauge Digitizer - Digitizing software, <http://digitizer.sourceforge.net/>) and the extracted data points were then exported to Microsoft Excel for further analysis. Table 93 below shows the parameters of the Weibull functions used in the model to estimate time-dependent mortality for the OPT arm of Population 1 model.

Table 93. Weibull model parameters for all-cause mortality – Population 1

Parameter	Mean (SE)			
	AVID ⁷³ ($R^2 = 0.994$)	MADIT II ¹⁰³ ($R^2 = 0.9903$)	SCD-HeFT ¹⁰⁷ ($R^2 = 0.993$)	SCD-HeFT ¹⁰⁷ non- ischaemic CHF subgroup ($R^2 = 0.985$)
$\ln(\lambda)$	-3.380 (0.026)	-4.628 (0.047)	-5.288 (0.039)	-4.821 (0.037)
γ	0.696 (0.009)	1.007 (0.017)	1.083 (0.011)	0.883 (0.011)

Weibull model: $\ln(-\ln(S)) = \ln(\lambda) + \gamma \ln(t)$; $S(t) = \exp(-\lambda \cdot t^\gamma)$

The effect of ICD compared with OPT on all-cause mortality of patients at increased risk of SCD is captured in the model by the RRs reported in Section 4.2.2.1. For the base case analysis (secondary prevention of cardiac arrest), the pooled RR of 0.75 (95% CI 0.61, 0.93) was used. For the subgroup analysis of patients with remote MI, a pooled RR from MADIT I and MADIT II of 0.57 (95% CI 0.33, 0.97) was used. The SCD-HeFT¹⁰⁷ RR of 0.77 (95% CI 0.66, 0.89) was used for the subgroup of patients with mild to moderate heart failure, and a pooled RR of 0.74 (95% CI 0.58, 0.93) was used for patients with cardiomyopathy (derived from the SCD-Heft¹⁰⁷ non-ischaemic congestive heart failure subgroup and the three cardiomyopathy trials (AMIOVIRT,⁷¹ CAT,⁸⁴ DEFINITE⁹²)).

Hospitalisation

Hospitalisation due to Heart Failure

MADIT II is the only RCT included in our systematic review (Section 4.2.2) reporting heart failure hospitalisations for patients at increased risk of SCD. The number of admissions per total number of trial participants (221 out of 1232 patients in both OPT and ICD arms) is reported for a 20 months follow-up period. The model accounts therefore for a risk of hospitalisation for heart failure of 0.0082 (95% CI 0 to 0.0202) per cycle for patients at risk of SCD being managed with OPT or ICD, assuming that ICDs have no effect on heart failure hospitalisations.

Hospitalisation due to non-fatal arrhythmia

The number of hospitalisations due to non-fatal arrhythmia is not reported by the trials included in our systematic review for population 1 (Section 4.2.2), and the number of patients who experienced arrhythmic events that is reported by some of the included trials is small. Following clinical advice, in our model the baseline probability for a patient at increased risk of SCD managed with OPT to be hospitalised for a non-fatal arrhythmia is assumed to be the same as that of patients with heart failure (0.0075, 95% CI 0.0002, 0.0148), derived from the number of events in both OPT and CRT-P arms of the MIRACLE trial.¹²³ The sensitivity of the cost-effectiveness results to this assumption is explored in 5.4.5.1 with a scenario analysis using the risk of ventricular arrhythmia for Population 3 patients.

Device implantation after hospitalisation

Patients being managed with OPT who experience hospitalisation due to non-fatal arrhythmia are assumed to be referred for ICD implantation (estimation described above). Patients hospitalised due to HF while being managed with OPT alone are assumed to be subject to a probability of being referred for ICD implantation of 0.0018 (95% CI 0 to 0.0059), the same as that for Population 2 patients in the CARE-HF trial OPT arm who were referred for CRT-D implantation (see Section 5.4.4.2 below).

Adverse events

Adverse events occurring in patients being managed with ICDs were categorised into those occurring at time of implantation (or during the initial in-patient stay) and a set of longer term adverse events that could occur around time of implantation and during all subsequent cycles. The former set of adverse events include procedure-related mortality, surgical complications and implant failure while the latter include lead displacements, infections and device malfunctions and dislodgements. As noted in the systematic review (Sections 4.2.2.11, 4.3.2.13 and 4.4.2.14) reporting of individual adverse events in the included trials is limited.

Procedure-related death

Most trials of patients at increased risk of SCD where surgical death was included explicitly as an outcome (MADIT II, DEFINITE, DINAMIT, DEBUT) report the occurrence of no deaths related to the implantation procedure, with only CASH reporting 5/99 perioperative deaths. A pooled probability of 0.003 (95% CI 0, 0.055) was used for our base case analysis, based on 5 procedure-related deaths among 1449 patients.

Implant failure

Two trials included in our systematic review of clinical effectiveness report implant failure as an outcome of the ICD implantation procedure. This is taken to indicate a failure to achieve the required outcome, rather than mechanical failure of the device or failure/ dislodgements of leads (which are reported separately). The AVID trial reports unsuccessful initial implant in approximately 1% of patients (5/507) in the defibrillator arm of the trial, corresponding to a probability of implant failure of 0.0098 (95% CI 0, 0.0962). The SCD-HeFT trial reports a lower proportion of patients with unsuccessful implantation (1 out of 829 patients). However, it is not clear whether this was a failure of initial implantation or followed revision of the initial implant procedure. The systematic review of RCTs and observational studies by Ezekowitz and colleagues²¹² reports a probability of 0.011 (95% CI 0.009, 0.013) which was used in the model.

Complications

Given the inconsistent reporting of peri-operative and post-operative complications related to ICDs among the trials included in our systematic review (Sections 4.2.2.11 and 4.4.2.14), estimates from the systematic review of RCTs and observational studies by Ezekowitz and colleagues²¹² were used in the model. Table 94 below presents the probabilities used for each type of event.

Table 94. Peri- and post-operative complications with ICD

Event	Risk ^a	95% CI Lower Limit	95% CI Upper Limit
<i>Peri-operative complications</i>			
Mechanical complication	0.053	0.046	0.062
<i>Post-operative complications</i>			
Lead problems	0.0012	0.0010	0.0014
Infections	0.0005	0.0004	0.0006

^a Risk estimates for post-operative complications reported by Ezekowitz *et al.*,²¹² per 100 patient-years were converted to risk per 4-week cycle.

Epidemiological data

Distribution of patients by NYHA class

The distribution of patients at increased risk of SCD by NYHA class was sourced from the baseline distribution of participants in the trials selected for our base case and alternative patient group analyses – AVID for secondary prevention, and MADIT II and SCD-HeFT for primary prevention of SCD (Table 95).

Table 95. Distribution of the participants of AVID, MADIT II, and SCD-HeFT trials by NYHA class at baseline

NYHA class	AVID ⁷³		MADIT II ¹⁰³		SCD-HeFT ¹⁰⁷	
	AAD	ICD	OPT	ICD	OPT	ICD
No HF	45	40	0	0	0	0
I, %	48	48	39	35	0	0
II, %			34	35	70	70
III, %	7	12	23	25	30	30
IV, %			4	5	0	0

A summary of the clinical variables in the model are shown in Table 96.

Table 96: Key clinical parameters used in the model for population 1

Parameter type	Parameter	Source Estimate				Distribution
		Mean	SE	LL	UL	
All-cause mortality	LN(λ)	-3.381	0.0257	-3.431	-3.330	Normal
	γ	0.696	0.0092	0.678	0.714	Normal
	HR ICD	0.75	0.0816	0.61	0.93	Lognormal
All-cause mortality by age	HR 18-59	0.62	0.0459	0.54	0.72	Lognormal
	HR 75+	1.41	0.0051	1.40	1.42	Lognormal
Death due to surgery	DFS_ICD	0.0034	0.0262	0	0.0548	Normal
Probability of surgical death transplant	DFS_TRP	0.122	0.007	0.109	0.136	Normal
Event Probabilities (per cycle)						
Hospitalisation due to HF	OPT	0.0082	0.0061	0	0.0201	Beta
	RR ICD	1	0.1	0.804	1.196	Beta
Probability of transplant following HF hospitalisation	HF_TRP	0.0014	0.0025	0	0.0062	Beta
Non-fatal arrhythmia requiring hospitalisation	HA_OPT	0.0075	0.0037	0.00016	0.0148	Beta
	HA_ICD	0.0075	0.0037	0.00016	0.0148	Beta
Probability of surgical failure	SF_ICD	0.011	0.001	0.009	0.013	Beta
Device replacement interval	LN(λ)	-15.784	0.203	-16.182	-15.385	Normal
	γ	1.942	0.0273	1.889	1.996	Normal
Upgrade after HF hospitalisation	OPT to ICD	0.0018	0.002	0	0.0059	Beta

5.4.4.2 Population 2 - Patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT

Effectiveness Data

Mortality and relative risks

Following Fox and colleagues⁴³ approach, Population 2 model accounts for cardiac mortality (SCD and due to worsening HF) and for non-cardiac mortality.

Cardiac mortality

CARE-HF is the trial with longest follow-up period (mean 37.4 months) from those included in the clinical effectiveness review for people with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT. CARE-HF reports survival curves for SCD and death due to worsening HF; hence, baseline time-dependent probabilities of SCD and death due to HF were derived from CARE-HF survival curves in the control group.¹¹³ The methodology used to derive baseline mortality is described in Section 5.4.4.1 and further details can be found in Appendix 16. Weibull approximations were fitted to the Kaplan-Meier curves for SCD and death due to worsening HF of patients from the CARE-HF trial. The scale (λ) and the shape (γ) parameters that define the Weibull models used for estimation of SCD and HF deaths for the OPT arm are shown on Table 97 below. Time-dependent death probabilities for Population 2 patients receiving devices (CRT-P, CRT-D, or ICD) were then derived applying device-specific HR or RR to the baseline probabilities (OPT arm).

Table 97. Weibull model parameters for SCD and HF mortality – Population 2

Parameter	Mean	95% CI	
		Lower limit	Upper limit
Sudden cardiac death			
ln(λ)	-6.069	-6.173	-5.964
γ	1.140	1.107	1.173
Heart failure			
ln(λ)	-6.115	-6.256	-5.974
γ	1.223	1.179	1.266

Weibull model: $\ln(-\ln(S)) = \ln(\lambda) + \gamma \ln(t)$; $S(t) = \exp(-\lambda \cdot t^\gamma)$

The relative effect of CRT-P on HF deaths was obtained from the meta-analysis in section 4.3.2.3 (encompassing CARE-HF and COMPANION; RR=0.67; 95% CI 0.51 to 0.88). That for CRT-D patients was sourced from the COMPANION trial (HR=0.73, 95% CI 0.47 to 1.11). The estimate for the relative risk of SCD for CRT-P patients obtained in the meta-analysis in section 4.3.2.4 (pooled from CARE-HF, COMPANION and MUSTIC) is of 0.97 (95% CI 0.44 to 2.14). Given its wide 95%

CI, a RR of 1 was used in our economic model and this estimate was assumed to range between the mean estimates of RR reported in the most relevant trials (0.54 from CARE-HF and 1.13 from the COMPANION trial). The RR for CRT-D patients was sourced from the COMPANION trial (HR=0.44, 95% CI 0.23 to 0.86).

For Population 2 patients who were using an ICD due to CRT-D implant failure, the relative risks for SCD and death due to worsening heart failure were sourced from the SCD-HeFT trial.¹¹⁰ This was considered to be the most representative study from the systematic review of ICDs, as it included a broad population of patients with mild to moderate heart failure. A relative risk of 1.14 (95% CI 0.88 to 1.48) is reported for non-arrhythmic cardiac death (assumed to be that due to HF) and of 0.44 (95% CI 0.31 to 0.61) for SCD. Considering that Population 2 patients are expected to be at higher risk of death due to HF and lower risk of SCD than the SCD-HeFT participants (Population 1), these parameters were subject to sensitivity analysis in Section 5.4.5.2.

Non-cardiac mortality

Non-cardiac related death rates were derived from the 2010 Mortality Statistics for England and Wales of the Office for National Statistics.¹³ All deaths not allocated an ICD-10 code I00-I52 (for heart disease) were included. Table 98 below shows the non-cardiac death rates by age used in the model for Population 2. Gender proportions of UK patients with heart failure were estimated based on the 2011 statistics for incidence of heart failure by gender reported by the British Heart Foundation.²¹³

Table 98: Non-cardiac mortality by age and sex

Age group	Probability of non-cardiac death per cycle
	M/F
15–24	0.000027
25–34	0.000045
35–44	0.000088
45–54	0.000177
55–64	0.000449
65–74	0.001084
75–84	0.002896
85 and over	0.008566

Hospitalisation

Hospitalisation due to Heart Failure

The hospitalisation baseline risk estimate (0.037, 95% CI 0.025, 0.049) was pooled from the number of events reported for the OPT arm in the relevant trials included in the systematic review of clinical effectiveness – CARE-HF¹¹¹ (252/404 events in 29.4 months), MIRACLE¹²³ (50/225 patients in 6 months), MUSTIC¹²⁷ (9/29 events in 3 months), and COMPANION¹¹⁸ (235/308 events in 11.9 months).

The relative risk of hospitalisation due to heart failure for patients with a CRT-P compared with those on OPT was estimated to be 0.58 (95% CI 0.35 to 0.96) pooling risks from CARE-HF, COMPANION, MIRACLE, and MUSTIC as described in Section 4.3.2 of this report. The COMPANION trial reports a relative risk of 0.77 (95% CI 0.63 to 0.93, p=0.008) for patients with CRT-D versus those on OPT. As per Fox and colleagues⁴³, the risk of hospitalisation due to heart failure for patients with ICD was assumed to be the same as for patients on OPT (RR= 1).

Hospitalisation due to non-fatal arrhythmia

Fox and colleagues⁴³ report using the number of severe arrhythmic events reported in the MIRACLE trial (26/532 participants) to estimate the risk of hospitalisation for non-fatal arrhythmic events. Considering the 6-month follow-up of the trial, this corresponds to a rate of 0.0977 events per patient-year and a 0.0075 (95% CI 0.0002, 0.0148) probability of experiencing an arrhythmic event per cycle. This probability was assumed to be the same for patients being managed with OPT and for patients with CRT-P. Given the lack of evidence on hospitalisation due to arrhythmia for Population 2 patients with a CRT-D or an ICD, these patients have been assumed to be at the same risk as those being managed with CRT-P or OPT alone.

Device-related adverse events

Adverse events occurring in patients being managed with CRT were categorised in a similar mode to those occurring with ICD, i.e. into those occurring at time of implantation or initial in-patients stay (procedure-related deaths, implant failures, and perioperative complications) and into longer term adverse events (lead displacements, infections, and device malfunctions).

Procedure-related death

The probability of death related to the surgical procedure for CRT implant was derived from the number of events reported in the trials included in our systematic review of clinical effectiveness. CARE-HF¹¹¹ reported 1 death in 409 patients, MIRACLE¹²³ 1 in 571 patients, MUSTIC¹²⁷ 1 in 64 patients, and COMPANION¹¹⁸ 5 in 617 patients randomised to the CRT-P arm. A probability of 0.048 (95% CI 0.0015 to 0.0081) per cycle is therefore considered in the model for CRT-P. The

COMPANION¹¹⁸ trial also reports 3 procedure-related deaths out of 595 patients in the CRT-D arm, which corresponds to a probability of 0.005 (95% CI 0 to 0.0107) per cycle.

Implant failure

The probability of implant failure for patients who attempt CRT implantation was derived from the relevant trials included in the systematic review. A pooled probability for implant failure of 0.084 (95% CI 0.070, 0.097) per cycle was estimated for patients with CRT-P from four trials - CARE-HF¹¹¹ (19/409), MIRACLE¹²³ (43/571), MUSTIC¹²⁷ (5/64), and COMPANION¹¹⁸ (78/617). COMPANION¹¹⁸ reports 54 implant failures in 595 patients with CRT-D, thus a probability of implant failure of 0.087 (95% CI 0.064 to 0.109) per cycle is used in the model for CRT-D.

Peri-operative complications

Given the limited and heterogeneous reporting of surgical complications related to CRT implantation among the trials included in our systematic review (Section 4.3.2.13), the probability of patients having an operative complication of a CRT implant was sourced from Fox and colleagues⁴³ who report a pooled risk of complications from CARE-HF, MIRACLE, MUSTIC, CONTAK-CD and both CRT arms of the COMPANION trial. The probability of 0.1063 (SE=mean/10) was used for both CRT-P and CRT-D.

Lead displacement

Three trials included in the systematic review of clinical effectiveness reported the number of lead-related complications that occurred with CRT-P during their follow-up periods - CARE-HF¹¹¹(24/409), MIRACLE¹²³(30/571) and MUSTIC¹²⁷ (8/58). These were used to estimate a pooled risk of 0.0037 (95% CI 0.0004 to 0.0071) used in our model for patients being managed with CRT-P or CRT-D.

Infection

The probability of device-related infections in patients being managed with CRT-P of 0.0006 (0 to 0.002) was derived from the relevant trials included in the systematic review of clinical effectiveness that explicitly reported this outcome – CARE-HF¹¹¹ (3/409 in 29.4 months) and MIRACLE¹²³(7/528 in 6 months). For CRT-D, the probability of infection of 0.0006 (0 to 0.0015) was derived similarly using the events reported for CONTAK-CD¹²⁸(7/517 in 6 months), RETHINQ¹⁴³ (6/172 in 6 months), RHYTHM ICD¹⁴⁵ (4/205 in 15.1 months), MADIT-CRT¹³² (12/1089 in 28.8 months), and RAFT¹⁴¹ (21/888 in 40 months).

Device upgrade after hospitalisation

Following hospitalisation, patients being managed with OPT can be referred to CRT-P or CRT-D implantation, whereas patients being managed with CRT-P can be referred to CRT-D. The probabilities of device upgrade after hospitalisation were derived from the CARE-HF trial,¹¹³ assuming that the upgrades reported occurred after hospitalisation due to heart failure. For the OPT arm (N=404), CARE-HF¹¹³ reports 43 upgrades to CRT-P and 23 for CRT-D in 29.4 months of follow-up of the trial, whereas in the CRT-P arm (N=409) 8 patients upgraded to a CRT-D. This corresponds to a 0.0033 (95% CI 0 to 0.009) probability of upgrading from OPT to CRT-P, 0.0018 (95% CI 0 to 0.0059) from OPT to CRT-D, and 0.0006 (95% CI 0 to 0.003) from CRT-P to CRT-D.

Clinical advice indicated that patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT would upgrade to ICD only in case of failure to implant CRT-D, which can be estimated by multiplying the probability of upgrading from OPT to CRT-D (0.001, 95% CI 0, 0.003) by the probability of CRT-D implant failure (0.087, 95% CI 0.064, 0.109).

For Population 2 patients who end up receiving an ICD, our model considers the same data for ICD-related adverse events reported in Section 5.4.4.1.

Epidemiological data

Distribution of patients per NYHA class

The distribution of heart failure patients by NYHA class used is the same as that for the previous model (see Table 99 below) by Fox and colleagues⁴³ who derived the distribution of patients per NYHA class at baseline and 90 days from the CARE-HF trial¹¹¹ and the conference proceedings of the BRESCIA study by Curnis and colleagues (2003).²¹⁴

Table 99: Distribution of patients by NYHA class

OPT	Mean	Lower limit	Upper limit
Proportion at baseline			
NYHA III ^a	93.8%	75.42%	100.00%
NYHA IV ^b	6.2%	4.98%	7.42%
Proportion at 90 days			
NYHA I ^a	10.1%	8.12%	12.08%
NYHA II ^a	29.9%	24.04%	35.76%
NYHA III	54.8%	44.06%	65.54%
NYHA IV	5.2%	4.18%	6.22%
Proportion at 18 months			
NYHA I ^c	12.7%	10.21%	15.19%
NYHA II ^a	37.3%	29.99%	44.61%
NYHA III	45.7%	36.74%	54.66%
NYHA IV	4.3%	3.46%	5.14%
CRT/ICD^d			
Proportion at baseline ^e			
NYHA III	93.8%	75.42%	100.00%
NYHA IV	6.2%	4.98%	7.42%
Proportion at 90 days			
NYHA I ^a	29.5%	23.72%	35.28%
NYHA II ^a	41.5%	33.37%	49.63%
NYHA III	27.2%	21.87%	32.53%
NYHA IV	1.8%	1.45%	2.15%
Proportion at 18 months			
NYHA I ^c	31.5%	25.33%	37.67%
NYHA II	44.4%	35.70%	53.10%
NYHA III	22.5%	18.09%	26.91%
NYHA IV	1.5%	1.21%	1.79%

Source: CARE-HF trial.¹¹¹ ^a Lower and upper limits were derived assuming SE=mean/10.

^b Assumed to be equal to 1 minus the proportion of patients NYHA III. ^c Curnis *et al.*, 2003²¹⁴ Conference proceeding. ^d Assumed the same for any device type – CRT-P, CRT-D, and ICD.

^e Assumed the same as for OPT.

A summary of the clinical variables in the model for population 2 is shown in Table 100.

Table 100: Key clinical parameters used in the SHTAC model for population 2

	Parameter	Source Estimate				Distribution
		Mean	SE	LL	UL	
Death due to HF(HDTH) OPT 65-74	LN(λ)	-6.115	0.070	-6.253	-5.977	Normal
	γ	1.223	0.022	1.180	1.265	Normal
	HR CRT-P	0.67	0.094	0.51	0.88	Lognormal
	HR CRT-D	0.73	0.163	0.47	1.11	Lognormal
	HR ICD	1.14	0.153	0.88	1.48	Lognormal
Post-transplant mortality	RR TRP	0.35	0.035	0.281	0.419	Lognormal
Death due to SCD	LN(λ)	-6.069	0.053	-6.173	-5.964	Normal
	γ	1.140	0.017	1.107	1.173	Normal
	HR CRT-P	1.00	0.1505	0.54	1.13	Lognormal
	HR CRT-D	0.44	0.1607	0.23	0.86	Lognormal
	HR ICD	0.44	0.0765	0.31	0.61	Lognormal
All cause mortality RR by age	18-64	0.62	0.05	0.54	0.72	Lognormal
	75+	1.41	0.01	1.4	1.42	Lognormal
Event Probabilities (per cycle)						
Surgical mortality	ICD	0.003	0.026	0.000	0.055	Beta
	CRT-P	0.005	0.002	0.001	0.008	
	CRT-D	0.005	0.003	0.000	0.011	
	TRP	0.122	0.007	0.109	0.136	
Hospitalisation due to HF	OPT	0.037	0.006	0.025	0.049	Beta
	RR ICD	1	0.1	0.804	1.196	
	RR CRT-P	0.58	0.1556	0.35	0.96	
	RR CRT-D	0.77	0.0765	0.63	0.93	
Transplant following HF hospitalisation	TRP	0.001	0.002	0	0.006	Beta
Non-fatal arrhythmia requiring hospitalisation	OPT	0.007	0.004	0.000	0.015	Beta
	ICD	0.007	0.004	0.000	0.015	
	CRT-P	0.007	0.004	0.000	0.015	
	CRT-D	0.007	0.004	0.000	0.015	
Probability of Upgrade after HF hospitalisation	OPT to ICD	0	0	0	0	Beta
	OPT to CRT-P	0.003	0.003	0.000	0.009	
	OPT to CRT-D	0.002	0.002	0.000	0.006	
	CRT-P to CRT-D	0.001	0.001	0.000	0.003	
Surgical failure	ICD	0.011	0.001	0.009	0.013	Beta
	CRT-P	0.084	0.007	0.070	0.097	
	CRT-D	0.087	0.012	0.064	0.109	

5.4.4.3 Population 3 - Patients with both conditions

Effectiveness Data

Mortality and relative risks

Estimates of survival over time were derived from Kaplan-Meier curves reported for relevant trials included in the systematic review. The two largest trials reporting the longest follow-up and comparing events between groups statistically (MADIT-CRT¹³² and RAFT¹⁴¹) were included in this analysis. As reported in Section 4.4.1, length of follow-up was an average of 28.8 months in MADIT-CRT¹³² and 40 months in RAFT.¹⁴¹ Survival estimates from the trial with longest follow-up (RAFT) were used for the base case analysis and those from MADIT-CRT were used in scenario analysis.

Both trials report Kaplan-Meier curves for all-cause mortality for CRT-D + OPT and ICD + OPT. As CRT-D + OPT was the intervention scoped by NICE for Population 3,⁶⁴ we used its mortality estimates as baseline for this population and used HR and RR to derive all-cause mortality for patients receiving OPT alone, ICD + OPT, or CRT-P + OPT.

The methodology used to derive baseline mortality is similar to that described for Populations 1 and 2 (Sections 5.4.4.1 and 5.4.4.2) and further details can be found in Appendix 16. Table 101 presents the parameters of the Weibull models obtained using data from RAFT and MADIT-CRT.^{132;141}

Table 101. Weibull model parameters for all-cause mortality – Population 3

Parameter	Mean	95% CI	
		Lower limit	Upper limit
<i>RAFT</i>			
ICD-CRT arm ($R^2 = 0.9894$)			
$\ln(\lambda)$	-6.334	-6.467	-6.202
γ	1.243	1.20	1.27
<i>MADIT – CRT</i>			
Men CRT-D arm ($R^2 = 0.989$)			
$\ln(\lambda)$	-6.935	-7.005	-6.865
γ	1.287	1.266	1.308

Relative risk for ICD

The risk of all-cause mortality for patients with ICD relative to those with CRT-D was derived from the pooled risk ratio estimated in Section 4.4.2.1 for CRT-D *versus* ICD of 0.84 (95% CI 0.73 to

0.96). A relative risk of 1.19 (95% CI 1.04, 1.37) for ICD *versus* CRT-D was used to estimate all-cause mortality in the ICD arm.

Relative risk for OPT

In the systematic review of clinical effectiveness studies of people with both conditions, only RCTs concerning the comparison of CRT-D and ICD were found. However, the COMPANION trial reports the hazard ratio for all-cause mortality for patients with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony, from which we derived the hazard ratio for OPT *versus* CRT-D of 1.56 (95% CI 1.16, 2.08), assuming that the same relative effect would be expected in population 3.

Relative risk for CRT-P

Given the lack of RCTs in people with both conditions directly comparing CRT-P with CRT-D or assessing interventions other than CRT-D or ICD, we used the evidence available on the clinical effectiveness of CRT-P and CRT-D in patients with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony. The only trial comparing CRT-P with CRT-D was the COMPANION trial. A non-statistically significant relative risk for all-cause mortality of 1.20 (95% CI 0.96 to 1.52) was reported for CRT-P *versus* CRT-D. However, the COMPANION trial was not powered for this comparison. Considering the inexistence of robust evidence on this comparison, the risk of all-cause mortality for patients with CRT-P was assumed to be the same as for those with CRT-D (RR =1). This assumption was subject to sensitivity analysis in Section 5.4.5.3 by varying the parameter between the assigned upper and lower limits (0.80 to 1.20).

Hospitalisation due to heart Failure

The trials included in the systematic review of clinical effectiveness (see Section 4.4.2.7) do not report the number of hospitalisations due to heart failure. Instead, CONTAK-CD,¹²⁸ Piccirillo,¹³⁹ and RAFT¹⁴¹ report the number of patients with CRT-D hospitalised for heart failure (at least once during the trial). In 6 months of follow-up, CONTAK-CD¹²⁸ reported 32 of 245 patients in the CRT-D arm were hospitalised, Piccirillo¹³⁹ reported none of 16 patients followed for 12 months, and RAFT¹⁴¹ reported 174 of 894 patients in the CRT-D arm were hospitalised during the 40 months follow up of the trial. The number of patients experiencing at least one hospitalisation during the follow-up period of the trials provides a minimum number of hospitalisations from which we derived a baseline risk of hospitalisation due to heart failure (0.0077, 95% CI 0.0027 to 0.0128). Given that our model is likely to be underestimating the total number of hospitalisations, and consequently the resource use involved, the probability of hospitalisation due to heart failure was subject to sensitivity analysis in Section 5.4.5.

The relative risk for hospitalisation due to heart failure of patients with ICD compared to those with CRT-D was estimated to be 1.33 (95% CI 1.14 to 1.56) as the reverse of the risk ratio of 0.75 (95% CI 0.64 to 0.88) obtained in Section 4.4.2.7 by pooling risks from CONTAK-CD¹²⁸, Piccirillo¹³⁹, and RAFT.¹⁴¹

The COMPANION trial¹¹⁸ reports no significant differences in hospitalisations due to heart failure between CRT-P and CRT-D for patients with heart failure (see Section 4.3.2.6). Hence, assuming that no significant differences would be expected either in patients with both conditions (at risk of SCD due to ventricular arrhythmia and with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony), the risk of hospitalisation due to heart failure estimated for CRT-D (0.0077) was used for CRT-P (RR=1).

Evidence on the relative risk of hospitalisation for heart failure in patients on OPT compared to CRT-D was only found for patients with heart failure (Population 2). The COMPANION trial¹¹⁸ reported a statistically significant difference in heart failure hospital admissions per patient between CRT-D and OPT arms (0.43 vs 0.73 admissions per patient year, respectively). The relative risk estimated for hospitalisations due to heart failure with OPT versus CRT-D was 1.67 (95% CI 1.51 to 1.86, $p < 0.00001$).

Hospitalisation due to non-fatal arrhythmia

The baseline risk of hospitalisation for arrhythmia used in the model (0.029, 95% CI 0.015 to 0.042) was derived from trials included in the systematic review of clinical effectiveness (Section 4.4.2) reporting the number of patients with CRT-D experiencing at least one episode of ventricular fibrillation: MIRACLE ICD¹³⁷(42/187), MICACLE ICD II¹³⁸ (19/85), CONTAK-CD¹²⁸ (36/245), and Pinter¹⁴⁰(7/36). Similar to the estimation of hospitalisations for heart failure, our model is likely to be underestimating the total number of hospitalisations for arrhythmic events which was therefore subject to sensitivity analysis in section 5.4.5.

The meta-analysis (see section 4.4.2) found a non-statistically significant difference between CRT-D and ICD in the number of patients experiencing at least one arrhythmic event (RR 0.90, 95% CI 0.71 to 1.14, $p=0.38$). Hence, the inverse relative risk of 1.11 (95% CI 0.88 to 1.41) for ICD compared with CRT-D was used in the model.

No evidence to derive a measure of relative effect was found for hospitalisation for arrhythmia comparing CRT-P or OPT with CRT-D. The COMPANION trial states that hospitalisations due to other cardiac causes were not significantly different between OPT and CRT groups. Therefore, our

model assumes that the risk for hospitalisation due to arrhythmia for patients managed with OPT alone or CRT-P is the same as that of patients with CRT-D (RR = 1).

Device-related adverse events

Given the inconsistent reporting and lack of clear definitions of device-related adverse events reported in the relevant trials included in the systematic review of clinical effectiveness for people with both conditions (Population 3), our model assumes the same risks for Population 3 as those for Population 2 (people with heart failure).

Epidemiological data

Distribution of patients per NYHA class

RAFT¹⁴¹ reported the number of patients by NYHA class at baseline (shown in Table 102 below). No evidence on the effect of the devices on heart failure progression was found; hence the model assumes no effect on patients distribution by NYHA class. An alternative scenario was created to explore the impact of accounting for the potential benefit of CRT devices for Population 3, assuming that 50% of patients with a CRT device improve 1 NYHA class at 6 months of treatment (Section 5.4.5.3).

Table 102: Distribution of patients per NYHA class

NYHA class	Proportion at baseline, n (%)	
	ICD (N=904)	CRT-D (N=894)
II	730 (80.8)	708 (79.2)
III	174 (19.2)	186 (20.8)

Source: RAFT trial.¹⁴¹

A summary of the clinical variables in the model for population 3 are shown in Table 103.

Table 103: Key clinical parameters used in the SHTAC model for population 3

	Parameter	Source Estimate				Distribution
		Mean	SE	LL	UL	
All-cause mortality Baseline - CRT-D	LN(λ)	-6.334	0.068	-6.467	-6.202	Normal
	γ	1.234	0.018	1.199	1.270	Normal
	HR CRT-P	1	0.100	0.804	1.196	Log-normal
	HR ICD	1.190	0.084	1.042	1.370	Log-normal
	HR OPT	1.563	0.235	1.163	2.083	Log-normal
All cause mortality RR by age	18-64	0.621	0.046	0.54	0.72	Log-normal
	75+	1.410	0.005	1.4	1.42	
Event Probabilities	CRT- D	0.008	0.003	0.003	0.013	Beta
Hospitalisation due to HF	RR ICD	1.333	0.133	1.136	1.563	Log-normal
	RR CRT-P	1	0.1000	0.804	1.196	
	RR OPT	1.67	0.0893	1.51	1.86	
Non-fatal arrhythmia requiring hospitalisation	CRT- D	0.029	0.007	0.015	0.042	Log-normal
	ICD RR	1.111	0.111	0.880	1.410	
	CRT-P RR	1	0.1	0.804	1.196	
	OPT RR	1	0.1	0.804	1.196	
Probability of Upgrade after HF hospitalisation	OPT to ICD	0.002	0.002	0	0.006	Beta
	OPT to CRT-P	0.003	0.003	0	0.009	
	OPT to CRT-D	0.002	0.002	0	0.006	
	CRT-P to CRT-D	0.001	0.001	0	0.003	
	ICD to CRT-D	0.007	0.003	0.001	0.013	
Surgical mortality	ICD	0.003	0.026	0	0.055	Beta
	CRT-P	0.005	0.002	0.001	0.008	
	CRT-D	0.005	0.003	0	0.011	
Surgical failure	ICD	0.011	0.001	0.009	0.013	Beta
	CRT-P	0.084	0.007	0.070	0.097	
	CRT-D	0.087	0.012	0.064	0.109	
Device lifetime	ICD	-15.784	0.203	-16.182	-15.385	Normal
		1.943	0.027	1.889	1.996	
	CRT-P	-14.222	0.242	-14.697	-13.747	
		1.677	0.032	1.613	1.740	
	CRT-D	-15.465	0.273	-16	-14.931	
		1.935	0.036	1.863	2.006	

5.4.4.4 Parameters common to all populations

Age-related mortality

The variation of death risk according to age was incorporated in our model using the same estimates as those used by Fox and colleagues for the previous TA120,⁴³ who derived the relative risk of death from the publication by Shahar and colleagues.²¹⁵ The relative risk of death for patients under 65 years is 0.62 (95% CI 0.54 to 0.72) compared to patients aged 65 to 74. For those aged 75 or older the relative risk is 1.41 (95% CI 1.40 to 1.42).

Distribution of patients eligible for ICD and CRT implantation by age

The distribution of heart device implants by age was derived from a report commissioned by the British Cardiovascular Society, the British Heart Foundation and the Cardio & Vascular Coalition on the access to cardiac care in the UK, including ICDs and CRTs.²¹⁶ Table 104 shows the derivations of the estimated proportion of implanted devices for each age group.

Table 104. Heart device implantation by age in the UK population

Age group	ICDs	CRTs	ICDs / CRTs
0-34	5.9%	1.5%	3.8%
35-44	6.4%	2.4%	4.5%
45-54	13.0%	9.7%	11.4%
55-64	22.6%	21.7%	22.1%
65-74	30.9%	36.7%	33.7%
75-84	19.8%	25.3%	22.5%
85+	1.4%	2.7%	2.0%
Total	100.0%	100.0%	100.0%

The distribution of patients with ICD implants was deemed to be a good proxy for Population 1 patients at increased risk of SCD, whereas the distribution of CRT implants was used for Population 2 patients with heart failure. For Population 3 with both conditions, the distribution of both ICD and CRT devices implants was input in the model.

Heart Transplant

Procedure-related mortality

The model takes into account that patients subject to heart transplant have a procedure-related risk of death of 12.2% (95% CI 10.9% to 13.6%), the 30-day mortality rate estimated by the UK Cardiothoracic Transplant Audit²¹⁷ from data of all patients transplanted between 1995 and 2011.

Post-transplant mortality

The risk of death post-transplantation was incorporated using the estimate derived by Fox and colleagues.⁴³ The relative risk of death from all causes for patients who had a heart transplant (0.35) was derived from the median survival estimates reported by Hussey and colleagues²¹⁸ for UK patients with heart transplant (10.6 years) compared to patients on OPT (3.7 years).

Transplant following hospitalisation due to heart failure

Abraham and colleagues¹²³ report 2 heart transplants in 532 participants from the MIRACLE trial. As Fox and colleagues⁴³, for population 2 we assumed that these patients were referred to transplantation after hospitalisation due to heart failure, estimating a 0.0014 (95% CI 0 to 0.0062) probability of transplantation per cycle for patients hospitalised for heart failure.

Given the paucity of data regarding the number of transplants after hospitalisation for heart failure in the trials for populations 1 and 3, our model assumes the same risk as that of patients with heart failure (Population 2).

Health-related quality of life

Utility values for the several health states modelled were used to estimate the benefit of each intervention in terms of quality-adjusted life years (QALYs). Overall, the HRQoL of patients in stable health states was modelled to vary according to their NYHA class. A specific utility value was used for hospitalisation and decrements were applied to health states involving surgery (including initial device implantation, device-related complications and device replacement) or infection.

Utilities by NYHA class

The utility values by NYHA class used in the model (see Table 105 below) were found in one study (Gohler and colleagues²⁰⁸) included in the systematic review of health-related quality of life studies (Section 5.2) that reported utility values for all NYHA classes.

Hospitalisation and heart transplant

One observational analysis within the UK (HeartMed RCT by Holland and colleagues²⁰⁹) was also found in the systematic review. Holland and colleagues²⁰⁹ reported utility estimates per NYHA class at baseline in patients with heart failure following emergency hospital admission, estimating an average score of 0.57. This utility value is similar to that estimated by McAllister and colleagues²¹⁹ as used in Fox and colleagues⁴³ model. Our model also assumed that the proportion of time hospitalised was on average a quarter of the month.

As in Fox and colleagues' model,⁴³ utility estimates for transplantation were assumed to be similar to those for hospitalised patients and post-transplanted patients were assumed to have similar HRQoL as NYHA class I patients.

Surgery and infection

None of the studies found in the systematic review reported the impact of surgery or infection on the quality of life of patients eligible for ICD or CRT. As per Fox and colleagues,⁴³ decrements of 0.05 for the impact of surgery and of 0.1 for infection were assumed.

HRQoL associated with ICD

One study (Buxton and colleagues⁴²) reporting utilities for UK patients at increased risk of SCD due to ventricular arrhythmia was found in the systematic review of HRQoL studies (Section 5.2). Buxton and colleagues⁴² concluded that there was no evidence that self-reported HRQoL changes substantially over time. Therefore, we assumed the NYHA class of modelled patients was constant over the modelled time horizon. The distribution of patients by NYHA class reported at baseline in the relevant trials for Population 1 were used in our model in combination with utility values by NYHA class by Gohler and colleagues²⁰⁸ (see Table 105 below) to estimate a NYHA-class weighted average utility value.

HRQoL associated with CRT

For Population 2, the impact of CRT on the HRQoL of patients with heart failure over time was captured in the model by changes in the distribution of patients with heart failure by NYHA class derived from the relevant trials (see 'Distribution of patients per NYHA class' on Section 5.4.4.2). Given that evidence of the impact on the distribution of patients by NYHA class was available only for Population 2 patients with CRT-P or OPT alone, the model assumed the same effect for any CRT device and ICDs were assumed to have the same impact as OPT alone.

For Population 3, robust evidence of the effect of devices on heart failure progression was not found; hence CRT and ICD devices were assumed to have no impact on the distribution of patients by NYHA class over time (i.e. this distribution was assumed constant). The distribution of patients by NYHA class reported in the relevant trials for the CRT-D and ICD arms at baseline (see Section 5.4.4.3) was applied to patients receiving CRT-P and OPT alone, respectively, in the model. As both arms of the trial show a similar distribution (approximately 80% and 20% of NYHA class II and III, respectively), the model assumes similar utility values for patients with CRT, ICD, or OPT alone (e.g. 0.75 for patients who are stable with therapy). Therefore, this base case approach might be underestimating the benefit of CRT devices in the HRQoL of Population 3. To estimate the impact of accounting for this potential benefit of CRT devices on the cost-effectiveness results for Population 3, an alternative approach was adopted for scenario analysis (Section 5.4.5.3) assuming that 50% of patients with a CRT device improve 1 NYHA class at 6 months of treatment.

Utility values by NYHA class from Gohler and colleagues²⁰⁸ (Table 105 below) were then used to estimate NYHA-class weighted average utility values for patients for all populations. Table 105 below summarises the utility values used in our model and their sources.

Table 105: Utilities for patients with heart failure

Health state	NYHA class	Utility value (95% CI)	Source
Stable	NYHA I	0.855 (0.845, 0.864)	Gohler et al ²⁰⁸
	NYHA II	0.771 (0.761, 0.781)	
	NYHA III	0.673 (0.727, 0.765)	
	NYHA IV	0.532 (0.48, 0.584)	
Hospitalisation and Heart transplantation		0.57	Holland et al ²⁰⁹
Decrement due to surgery		0.05	Assumption ⁴³
Decrement due to infection		0.1	Assumption ⁴³

Resource use and costs

Resource use and cost estimation aimed at costing all relevant resources consumed in the care of patients of the three populations being studied. Similar to the previous model for assessment of CRT devices,⁴³ the resources considered in the current model include medication, resources involved in device implantation, device-related complications and maintenance, hospitalisation due to heart failure or severe arrhythmia, and heart transplantation.

The economic model estimates resource use associated with each intervention based on event rates and patient transition probabilities among the different health states. Unit costs associated with each resource used are then applied for estimation of total cost per intervention.

Device costs

The device-related costs used in the economic model (Table 106) correspond to the estimates provided in the ABHI submission. These were derived from average selling prices aggregated across all manufacturers for ICD, CRT-P and CRT-D devices, and for leads sold in the UK to the NHS.

Table 106: Device costs

Device component	Mean cost (£)	Lower value (£)	Upper value (£)
<i>Whole system</i>			
CRT-P	3,411	2,742	4,080
CRT-D	12,293	9,884	14,702
ICD	9,692	7,792	11,592
<i>Leads^a</i>			
CRT-P	811	652	970
CRT-D	541	435	647
ICD	543	437	649
<i>Battery</i>			
CRT-P	2,600	2,090	3,110
CRT-D	11,752	9,449	14,055
ICD	9,149	7,356	10,942

Source: ABHI submission. Lower and upper values were estimated assuming a $SE = \text{mean}/10$. ^a Leads costs were estimated from the difference between the whole system costs and the generator unit costs.

Estimates of device longevity were also sourced from the ABHI joint manufacturers' submission that reports the Kaplan-Meier plots of time to device replacement derived from data submitted to the Central Cardiac Audit Database (CCAD). Estimates of mean time to replacement were derived from the reported survival functions for use in the model. Table 107 presents the parameters of the Weibull approximations obtained for each device type and the respective mean lifetimes. Clinical advice indicated that devices' longevity might be overestimated; hence these parameters were subject to sensitivity analysis in Section 5.4.5 and a scenario of shorter device longevity was explored in Section 5.4.5.2.

Table 107: Mean device lifetime

Parameter	Mean	95% CI	
		Lower limit	Upper limit
<i>ICD</i>			
ln(λ)	-15.784	-16.182	-15.385
γ	1.943	1.889	1.996
Device longevity (years)	8.20	12.76	5.40
<i>CRT-P</i>			
ln(λ)	-14.222	-13.747	-14.697
γ	1.677	1.613	1.74
Device longevity (years)	11.81	22.22	6.58
<i>CRT-D</i>			
ln(λ)	-15.465	-16.000	-14.931
γ	1.935	1.863	2.006
Device longevity (years)	7.19	13.05	4.14

Source: ABHI submission. Mean replacement frequency calculated as $(1/\lambda)^{(1/\gamma)} \times \Gamma(1+(1/\gamma))$ where Γ is the mathematical gamma function (see Tappenden *et al.*,²²⁰).

Procedure-related costs

Costs associated with device implantation, complications or maintenance were sourced from the 2012/13 UK NHS Tariff,²²¹ whereas the costs of hospitalisations and transplantation were derived from the 2010/11 NHS Schedule of Reference Costs (NHS Trusts and PCTs combined HRG Data).²²²

Table 108 presents the procedure costs used in the economic model. Only elective care estimates were used to derive the mean cost of device-related procedures. For HRGs concerning non-device related procedures, the mean cost was estimated as a weighted average of the National Average Unit Costs reported for elective and long stay non-elective care. Lower and upper values of all procedure costs were derived from the 2010/11 NHS Schedule of Reference Costs²²² as a weighted average of the Lower and Upper Quartile Unit Costs reported for elective and long-stay non-elective care.

Table 108: Procedure costs

Procedure	Mean cost (£)	Lower value (£)	Upper value (£)	Source
Device-related procedures				
<i>Implantation, Reimplantation, and Lead displacement/ replacement</i>				
CRT-P	4,870	3,356	7,816	UK Tariff 2012/13 ²²¹ elective EA07Z and ABHI submission ^a
CRT-D	5,556	5,363	18,267	UK Tariff 2012/13 elective EA12Z
ICD	5,556	5,363	18,267	UK Tariff 2012/13 elective EA12Z
<i>Explant</i>				
CRT-P	2,748	2,153	4,542	UK Tariff 2012/13 elective EA39Z
CRT-D	2,748	2,153	4,542	UK Tariff 2012/13 elective EA39Z
ICD	2,748	2,153	4,542	UK Tariff 2012/13 elective EA39Z
<i>Battery failure/ device replacement</i>				
CRT-P	2,748	2,153	4,542	UK Tariff 2012/13 elective EA39Z
CRT-D	5,556	5,363	18,267	UK Tariff 2012/13 elective EA12Z ^b
ICD	5,556	5,363	18,267	UK Tariff 2012/13 elective EA12Z ^c
Hospitalisation				
Heart failure	2,308	1,669	2,578	NHS Reference Costs 2010/11 EB03H/EB03I
Arrhythmia	1,372	922	1,601	NHS Reference Costs 2010/11 EB07H/EB07I
Heart Transplant	£35,606	£21,449	£43,315	NHS Reference Costs 2010/11 EA02Z

^a Difference between the UK Tariff for EA07Z and the ABHI CRT-P whole system cost.

^b Clinical advice indicated CRT-D battery replacement cost should be the same as that for ICD.

^c As per Fox and colleagues, the cost of the procedure for ICD battery replacement was assumed to be the same as for the initial implantation.⁴³

Hospitalisation

The economic model developed for the current assessment accounts for hospitalisation due to heart failure and hospitalisation due to severe arrhythmia. According to Fox and colleagues,⁴³ resources used to manage hospitalised patients with a device are expected to be less than for managing those on OPT. Thus, the conservative approach of assuming the same resource use was taken. The costs associated with management of hospitalisation for heart failure and for arrhythmia were derived from the 2010/11 NHS Schedule of Reference Costs²²² and are presented in Table 108 above.

HRGs EB03H and EB03I refer to heart failure or shock events with or without complications, respectively. Hence, a weighted average of the National Average Unit Costs reported for each HRG was estimated including both elective and long stay non-elective care. Similarly, EB07H and EB07I concern arrhythmia or conduction disorders with or without complications. Thus, the cost of hospitalisation due to arrhythmia was estimated as that for hospitalisation for heart failure.

Transplantation

Heart transplantation cost was estimated as a weighted average of the National Average Unit Costs reported for elective and long stay non-elective care concerning EA02Z.

Device implantation

Device implantation involves surgical procedure and device-related resources, hence the costs of a whole system and of the implantation procedure (shown in Table 106 and Table 108 above) were included. The HRG code specific to ICD implantation is EA12Z and the code for biventricular resynchronisation therapy procedures is EA07Z. The CRT-D implantation cost was assumed to be the same as that for ICD (a conservative approach was taken given the higher cost of EA12Z than that of EA07Z).

Upgrades and routine replacements

Device upgrades and routine/maintenance replacements were assumed to be similar in resource use and costs as the initial implantation.

Operative complications

The resources used for managing operative complications were also accounted for in the economic model. The definition of operative complications and the detail of their reporting varied among the RCTs included in our systematic review of clinical effectiveness. Therefore, the proportions of operative complications were sourced from the RAFT trial,¹⁴¹ a large RCT of patients who are at risk of sudden cardiac death due to ventricular arrhythmia and with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony, managed with CRT-D or ICD devices. For the estimation of an average cost of operative complications, we assumed these to be a combination of lead displacements, infections and device-related problems requiring intervention or device substitution. Thus, the cost of operative complications was estimated as a weighted average of these events using the proportions presented in Table 109 below for each device type.

Table 109: Proportion of operative complications in included CRT trials

Complications	CRT (n)	ICD (n)
Device –related problems requiring replacement ^a	4	1
Complications requiring intervention ^b	75	31
Infections	21	16
Total	100	48

Source: RAFT trial.¹⁴¹ ^a Reported as device-pocket problems requiring revision. ^b Includes lead-displacement and device-pocket hematoma requiring intervention.

The unit cost estimation for lead displacements, infections and device malfunctions is described below under device-related complications. The unit cost for complications requiring intervention was assumed to be that of lead displacements, and device-related problems requiring replacement were assumed to cost as much as an initial implant.

Device-related complications

Management of device-related problems requires a different approach according to each type of event, as different components of the device may need replacement or adjustment and different lengths of hospital admission might be necessary. Fox and colleagues⁴³ considered lead displacement or failure, lead infection, and battery replacement or failure to be the most frequent device-related complications. All types of devices (ICD and CRT) are assumed to have the same types of problems and these are assumed to require similar management regardless of device type. Only costs (device and procedural) are expected to differ according to the type of device.

Lead displacement or replacement:

Managing a lead displacement/failure occurrence is assumed to require a surgical intervention to adjust or replace the lead that is expected to use resources similarly to an initial implantation. For cost estimation, the cost of the leads and of an implantation surgery were considered.

Lead infection:

The treatment of lead infections usually requires surgery for explant of the infected device, a prolonged hospital stay to control the infection, a post-discharge outpatient visit to confirm the absence of infection, and the implantation of a new system. For resource use and costs involved in treatment of infections see Table 110.

HRG EA39Z includes procedures for removal of the cardiac pacemaker system and it was applied as the explant cost for all types of devices. Mean length of stay was derived as a weighted average of the length of stay reported for elective and long stay non-elective care. The lower limit corresponds to an

average length of stay for elective care, whereas the upper limit is the average length of stay for long stay non-elective care. The cost of each additional bed day was derived from the excess bed day national average unit costs for elective and long stay non-elective care for explants (EA39Z). The post-discharge outpatient visit cost was assumed to be a weighted average of those reported for single and multiprofessional visits of Service 320 – cardiology – under non-admitted face to face consultant led follow up attendance (TPCTCLFUSFF and TPCTCLFUMFF).

Table 110: Resource use and costs associated with treatment of infection

Item	Mean	LL	UL	Source
Explant cost (£)	2,748	2,153	4,542	UK Tariff 2012/13 elective EA39Z
Extra bed day cost (£)	316	190	370	NHS Reference costs EA39Z
LoS (days)	4.43	2.65	7.12	NHS Reference costs EA39Z
Outpatient visit cost (£)	123	94	148	NHS Reference costs - Service 320 - Cardiology
<i>Infection Total Cost (£)^a</i>				
CRT-P	12,553	7,285	15,265	
CRT-D	21,580	17,202	38,966	
ICD	18,977	15,109	35,853	

^a Includes explant, whole device system, extra inpatient stay and implantation costs detailed in Table 106 and Table 108 above.

Battery replacement and device malfunctions:

Battery replacement or failure and device malfunctions are assumed in the model to require a short admission to hospital to replace the device. As the battery is part of the generator unit of the device, its replacement is implied. Following Fox and colleagues⁴³ approach, the cost of the procedure for battery replacement of an ICD was assumed to be the same as for the initial implantation (EA12Z), whereas that of a device explant (EA39Z) was used for CRT-P. Clinical advice indicated that the cost of the procedure for battery replacement of a CRT-D should be the same as that of an ICD.

Device-related total costs

Table 111 summarises the device-related total costs used in the economic model. These include the costs of device-components and procedure by event.

Table 111: Device-related total costs used in the model

Event	Mean cost (£)	Lower value (£)	Upper value (£)	Components
Initial implant and re-implantation				
CRT-P	8,281	6,098	11,895	Whole system and implantation costs
CRT-D	17,849	15,246	32,969	
ICD	15,248	13,155	29,858	
Lead displacement/ replacement				
CRT-P	5,681	4,008	8,786	Lead and initial implantation costs
CRT-D	6,097	5,798	18,914	
ICD	6,099	5,799	18,916	
Battery failure / replacement				
CRT-P	5,348	3,884	6,974	Generator and battery replacement costs (EA39Z)
CRT-D	17,308	14,811	32,322	Generator and battery replacement costs (EA12Z)
ICD	14,705	12,718	29,209	
Infection				
CRT-P	12,553	7,285	15,265	Includes explant, re-implantation, extra bed days, and outpatient visits
CRT-D	21,580	17,202	38,966	
ICD	18,977	15,109	35,853	
Operative complications^a				
CRT-P	4,884	2,442	9,768	Includes device –related problems requiring replacement (initial implantation cost), complications requiring intervention (lead replacement cost),infections (infection cost)
CRT-D	6,634	3,317	13,268	
ICD	3,432	1,716	6,864	

^a Arbitrary range used for lower and upper values assuming half and the double of the mean cost.

Drug costs

Patients with heart failure being managed with a device or with OPT alone receive a combination of drugs of several classes for this condition according to their NYHA class. The approach for estimation of drug use by NYHA class and costs is similar to that taken by Fox and colleagues⁴³ and by the ABHI, where a given proportion of patients in each NYHA class is assumed to consume a selected range of drugs. The drugs, daily doses, and proportions chosen for our base case analysis are those presented in ABHI submission, based on their systematic review and expert opinion, and are presented in Table 112 below.

Table 112: Proportion of drug (OPT) by NYHA class

Drug (mg/day)	Proportion of patients by NYHA class			
	I	II	III	IV
Atorvastatin (10)	20%	20%	20%	20%
Simvastatin (20)	55%	55%	55%	55%
Warfarin (1)	10%	15%	25%	40%
Clopidogrel (75)	15%	15%	15%	15%
Ramipril (10)	90%	90%	90%	90%
Carvedilol (25)	85%	85%	75%	70%
Spironolactone (25)	0%	30%	30%	30%
Digoxin (125) ^a	5%	25%	25%	25%
Furosemide (60)	75%	80%	90%	95%
Eplerenone (25)	0%	30%	30%	30%

^a Dosing measured in µg per day.

Unit costs for the selected drugs were derived from the British National Formulary (BNF) 61.²²³ The 4-week cycle cost was assumed to be that of the 28-tablet pack of the correspondent dosage (assuming 1 tablet/day) for all drugs except for furosemide, where the cost of 3 packs of 28 tablets dosed at 20 mg was used. The drug cost by NYHA class is presented in Table 113. The cost of OPT management for Population 1 patients without HF was assumed to be the same as that for NYHA I patients.

Table 113: Drug costs (OPT) by NYHA class

Drug (mg/day)	Cost (£) by NYHA class			
	I	II	III	IV
Atorvastatin (10)	0.38	0.38	0.38	0.38
Simvastatin (20)	0.50	0.50	0.50	0.50
Warfarin (1)	0.09	0.13	0.21	0.34
Clopidogrel (75)	0.35	0.35	0.35	0.35
Ramipril (10)	1.25	1.25	1.25	1.25
Carvedilol (25)	1.37	1.37	1.21	1.13
Spironolactone (25)	0	0.43	0.43	0.43
Digoxin (125) ^a	0.05	0.25	0.25	0.25
Furosemide (60)	1.8	1.92	2.16	2.28
Eplerenone (25)	0	12.82	12.82	12.82
<i>Total</i>	5.78	19.39	19.56	19.73

^a Dosing measured in µg per day.

5.4.5 Results of independent economic analysis

5.4.5.1 Population 1 - patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT

Base case analysis – ICD for secondary prevention of SCD

AVID⁷³ provided the estimates for all-cause mortality and distribution of patients by NYHA class used for our base case analysis of patients at increased risk of SCD due to ventricular arrhythmia, as it was the largest trial for patients who were resuscitated from near-fatal VF or symptomatic sustained VT with hemodynamic compromise. Appendix 15 presents all variables used in the model for the base case analysis. The estimated base case results for a mixed gender cohort of 65-year old patients are reported in Table 114 below in terms of estimated costs and QALYs accrued for patients managed with OPT or ICD, as well as incremental costs and QALYs gained with ICD + OPT versus OPT.

A gain of 0.80 QALYs (equivalent to 290 days in full health) is estimated for the addition of ICD to the management of patients at increased risk of SCD with OPT at an incremental cost of £15,492, and an ICER of £19,479 per QALY gained.

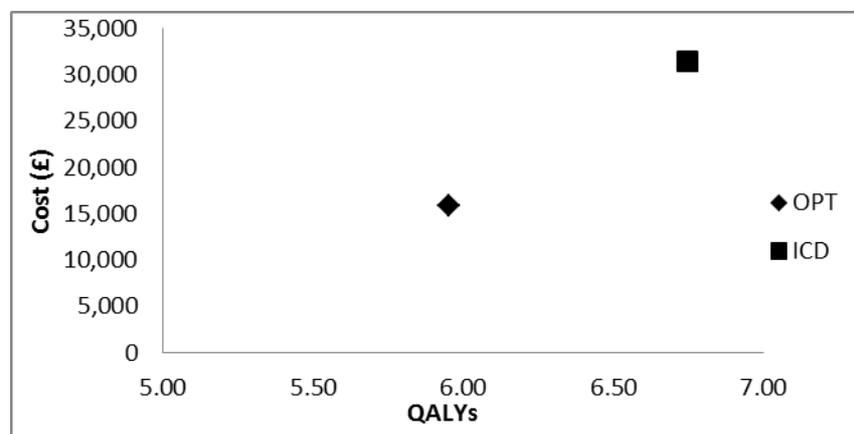
Table 114: Population 1 base case results for 65-year old patients from AVID trial

Intervention	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
OPT	15,890	7.32	5.95	-
ICD + OPT	31,382	8.25	6.75	19,479

QALY, Quality-adjusted life year. ICER, Incremental cost-effectiveness ratio.

The costs and QALYs estimated for each intervention are plotted on Figure 34 below.

Figure 34. Cost-effectiveness plane for Population 1



Model outputs and validation

Overall survival estimated in the model was compared to that reported in the relevant trials, see Appendix 17 for details.

Events

The number of major events estimated in the economic model for the base case analysis is presented in Table 115 below for both strategies being compared for Population 1. Initially managing patients with OPT alone is estimated to lead to 454 ICD implants in patients hospitalised due to a serious arrhythmic event and in those who are referred for ICD following hospitalisation for HF. As the number of implanted patients in the OPT alone arm is much smaller than that for ICD + OPT, less replacements and complications requiring a new device are estimated for this cohort. The risks of hospitalisation due to HF and due to arrhythmia are similar for patients being managed with OPT alone or with ICD + OPT, thus the number of these events is similar among arms as well.

Table 115. Number of events for cohorts of 1,000 patients – Population 1

Events	Strategy	
	OPT	ICD + OPT
Initial implants	0	1,000
Upgrades ^a	454	0
Implant re-attempts ^b	10	22
Hospitalisations	1,966	2,244
Routine replacements	541	921
Postoperative complications	58	114
Lead displacement	77	171
Infections	32	71
Total number of devices ^c	1,037	2,014

^a ICD implants referred to patients initially managed with OPT alone, ^b following surgical failure, ^c sum of initial implants, upgrades, re-attempts from surgical failures, routine replacements, and infections.

The percentage of time spent in the main categories of health states by an average patient for each strategy is presented in Table 116 below. Patients in both arms spend most of their time stable with therapy, and the proportions were similar between arms. A reduced proportion of time was then spent with device-related interventions and hospitalisations.

Table 116. Overall distribution of health state categories over patients' lifetime for Population 1

Health state categories	% of remaining life	
	OPT	ICD + OPT
Stable with therapy	97.61%	96.50%
OPT	47.78%	0.00%
ICD	49.83%	96.50%
Hospitalisations	1.19%	1.55%
Implant surgery	0.37%	0.71%
Routine replacements	0.43%	0.63%
Postoperative complications	0.06%	0.12%
Lead displacement	0.05%	0.08%
Infections	0.03%	0.05%
Device-related interventions ^a	0.93%	1.59%
^a Sum of occupancy in implant surgery, post-operative complications, routine replacements, lead displacements, and infections		

Deterministic sensitivity analysis

Deterministic sensitivity analyses were undertaken to explore the effect of uncertainty related to key parameters and methodological and structural assumptions on the cost-effectiveness results. Scenario analyses were performed to explore modelling relevant population groups as well as using alternative utility estimates to derive QALYs. Univariate sensitivity analyses were also conducted on parameters expected a priori to be influential on results.

Mixed-age cohort

Cost-effectiveness results were estimated for a scenario of a mixed-age and gender cohort of patients eligible for ICD for secondary prevention of SCD. The distribution of ICD implants by age in the UK reported by the British Cardiovascular Society, the British Heart Foundation and the Cardio & Vascular Coalition²¹⁶ was used as a proxy for the distribution of patients at increased risk of SCD due to ventricular arrhythmia. Table 117 shows the results for the mixed cohort and per age group.

Overall, the ICER increases with age, as the QALY gain with ICD + OPT decreases compared to OPT alone as the decrement in incremental benefits from treatment over time is steeper than that for incremental costs. The ICER of £24,967/QALY gained for the mixed age cohort shows that ICD + OPT is within the willingness-to-pay range of £20,000 to £30,000 per QALY gained.

Table 117: Population 1 base case results by age and mixed age cohort

Start age	OPT Costs (£)	ICD Costs (£)	OPT QALYs	ICD QALYs	ICER (£/QALY gained)
30	27,207	43,410	9.74	10.69	17,083
40	25,982	41,968	9.33	10.23	17,856
50	23,535	39,238	8.54	9.35	19,228
60	16,947	32,673	6.29	7.15	18,182
70	14,268	29,361	5.41	6.12	21,298
80	9,681	24,129	3.85	4.36	28,211
90	5,382	18,232	2.40	2.45	288,611
Mixed	16,559	31,838	6.17	6.91	24,967

ICD for primary prevention of SCD***1. MADIT II***

MADIT II¹⁰³ was the trial with largest number of patients with remote myocardial infarction and was considered representative of a relevant group who might benefit from ICD for primary prevention of SCD. Cost-effectiveness results for the subgroup analysis of patients with remote MI, using MADIT II all-cause mortality for a cohort of 64-year old patients and the pooled RR of 0.57 (effect of ICD + OPT on all-cause mortality relative to OPT), are presented below in Table 118.

An increment of 1.18 QALYs per patient is estimated using ICD + OPT for primary prevention of SCD at an additional cost of £16,800. The health benefit estimated from using ICD + OPT for primary prevention of SCD in patients remote from their MI instead of OPT alone is greater than that for secondary prevention, in accordance with the lower pooled RR (0.57) estimated for patients with remote MI compared to that for the base case analysis (RR=0.75). The estimated ICER for this patient group is £14,231 per QALY gained.

Table 118: MADIT II subgroup analysis results

Intervention	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
OPT	14,783	6.77	5.17	-
ICD + OPT	31,583	8.36	6.35	14,231

QALY, Quality-adjusted life year.

2. SCD-HeFT

The all-cause mortality of the placebo arm, the RR for ICD of 0.77 (95% CI 0.66, 0.89), and the distribution of patients by NYHA class from the SCD-HeFT¹⁰⁷ were used to inform an analysis of 60

year-old patients with mild-moderate heart failure with indication for an ICD. Table 119 shows the cost-effectiveness results for this subgroup analysis.

An additional benefit of 0.49 QALYs (approximately 180 days in full health) is estimated for primary prevention of SCD in patients with mild-moderate heart failure with ICD + OPT at an additional cost of £14,655 compared to OPT alone. The estimated ICER for this subgroup of patients (£29,756/QALY gained) is just below the willingness to pay of £30,000 per QALY gained.

Table 119. SCD-HeFT s subgroup analysis results

Intervention	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
OPT	17,760	7.84	5.79	-
ICD	32,416	8.51	6.28	29,756

QALY, Quality-adjusted life year.

Both cohorts initially managed with OPT alone or ICD + OPT for primary prevention of SCD showed higher costs and slightly longer life expectancy compared with the base case analysis (secondary prevention of SCD). However, given the greater severity of HF in these patients (see distribution by NYHA class in Section 5.4.4.1), both cohorts gained fewer QALYs compared with secondary prevention patients (base case analysis).

3. Patients with cardiomyopathy

The all-cause mortality reported for the SCD-HeFT¹⁰⁷ subgroup of patients with non-ischaemic congestive heart failure in the placebo arm was used as baseline mortality for a subgroup analysis of 60 year-old patients with cardiomyopathy. The mortality preventive effect of ICDs was incorporated using a pooled RR of 0.74 (95% CI 0.58, 0.93) from the non-ischaemic subgroup of SCD-HeFT,¹⁰⁷ AMIOVIRT,⁷¹ CAT,⁸⁴ and DEFINITE.⁹² The SCD-HeFT¹⁰⁷ distribution of patients by NYHA class was used as well. Table 120 reports the estimated cost-effectiveness results for this subgroup.

The primary prevention of SCD with ICD + OPT in patients with cardiomyopathy is expected to cost £15,373 more than initial prevention with OPT alone and subsequent implantations for an incremental benefit of 0.59 QALYs (216 days in full health). Compared to the base case (secondary prevention of SCD), both treatment strategies for patients with cardiomyopathy present a higher cost and a greater benefit (about £9,000 more for 1.67 or 1.88 QALYs further with ICD + OPT or OPT alone, respectively) over lifetime. The ICER estimated for the cardiomyopathy subgroup is £26,028 per QALY.

Table 120. Cardiomyopathy subgroup analysis results

Intervention	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
OPT	24,845	10.59	7.83	-
ICD	40,218	11.39	8.42	26,028

QALY, Quality-adjusted life year.

Univariate sensitivity analysis

Table 121 below shows the results of univariate sensitivity analyses conducted on key inputs of the model, allowing the estimation of their impact on the cost-effectiveness results. The range used for most parameters was their 95% CI.

Table 121: Univariate sensitivity analysis results for Population 1

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALY	ICER (£/QALY gained)
Base case	-	-	15,492	0.80	19,479
<i>Structural parameters</i>					
Time horizon	Lifetime	AVID FU (3y)	13,330	0.09	141,235
Costs and Benefits discount rates	3.5%, 3.5%	0%, 0%	16,836	1.18	14,271
		6%, 1.5%	14,908	0.99	15,069
<i>Survival and HRs</i>					
Baseline all-cause mortality, $\ln(\lambda)$, γ	-3.381, 0.696	-3.431, 0.678	15,496	0.78	19,854
		-0.330, 0.714	15,449	0.80	19,416
All-cause mortality HR (ICD)	0.75	0.61	17,126	1.37	12,480
		0.93	13,772	0.18	78,268
Age-related relative risk of death > 75 years	1.41	1	15,551	0.81	19,241
		2	15,367	0.76	20,137
<i>Event probabilities</i>					
Risk of hospitalisation due to HF (OPT)	0.008	0	15,251	0.79	19,197
		0.020	15,869	0.80	19,920
Relative risk of hospitalisation due to HF (ICD)	1	0.804	15,262	0.80	19,184
		1.196	15,723	0.80	19,773

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALY	ICER (£/QALY gained)
Risk of implantation following HF hospitalisation	0.002	0	15,506	0.80	19,484
		0.006	15,461	0.79	19,466
Risk of surgical death (ICD)	0.003	0	15,491	0.82	18,950
		0.055	15,507	0.48	32,605
Risk of surgical death (Transplant)	0.122	0.109	15,492	0.80	19,476
		0.136	15,492	0.80	19,481
Risk of surgical failure	0.011	0.009	15,464	0.80	19,442
		0.013	15,521	0.80	19,516
Risk of perioperative complications	0.053	0.046	15,469	0.80	19,448
		0.062	15,523	0.80	19,518
Risk of lead infections	0.0005	0.0004	15,371	0.80	19,321
		0.0006	15,614	0.80	19,636
Risk of lead displacements	0.0012	0.001	15,415	0.80	19,372
		0.0014	15,570	0.80	19,585
Device lifetime $\ln(\lambda)$ and γ	-15.78 1.94 (~ 8 years)	-16.182 1.889 (~13 years)	13,158	0.80	16,456
		-15.385 1.996 (~5 years)	19,467	0.79	24,706

FU = follow-up

The univariate sensitivity analysis for structural parameters did not show large changes to the ICER, apart from the model time horizon. The only analysis that increased the ICER above £30,000/QALY gained was that of shortening the time horizon to the survival follow-up period reported in AVID (as very few health benefits are accrued over that time period compared to the incremental cost of ICD implantation).

Among the mortality-related estimates, model results showed particular sensitivity to the HR for all-cause mortality associated with the ICD + OPT arm, more than tripling to £78,268/QALY gained when the upper limit of the HR (0.93) was used.

The event-related estimates that had greatest impact on the ICER were the risk of surgical death during ICD implantation and the device lifetime. When the risk of death from ICD surgery was varied according to the limit values of its 95% CI, the ICER ranged from £18,950 to £32,605 per QALY gained, and from £16,456 to £24,706 per QALY gained when the device lifetime was input as 13 and 5 years, respectively.

Hospitalisation due to arrhythmia

There is limited reporting of the number of hospitalisations due to non-fatal arrhythmia in the trials included in our systematic review for Population 1 (patients at increased risk of SCD). Following clinical advice, our basecase analysis assumes the same risk as that of patients with heart failure (0.0075, 95% CI 0.0002, 0.0148) derived from the MIRACLE trial.¹²³ As this estimate is likely to be underestimating the risk of Population 1 patients, a scenario analysis using the risk of hospitalisation due to ventricular arrhythmia of patients with ICD of Population 3 (also at increased risk of SCD due to ventricular arrhythmia) was conducted.

In the Population 3 model, the risk of hospitalisation due to arrhythmia used for patients with ICD is 0.032 (95% CI 0.017, 0.046) obtained by applying the pooled RR of 1.11 to the baseline risk of patients with CRT-D (0.029) derived in Section 4.4.2.8. For this Population 1 scenario, the risk of hospitalisation due to arrhythmia was assumed to be 0.032 for patients with ICD and for patients being managed with OPT alone. Table 122 below summarises the cost-effectiveness results for this scenario. Compared to the base case analysis, a slightly lower ICER (£18,185/QALY) is estimated using a higher risk of hospitalisation for arrhythmia, as the OPT arm shows a substantial gain in QALYs compared to the ICD+OPT arm, despite the greater increment in cost.

Table 122. Hospitalisation due to arrhythmia scenario analysis results

Intervention	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
OPT	29,759	7.78	6.34	-
ICD	37,120	8.26	6.74	18,185

QALY, Quality-adjusted life year.

Utilities

In the base case analysis, an NYHA class weighted average utility estimate of 0.81 was estimated for the OPT arm and of 0.82 for the ICD arm, using the distribution of patients per NYHA class in the AVID trial. A scenario analysis was conducted using a mean utility estimate of 0.75 irrespective of NYHA class and treatment arm as per Buxton and colleagues.⁴² This lower average utility value led to

an estimated 0.69 QALY gain (instead of the 0.80 estimated for the base case). Therefore, the ICER of ICD + OPT versus OPT alone for secondary prevention of SCD increased to £22,372 per QALY gained.

Device-related costs

When the all device-related costs (i.e. costs associated with the implantation, perioperative complications, treatment of lead displacement, infection, and device replacement) were varied to the lower and upper limits of their 95% CI, the ICER ranged from £16,888 to £37,832 per QALY gained.

Probabilistic sensitivity analysis

PSA was performed for the base case to estimate the impact of joint parameter uncertainty on the model's cost-effectiveness results. Appendix 15 reports the variables (mean values and confidence intervals) included in the PSA, the form of distribution used for sampling and the parameters of the distribution. PSA results of 10,000 iterations are presented in Figure 35 in terms of cost and QALYs for each strategy. The probabilistic mean ICER is £20,479 per QALY gained (inter-quartile range (IQR) of £9,857 to £61,685 per QALY gained).

Figure 35. Cost-effectiveness scatter plot for Population 1

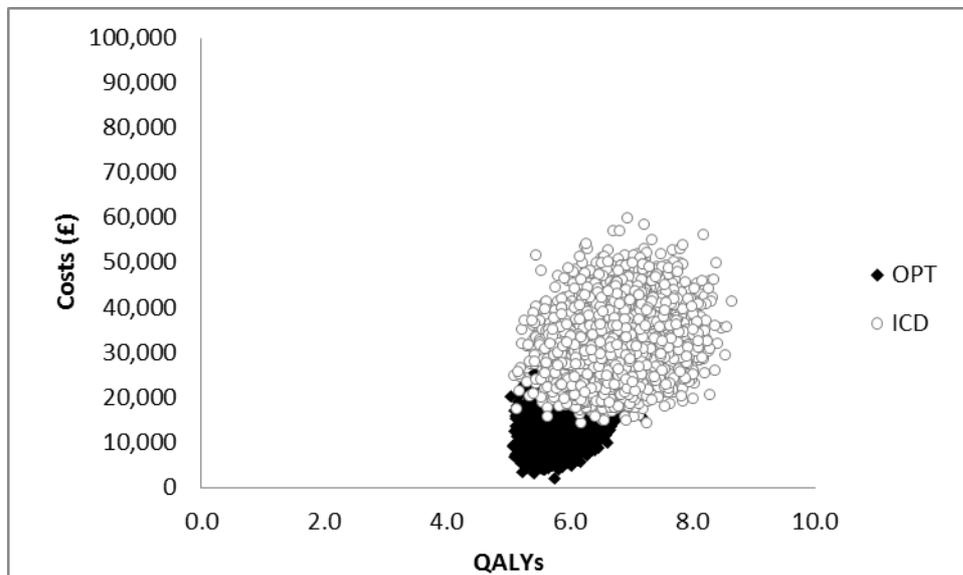
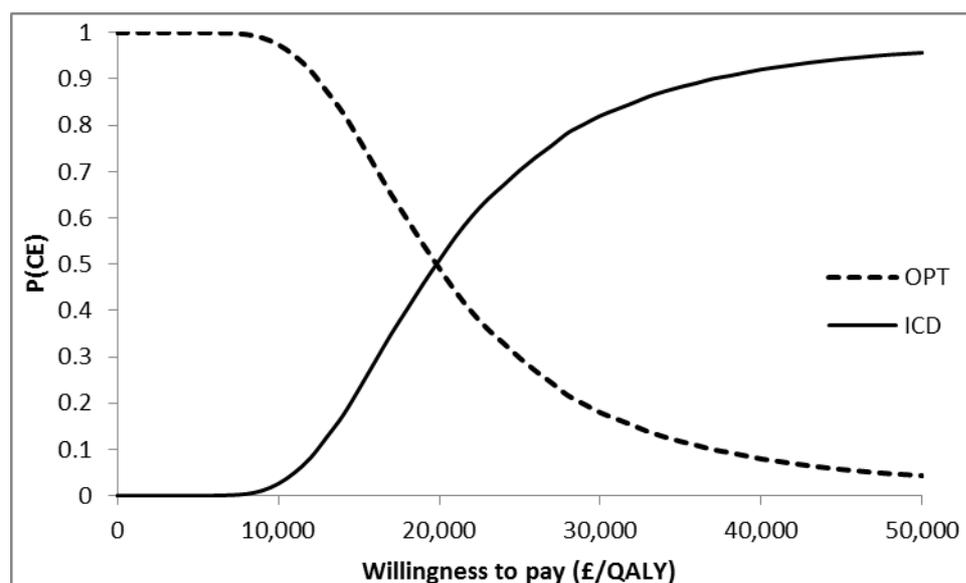


Figure 36 shows the variation of the probability of cost-effectiveness for both interventions as the willingness to pay increases from £0 to £50,000 per QALY gained. The addition of ICD to OPT for SCD secondary prevention has a 51% probability of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained, and a 82% probability at £30,000 per QALY gained.

Figure 36. Cost-effectiveness acceptability curve for Population 1



5.4.5.2 Population 2 - Patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT

People with heart failure as a result of LVSD and cardiac dyssynchrony despite OPT were modelled receiving initially OPT alone, or CRT-P or CRT-D alongside OPT. This allowed for the estimation of the relative cost-effectiveness of these treatment strategies, and results for the comparisons specified in the NICE scope⁶⁴ (CRT-P + OPT versus OPT, CRT-D + OPT versus OPT, and CRT-D + OPT versus CRT-P + OPT) are given in this section.

Base case analysis

For our base case analysis, a 70 year-old mixed-gender cohort of patients with heart failure was modelled receiving the relevant treatment strategies. Table 123 below presents the estimated discounted costs, life years, and QALYs accrued for patients managed with OPT, CRT-P + OPT, or CRT-D + OPT as well as incremental cost per QALY gained for the relevant comparisons.

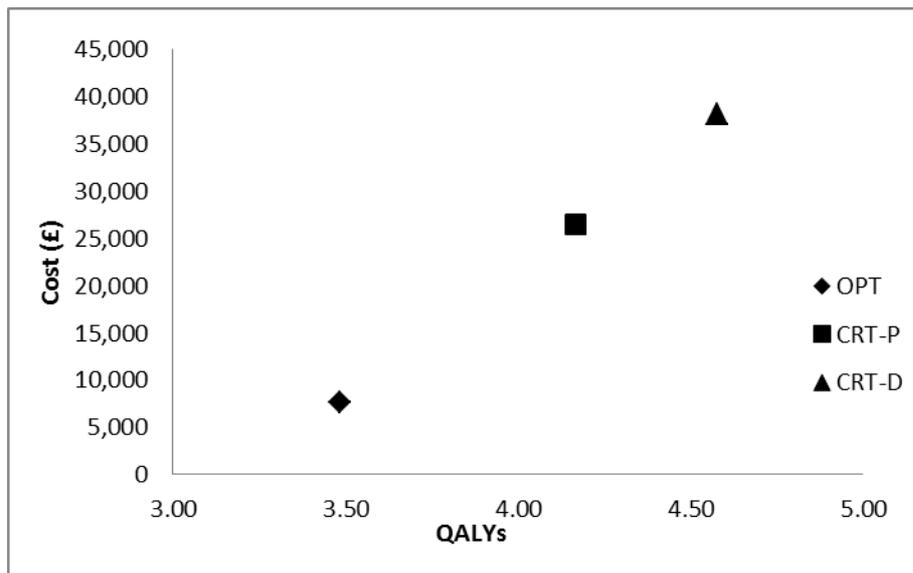
Table 123. Base case summary of cost-effectiveness results for Population 2

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs OPT	ICER (£/QALY gained) vs CRT-P + OPT
OPT	7,615	4.86	3.48	-	-
CRT-P + OPT	26,460	5.51	4.17	27,584	-
CRT-D + OPT	38,163	7.21	4.58	27,899	28,420

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Initial management with CRT-P or CRT-D alongside OPT had similar ICERs to each other compared with initial management with OPT alone (£27,584 and £27,899 per QALY gained, respectively). The addition of CRT-P to OPT improves 0.68 QALYs at a cost of £18,845, and the addition of CRT-D yields a gain of 1.09 QALYs at a cost of £30,548 compared with OPT. CRT-D + OPT was more costly (£11,703 more) and more effective (0.41 QALYs) than CRT-P + OPT, presenting an ICER of £28,420 per QALY gained compared with CRT-P + OPT. The costs and QALYs estimated for each intervention are plotted on Figure 37 below.

Figure 37. Cost-effectiveness plane for Population 2



Model outputs and validation

HF deaths and SCD estimated in the model were compared with those reported in CARE-HF, see Appendix 17 for details.

Events

The percentage of time spent in the main categories of health states by an average patient of each strategy is presented on Table 124. Patients spent most time stable with the therapy in all strategies. The cohort initially managed with OPT alone shows a slightly greater proportion of patients lifetime spent stable with therapy, but it is also the strategy with higher proportion of lifetime spent in hospital. The CRT cohorts spent slightly less time hospitalised, however spent more time with device-related interventions (i.e. time in implant surgery, post-operative complications, routine upgrades, lead displacements, and infections). About 27% of the lifetime of patients initially managed with CRT-P + OPT was spent stable with a CRT-D device as result of the upgrade.

Table 124. Overall distribution of patients' lifetime by health state categories for Population 2

Health state categories	% of remaining life		
	OPT	CRT-P + OPT	CRT-D + OPT
Stable with therapy	95.15%	94.17%	93.44%
OPT	93.85%	7.90%	0.15%
CRT-P	0.54%	55.86%	0.00%
CRT-D	0.67%	26.86%	83.06%
ICD	0.09%	3.54%	10.24%
Hospitalisation	4.22%	2.80%	3.63%
OPT	4.18%	0.36%	0.01%
CRT-P	0.01%	1.26%	0.00%
CRT-D	0.03%	1.02%	3.14%
ICD	0.00%	0.17%	0.48%
Implant surgery	0.03%	1.70%	1.24%
Routine replacements	0.01%	0.32%	0.56%
Lead displacement	0.00%	0.33%	0.34%
Postoperative complications	0.00%	0.25%	0.22%
Infections	0.00%	0.06%	0.06%
Device-related interventions ^a	0.05%	2.65%	2.42%

^a Sum of occupancy in implant surgery, post-operative complications, routine upgrades, lead displacements, and infections

Table 125 shows the number of events for each cohort of population 2 patients. The cohorts initially managed with CRT alongside OPT (CRT-P + OPT or CRT-D + OPT) are estimated to require a similar total number of devices (comprising initial implants, upgrades, infections, and replacements) over a lifetime. Although CRT-P + OPT required fewer device replacements given the longer CRT-P lifetime, more upgrades were needed than in the CRT-D + OPT arm. The 228 ICDs reported as upgrades from CRT-D in Table 125 in the CRT-D + OPT strategy consist of estimated CRT-D implant failures assumed to turn out in successful ICD implants.

Table 125. Number of events for cohorts of 1,000 patients – Population 2

Event	Strategy		
	OPT	CRT-P + OPT	CRT-D + OPT
Initial implants	0	1,000	1,000
ICD	0	0	0
CRT-P	0	1,000	0
CRT-D	0	0	1,000
Hospitalisations	3,043	2,349	3,385
OHP	3,013	299	6
PHP	9	1,057	0
DHP	18	854	2,929
IHP	3	140	450
Upgrades	20	421	156
ICD	1	58	156
CRT-P	10	1	0
CRT-D	8	362	0
Surgical complications	3	208	204
ICD	0	5	13
CRT-P	1	132	0
CRT-D	2	71	191
Lead displacements	3	275	315
ICD	0	4	12
CRT-P	2	183	0
CRT-D	2	88	303
Infections	0.6	46.3	55.7
ICD	0.0	1.6	5.1
CRT-P	0.3	29.9	0.0
CRT-D	0.3	14.8	50.7
Replacements	6.6	269.3	523.9
ICD	0.7	29.6	66.7
CRT-P	1.1	32.6	0.0
CRT-D	4.8	207.2	457.2
Number of devices ^a	27	1,737	1,736
ICD	2	89	228
CRT-P	11	1,063	0
CRT-D	14	584	1,508

^a Sum of number of device initial implants, upgrades, infections (required new device), and replacements

Deterministic sensitivity analysis

The effect of uncertainty related to key parameters and methodological and structural assumptions on the cost-effectiveness results was explored through subgroup, univariate, and scenario analyses.

Mixed-age cohort

Cost-effectiveness results were estimated for a scenario of a mixed-age and gender cohort of patients with heart failure. The distribution of patients with heart failure by age group reported by Cowie and colleagues²⁰ was used, and the male proportion was derived from the prevalence of HF per sex in the UK by the British Heart Foundation Statistics.²⁹ The model results for different starting ages are detailed in Table 126. These results show that the ICER increases non-linearly with age and that the ICERs of the three comparisons are consistently similar among age groups. For most age groups, CRT-P + OPT versus OPT alone is the strategy with lowest ICER and CRT-D + OPT versus CRT-P + OPT is that with the highest ICER. The exception is for 80-year old patients, for whom the opposite is estimated to occur, as CRT-D + OPT shows a smaller gain (0.33) at lower cost (£10,757) compared with CRT-P + OPT than that estimated for CRT-P + OPT (0.49 QALYs gained at £16,000) relative to OPT alone.

Table 126. Base case results by age and mixed age cohort for Population 2

Start age	Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs OPT	ICER (£/QALY gained) vs CRT-P + OPT
30	OPT	12,614	7.98	5.77	-	-
	CRT-P + OPT	40,482	9.30	7.05	21,678	-
	CRT-D + OPT	54,997	15.65	7.69	22,065	22,848
40	OPT	12,419	7.80	5.63	-	-
	CRT-P + OPT	39,572	9.00	6.82	22,870	-
	CRT-D + OPT	53,849	13.44	7.40	23,413	24,519
50	OPT	11,862	7.47	5.39	-	-
	CRT-P + OPT	37,713	8.51	6.45	24,444	-
	CRT-D + OPT	51,531	12.17	6.97	25,106	26,447
60	OPT	10,081	6.39	4.60	-	-
	CRT-P + OPT	32,755	7.22	5.47	26,029	-
	CRT-D + OPT	45,486	9.76	5.91	26,953	28,771
70	OPT	7,615	4.86	3.48	-	-
	CRT-P + OPT	26,460	5.51	4.17	27,584	-
	CRT-D + OPT	38,163	7.21	4.58	27,899	28,420
80	OPT	5,882	3.77	2.69	-	-
	CRT-P + OPT	21,882	4.23	3.18	32,656	-
	CRT-D + OPT	32,639	5.33	3.52	32,598	32,511
90	OPT	4,075	2.64	1.87	-	-
	CRT-P + OPT	16,509	2.78	2.08	61,057	-
	CRT-D + OPT	25,261	3.15	2.20	64,917	71,322
Mixed	OPT	8,218	5.23	3.75	-	-
	CRT-P + OPT	28,016	5.91	4.47	28,928	-
	CRT-D + OPT	39,932	7.93	4.88	29,416	30,321
QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio						

Univariate sensitivity analysis

Table 127 to Table 129 present the results of the deterministic sensitivity analyses of the most influential parameters for each of the relevant comparisons (i.e. those that when varied between the 95% CI limits caused a variation $>£10,000/\text{QALY}$ in the ICER). The other variables were varied but had a smaller impact on results.

Table 127 shows that the risk of hospitalisation for a serious arrhythmic event for HF patients with CRT-P, the RRs of HF death for patients managed with CRT-P and CRT-D, and the RR of SCD of HF patients with CRT-P are the most influential parameters on the cost-effectiveness results for the comparison of CRT-P + OPT and OPT alone as initial treatment.

The results for the comparison of CRT-P + OPT with OPT are particularly sensitive to the risk of hospitalisation for non-fatal arrhythmia with CRT-P, as the ICER decreases £15,780 per QALY gained when the lower limit of the 95% CI of the estimate is used. On the other hand, the ICER rises to £31,978 per QALY gained when the upper limit of risk is used, as the cost of the CRT-P + OPT cohort increases substantially whereas that for OPT alone stays the same. Patients being managed with CRT-P experiencing hospitalisation due to arrhythmia are assumed to be referred to CRT-D implantation. The cost increment for the CRT-P cohort is hence accompanied by small health gain.

The RR of SCD with CRT-P was varied between the HRs reported from the CARE-HF and the COMPANION trials, as these indicate a relative effect in opposite directions. The ICER for CRT-P + OPT versus OPT alone decreases to £23,307 per QALY gained when the RR of SCD with CRT-P from the CARE-HF trial (0.54) is used, i.e. when CRT-P is assumed to considerably reduce the risk of SCD. A cost of £30,925 per QALY gained is estimated when the RR from the COMPANION trial (1.13) is input, assuming a scenario where CRT-P would increase the risk of SCD.

Table 127 Univariate sensitivity analysis results for CRT-P + OPT versus OPT (Population 2)

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	-	-	18,845	0.68	27,584
Risk of hospitalisation for non-fatal arrhythmia (CRT-P)	0.0075	0.0002	8,765	0.56	15,780
		0.0148	24,169	0.76	31,978
RR of HF death (CRT-P)	0.67	0.51	19,575	0.84	23,307
		0.88	17,993	0.50	36,019
RR of HF death (CRT-D)	0.73	0.47	19,788	0.84	23,522
		1.11	17,836	0.51	34,720
RR of SCD (CRT-P)	1	0.54	20,471	1.03	19,825
		1.13	18,443	0.60	30,925

Generally, the results for the addition of CRT-D to OPT were robust to the variation of most parameters' estimates (see Table 128 below) compared to those for the other two comparisons (CRT-P + OPT versus OPT and CRT-D + OPT versus CRT-P+OPT). They were mainly sensitive to the RR of HF death and the RR of SCD for patients with CRT-D, and to the CRT-D lifetime, confirming that the cost-effectiveness of the addition of CRT-D to OPT is determined by the survival benefit associated to this device. The most influential parameter for this comparison was the RR of HF death associated with CRT-D (RR=0.73), which made the ICER range £31,411. When the upper limit of this estimate is considered (RR=1.11), the preventive benefit of CRT-D for HF death disappears and the ICER for CRT-D +OPT compared with OPT alone rises to more than £50,000 per QALY gained.

Table 128. Univariate sensitivity analysis results for CRT-D + OPT versus OPT (Population 2)

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	-	-	30,548	1.09	27,899
RR of HF death (CRT-D)	0.73	0.47	33,541	1.62	20,671
		1.11	27,381	0.53	52,082
RR of SCD (CRT-D)	0.44	0.23	32,147	1.38	23,283
		0.86	27,962	0.63	44,659
Device lifetime (CRT-D), $\ln(\lambda), \gamma$	-15.465, 1.935 (~7y)	-16.000, 1.863 (~13y)	25,309	1.12	22,643
		-14.931, 2.006	39,322	1.05	37,363

		(~4y)			
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The results for the comparison of CRT-D and CRT-P alongside OPT were the most sensitive to the variation of individual parameters, with 8 parameters that made the ICER range by more than £10,000 (see Table 129 below). The most influential parameter for this comparison was the RR of HF death of CRT-D, followed by the RRs of SCD of both CRT-D and CRT-P devices relative to OPT alone.

The estimate of RR of HF death for CRT-D was sourced from the COMPANION trial (HR=0.73, 95% CI 0.47 to 1.11). When a higher risk of HF death is assumed for CRT-D than that for OPT alone is assumed (RR=1.11), the incremental benefit of CRT-D + OPT is almost null relative to CRT-P + OPT (0.01), originating an extremely high ICER.

The ICER for CRT-D + OPT versus CRT-P + OPT becomes extremely high as well when the RR of SCD with CRT-P is changed to the lowest limit. The pooled RR of SCD for CRT-P patients of 0.97 (95% CI 0.44 to 2.14) was obtained in the meta-analysis in section 4.3.2.4. Given its wide 95% CI, a RR of 1 was used in the model and ranged between the mean estimates of RR reported in the most relevant trials (0.54 from CARE-HF and 1.13 from the COMPANION trial). Under a CARE-HF scenario, the preventive effect of SCD of CRT-P becomes higher than that of CRT-D, i.e. the incremental benefit of CRT-D + OPT relative to CRT-P + OPT (0.06) is much smaller than in the base case (0.41).

Similarly, if the RR of SCD for CRT-D is increased to 0.86 (the upper limit of its 95% CI, sourced from the COMPANION trial), only 0.08 incremental QALYs are estimated for CRT-D + OPT compared to CRT-P + OPT, and therefore an particularly high ICER is estimated.

The life expectancy of CRT-Ds, the RR of HF death of CRT-P, and the risk of hospitalisation due to severe arrhythmia with CRT-P also showed substantial influence on the ICER, making it range by more than £20,000. The ICER for CRT-D + OPT versus CRT-P + OPT decreased substantially when a longer device lifetime was used (13 years), the RR of HF death with CRT-P was increased, or the risk of hospitalisation for arrhythmia with CRT-P became higher.

Table 129. Univariate sensitivity analysis for CRT-D + OPT versus CRT-P + OPT (Population 2)

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	-	-	11,703	0.41	28,420
RR of HF death (CRT-D)	0.73	0.47	13,754	0.78	17,602
		1.11	9,545	0.01	793,839
RR of SCD (CRT-P)	1	0.54	10,063	0.06	169,196
		1.13	12,108	0.50	24,250
RR of SCD (CRT-D)	0.44	0.23	12,817	0.62	20,180
		0.86	9,912	0.08	129,220
Device lifetime (CRT-D), $\ln(\lambda), \gamma$	-15.465, 1.935 (~7y)	-16, 1.863 (~13y)	8,608	0.43	20,238
		-14.931, 2.006 (~4y)	17,811	0.38	46,640
RR of HF death (CRT-P)	0.67	0.51	10,966	0.25	43,231
		0.88	12,563	0.60	21,042
Risk of hospitalisation for non-fatal arrhythmia (CRT-P)	0.0075	0.0002	21,857	0.54	40,450
		0.0148	6,335	0.34	18,707
Baseline mortality due to HF, $\ln(\lambda), \gamma$	-6.115, 1.223	-6.253, 1.180	12,546	0.52	24,157
		-5.977, 1.265	10,864	0.31	35,220
Baseline mortality due to SCD, $\ln(\lambda), \gamma$	-6.069, 1.140	-6.173, 1.107	11,460	0.33	34,318
		-5.964, 1.173	11,924	0.49	24,316

Overall, the incremental cost-effectiveness results for the comparisons relevant for Population 2 are sensitive mainly to survival-related parameters that determine the incremental benefit of the devices on patients' survival, such as the RRs of SCD and HF death for CRT-P and CRT-D, the risk of hospitalisation due to arrhythmia with CRT-P, and CRT-D devices longevity. Device lifetime was also influential due to the incremental costs incurred if devices need replacement more frequently.

Scenario analysis

Device longevity

Clinical advice indicated that device longevity estimates used in the base case analysis could be overestimated, particularly for CRT-P. Table 130 presents the device lifetime estimates used in the previous model by Fox and colleagues⁴³ and those used in the current model.

Table 130. Device lifetime estimates

Device	Fox et al. ⁴³	SHTAC
	Mean, years	Mean (95% CI), years
ICD	5.0	8.2 (5.4 – 12.8)
CRT-D	5.5	7.2 (4.1 – 13.1)
CRT-P	6.5	11.8 (6.6 – 22.2)

A scenario analysis was conducted using the mean device lifetime estimates used by Fox and colleagues.⁴³ Results for this scenario are presented in Table 131 below. Compared with the base case analysis, higher costs are estimated for CRT-D and CRT-P alongside OPT due to shorter device longevity (approximately £4,500 and £2,000, respectively). Also, slightly fewer QALYs (-0.02) are estimated to be accrued compared with the base case analysis, as patients are estimated to spend more time with device-related interventions and less time stable with therapy.

Table 131. Shorter devices' lifetime scenario results (Population 2)

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs OPT	ICER (£/QALY gained) vs CRT-P + OPT
OPT	7,652	4.86	3.48	-	-
CRT-P + OPT	28,555	5.50	4.15	31,334	-
CRT-D + OPT	42,627	7.18	4.56	32,505	34,416

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Utilities

A scenario with the utility estimates used by Fox and colleagues⁴³ (presented in Table 132 below) was explored. The utility estimates used in the base case analysis can be found in Table 105 (Section 5.4.4.4).

Table 132. Utility values used in scenario analysis for Population 2

Health state	Mean utility value	Sources
NYHA class I	0.93	Kirsch and McGuire 2000 ²⁰⁴
NYHA class II	0.78	Kirsch and McGuire 2000 ²⁰⁴
NYHA class III	0.61	Calvert 2005 ²⁰⁵
NYHA class IV	0.44	Calvert 2005 ²⁰⁵

Hospitalisation and Transplantation	0.57	McAllister 2004 ²¹⁹
Decrement due to surgery	0.05	Assumption
Decrement due to infection	0.1	Assumption

Table 133 shows the cost-effectiveness results for this scenario, with the same costs per strategy as those estimated for the base case analysis. In this scenario, fewer QALYs (-0.09) were estimated for OPT alone and more QALYs were estimated for the CRT strategies (0.04 and 0.05 for CRT-P and CRT-D respectively). The lower ICERs presented in this scenario for the comparisons of CRT-P and CRT-D versus OPT alone are explained by the greater differences in QALYs gained among strategies than in the base case analysis. As both CRT cohorts presented similar QALY increments in this scenario, the ICER for CRT-D versus CRT-P in this scenario (£27,893 per QALY) does not differ as much from that of the base case (£28,420 per QALY gained).

Table 133. Utilities scenario results for Population 2

Intervention	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs OPT	ICER (£/QALY gained) vs CRT-P + OPT
OPT	7,615	4.86	3.39	-	-
CRT-P + OPT	26,460	5.51	4.21	22,892	-
CRT-D + OPT	38,163	7.21	4.63	24,580	27,893
QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio					

Costs

All device-related costs (including those associated with implantation, perioperative complications, treatment of lead displacement, infection, and device replacement) were varied as a group to the lower and upper limits of their 95% CI (see Table 111). The ICER ranged from £20,977 to £48,486 per QALY gained for CRT-P + OPT compared with OPT, from £23,652 to £53,556 per QALY gained for CRT-D + OPT versus OPT, and from £28,090 to £61,967 per QALY gained for CRT-D + OPT versus CRT-P + OPT. Considering a WTP of £30,000/ QALY gained, when the upper limit estimates of device-related costs are used, both CRT strategies become non-cost-effective compared with OPT alone, and CRT-D + OPT becomes non-cost-effective compared with CRT-P + OPT. The scenario using the lower limits showed a reduction in costs of more than £4,500 for both CRT strategies and of less than £100 for OPT alone. Thus, the ICERs for the comparisons of CRT devices with OPT alone have reduced much more substantially than that for the comparison of CRT-D with CRT-P (£4,712 and £4,576 reduction in costs compared with base case analysis for CRT-D and CRT-P, respectively).

Probabilistic sensitivity analysis

PSA was performed for the base case to estimate the impact of joint parameter uncertainty on the model's cost-effectiveness results. Appendix 15 reports the variables (mean values and confidence intervals) included in the PSA, the form of distribution used for sampling and the parameters of the distribution. Table 134 reports the estimated probabilistic results of 10,000 iterations in terms of costs and QALYs for each strategy and their relative cost-effectiveness.

Table 134. Base case summary of probabilistic cost-effectiveness results for Population 2

Strategy	Cost (£)	QALYs	ICER (£/QALY gained) vs OPT (IQR)	ICER (£/QALY gained) vs CRT-P + OPT (IQR)
OPT	7,604	3.48	-	-
CRT-P + OPT	25,874	4.14	27,434 (16,314; 47,527)	-
CRT-D + OPT	38,156	4.56	28,158 (17,431; 49,839)	27,899 (-175; 159,172)
QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; IQR – Interquartile range				

Probabilistic results are consistent with the deterministic base case analysis. Both CRT-P + OPT and CRT-D + OPT have ICERs below £30,000 per QALY gained compared with initial management with OPT alone, as well as CRT-D + OPT compared with CRT-P + OPT. The wide IQR estimated for the probabilistic ICER of the comparison of CRT-D + OPT and CRT-P + OPT reflects the overlap in model results for CRT-P and CRT-D (Figure 38).

PSA results are presented on Figure 38 in terms of incremental cost and QALYs, showing their dispersion on the cost-effectiveness scatterplot and the partial overlap of the cost-effectiveness results for the 3 strategies, particularly among CRT-P and CRT-D.

Figure 38. Cost-effectiveness scatter plot for Population 2

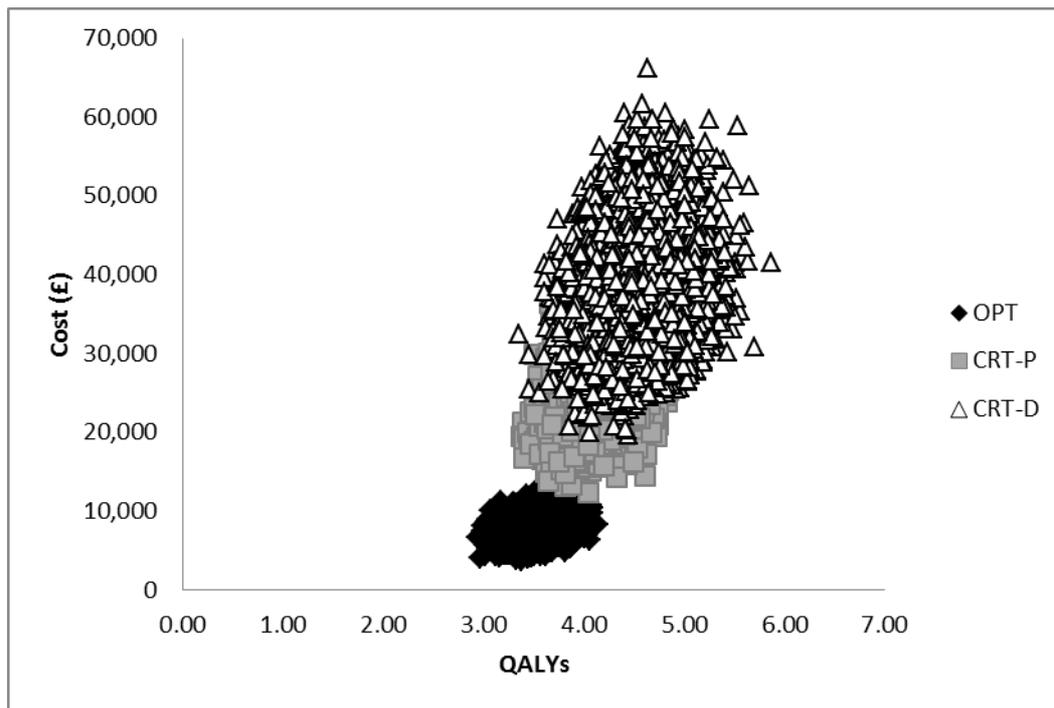
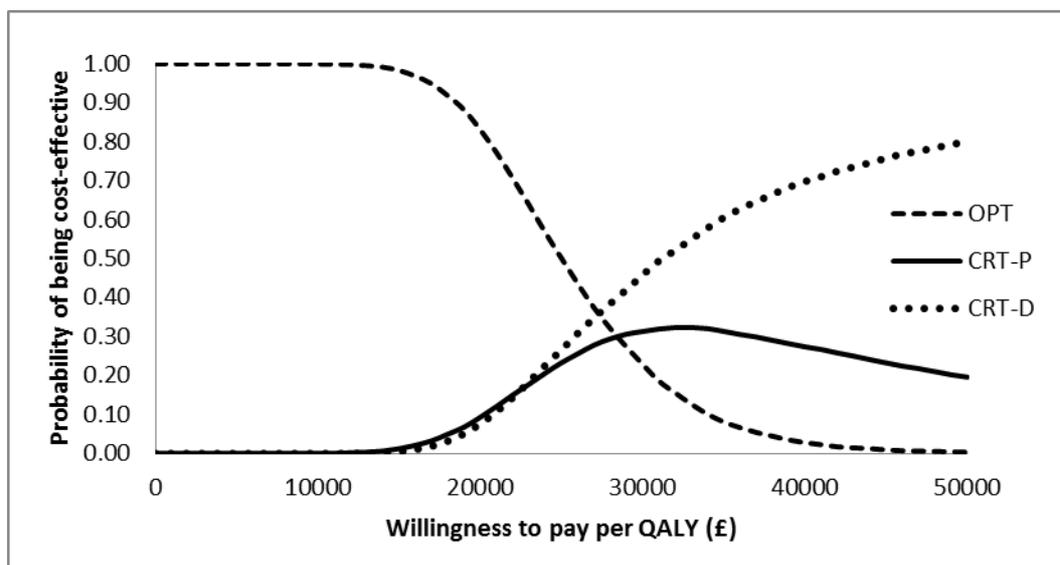


Figure 39 below shows the variation in the probability of the three treatment strategies being cost effective as the WTP increases from £0 to £50,000 per QALY gained. At a WTP of £20,000 per QALY gained, the probability of OPT alone (with subsequent upgrades) being cost-effective is 83%, 9% for CRT-P + OPT, and 8% for CRT-D + OPT. Above a WTP of £28,000 per QALY, the intervention with highest probability of being cost effective is CRT-D + OPT (38%). At a WTP of £30,000/QALY gained, CRT-D + OPT and CRT-P + OPT have 46% and 31% probability of being cost-effective, respectively, whilst OPT alone has 23%.

Figure 39. Cost-effectiveness acceptability curve for Population 2



5.4.5.3 Population 3 - Patients with both conditions

Patients with both conditions were modelled receiving initially OPT alone, ICD + OPT, CRT-P + OPT, or CRT-D + OPT, to estimate the relative cost-effectiveness of these four treatment strategies. The relevant comparisons for this population are therefore CRT-D + OPT versus OPT alone (allowing for subsequent device implantations), or CRT-P or ICD alongside OPT.

Base case analysis

RAFT¹⁴¹ provided the estimates for all-cause mortality and distribution of patients by NYHA class used for our base case analysis for Population 3. Table 135 presents the estimated discounted costs, life years, and QALYs gained for each strategy, as well as the incremental cost-effectiveness ratios for the relevant comparisons.

The initial management of Population 3 patients with ICD+OPT is estimated to be the least costly and least effective strategy. Initial management with OPT alone (followed by necessary device implants) has a similar estimated cost (£287 higher) than for ICD + OPT, and 0.10 more QALYs gained than with ICD + OPT. Thus, each additional QALY gained with OPT alone is estimated to cost £2,824 more.

Similar costs and QALYs are estimated for the CRT-P + OPT and CRT-D + OPT strategies. As marginally higher cost and slightly fewer QALYs are estimated for CRT-P + OPT than for CRT-D + OPT, CRT-P + OPT is dominated by CRT-D + OPT. When compared with the next most cost-effective option (OPT alone), CRT-P + OPT is extendedly dominated by CRT-D + OPT versus OPT alone, as this latter comparison presents a smaller ICER (ICER £35,193/QALY) than that for CRT-P + OPT versus OPT alone (ICER £41,414/QALY).

Compared with OPT alone, every additional QALY gained with CRT-D + OPT costs £35,193 more. CRT-D + OPT compared with ICD + OPT has an ICER of £27,195 per QALY gained.

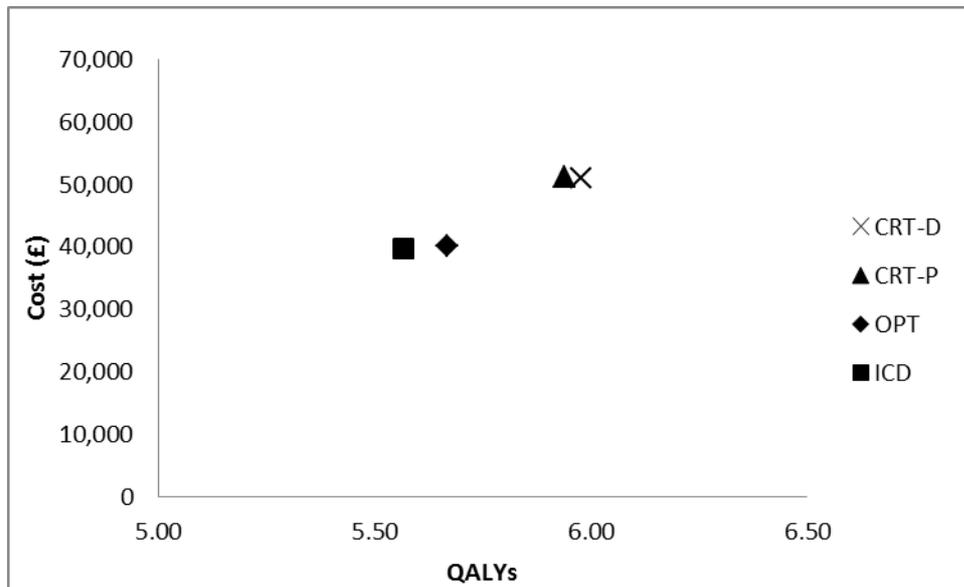
Table 135. Base case summary of cost-effectiveness results for Population 3

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs next best option ^a	ICER (£/QALY gained) vs ICD + OPT
ICD + OPT	39,719	7.45	5.57	-	-

OPT	40,006	7.59	5.67	2,824	-
CRT-P + OPT	51,202	7.96	5.94	Extendedly dominated	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	35,193	27,195
QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio ^a Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated					

The costs and QALYs gained per strategy are graphically presented in Figure 40, where the proximity between CRT strategies and that among OPT alone and ICD + OPT is noticeable.

Figure 40. Cost-effectiveness plane for Population 3



Model outputs and validation

Overall survival estimated in the model was compared to that reported in the relevant trials, see Appendix 17 for details.

Events

The percentage of time spent in the main categories of health states by an average patient for each strategy is presented in Table 136 below. All strategies being compared show similar occupancies for health states where the patient is stable with therapy (most of the patient’s lifetime) or experiences device-related interventions (implant surgery, post-operative complications, routine replacements, lead displacements, and infections). The model estimates small differences in time spent in hospital between strategies as well.

Table 136. Overall distribution of patients' lifetime by health state categories for Population 3

Health state categories	% of remaining life			
	OPT	ICD	CRT-P	CRT-D
Stable with therapy	94.32%	93.28%	93.53%	93.33%
OPT	22.68%	0.42%	1.99%	0.07%
ICD	10.52%	89.70%	10.44%	13.00%
CRT-P	0.03%	0.00%	20.59%	0.00%
CRT-D	61.10%	3.15%	60.50%	80.26%
Hospitalisations	3.07%	4.08%	2.95%	3.62%
Implant surgery	0.78%	0.87%	1.54%	0.91%
ICD	0.13%	0.84%	0.13%	0.15%
CRT-P	0.00%	0.00%	0.76%	0.00%
CRT-D	0.65%	0.04%	0.65%	0.76%
Routine replacements	0.66%	0.54%	0.67%	0.70%
Lead displacement	0.25%	0.13%	0.33%	0.33%
Postoperative complications	0.17%	0.09%	0.26%	0.20%
Infections	0.05%	0.05%	0.06%	0.06%
Device-related interventions ^a	1.90%	1.67%	2.85%	2.19%
^a Sum of occupancy in implant surgery, post-operative complications, routine upgrades, lead displacements, and infections				

The number of the most relevant events estimated for each arm of the Population 3 model is presented below in Table 137. The cohort of patients initially managed with OPT alone is estimated to receive 1,850 implants (1,552 CRT-D, 297 ICD, and 1 CRT-P) of which 820 are estimated to be associated with routine replacements according to the estimated battery lifetime. In the cohort initially implanted ICD, 47 are expected to upgrade to CRT-D and 9 are expected to receive ICD later on due to CRT-D implant failure. Both strategies where the defibrillator function is implanted initially (ICD + OPT and CRT-D + OPT) involve fewer device upgrades, with the reported ICD upgrades resulting from CRT-D implant failure.

Table 137. Number of events for cohorts of 1,000 patients – Population 3

Event	Strategy			
	OPT	ICD	CRT-P	CRT-D
Initial implants	0	1,000	1,000	1,000
ICD	0	1,000	0	0
CRT-P	0	0	1,000	0
CRT-D	0	0	0	1,000
Hospitalisations	5,446	4,957	4,797	4,790
OPT	1,171	21	110	4
ICD	578	4,776	603	757
CRT-P	808	15	1,072	3
CRT-D	2,889	144	3,012	4,025
Total upgrades	974	56	1,025	203
ICD	160	9	169	195
CRT-P	1	0	0	0
CRT-D	812	47	856	8
Surgical complications	212	107	343	259
ICD	17	96	17	20
CRT-P	0	0	119	0
CRT-D	196	11	206	239
Lead displacements	313	151	432	435
ICD	17	137	17	22
CRT-P	0	0	106	0
CRT-D	296	15	309	413
Infections	57	59	76	78
ICD	7	57	7	9
CRT-P	0	0	17	0
CRT-D	50	2	52	69
Replacements	820	647	874	919
ICD	130	609	137	148
CRT-P	0	0	4	0
CRT-D	690	38	733	771
Number of devices ^a	1,850	1,762	2,974	2,201
ICD	297	1,674	313	353
CRT-P	1	0	1,021	0
CRT-D	1,552	88	1,640	1,848

^a Sum of number of device initial implants, upgrades, infections (required new device), and replacements

Deterministic sensitivity analysis

MADIT-CRT

All-cause mortality reported for males in the CRT-D arm of MADIT-CRT¹³² and the respective HR for ICD for the whole population of MADIT-CRT¹³² (1.00, 95% CI 0.69, 1.44) were used as an alternative scenario to the outcomes used in the base case analysis from RAFT.¹⁴¹ Table 138 below summarises the cost-effectiveness results for this scenario.

Generally, most strategies became more costly and yielded greater health benefit in this scenario than in the base case. OPT alone (and subsequent device implants) is the least costly and least effective strategy in this scenario. ICD + OPT is slightly more costly but yields a greater benefit than OPT alone. As CRT-P + OPT and CRT-D + OPT are less effective than ICD + OPT and much more costly, both CRT strategies are extendedly dominated by ICD + OPT compared with OPT alone. Therefore, the results obtained with MADIT-CRT data indicate ICD + OPT as the most cost-effective strategy, with an ICER of £154 per QALY gained compared with OPT alone.

As MADIT-CRT found no statistically significant difference in all-cause mortality between ICD and CRT-D, for this scenario, the model assumed the same risk of death for ICD and CRT-D. Similar benefit was therefore estimated for the ICD + OPT and CRT-D + OPT strategies (the 0.04 difference in QALYs gained is due to less time spent with device-related interventions in the ICD + OPT cohort than in the CRT-D + OPT one). A much lower cost was estimated for ICD + OPT than for CRT-D + OPT, as the first is estimated to involve less device upgrades and replacements.

Table 138. MADIT-CRT scenario cost-effectiveness results (Population 3)

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs next best option ^a
OPT	49,908	9.59	7.17	-
CRT-P + OPT	60,736	9.89	7.39	Extendedly dominated
CRT-D + OPT	60,051	9.97	7.45	Extendedly dominated
ICD + OPT	49,957	10.01	7.49	154

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio
^aTreatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated

Univariate sensitivity analysis

Comprehensive univariate sensitivity analyses were performed on the parameters informing Population 3 model as well. Table 139 to Table 142 present the sensitivity analysis results of the most influential parameters (i.e. those that when varied between the 95% CI limits caused a variation $>£20,000/\text{QALY}$ in the ICER) for each of the relevant comparisons: CRT-D + OPT versus OPT alone (allowing for subsequent device implantations), CRT-D + OPT versus CRT-P + OPT, and CRT-D + OPT versus ICD + OPT.

The cost-effectiveness results for the comparison of initial treatment with CRT-D + OPT versus OPT alone (Table 139 below) were quite robust to the variation of the parameters input in the model, with only two parameters varying the ICER more than £20,000. The comparison of CRT-D + OPT versus OPT alone showed great sensitivity to the RR of all-cause mortality for the OPT alone arm. The ICER of CRT-D + OPT decreased to £22,240/QALY gained when a greater risk of death is assumed for OPT than for CRT-D + OPT (due to the incremental QALY gain with the latter). When a shorter time horizon was considered (assuming the same as the CRT-D device lifetime), less benefit from CRT-D + OPT relative to OPT alone was accrued, and therefore the ICER rose as the time horizon decreased.

Table 139. Univariate sensitivity analysis results for CRT-D + OPT vs OPT

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	-	-	10,906	0.31	35,193
RR of all-cause mortality (OPT)	1.563	1.163	9,109	0.07	124,733
		2.083	12,972	0.58	22,240
Time horizon	Lifetime	CRT-D lifetime (7y)	9,347	0.15	63,837

Table 140 below shows the univariate sensitivity analysis results for CRT-D + OPT compared with ICD + OPT. The most influential parameters for this comparison were the RR of all-cause mortality with ICD and the lifetime of CRT-D and ICD devices.

Assuming a lower RR of death with ICD would substantially increase the ICER for CRT-D + OPT versus ICD + OPT, as there is a very small QALY gain (0.07). Also, assuming a 4-year device lifetime for CRT-Ds would almost double the ICER for CRT-D + OPT versus ICD + OPT.

Varying ICD's longevity-related parameters also had a substantial impact on the incremental cost of CRT-D versus ICD. When ICD were assumed to have a longer lifetime (13 years), a higher incremental cost with CRT-D was estimated and this strategy became non cost-effective (ICER

£35,034/QALY). The opposite happened when a 5-year longevity for ICD was used (alongside the 7-year CRT-D lifetime).

Table 140. Univariate sensitivity analysis results for CRT-D + OPT vs ICD + OPT

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	-	-	11,193	0.41	27,195
RR of all-cause mortality (ICD)	1.19	1.04	9,407	0.07	127,299
		1.37	12,981	0.75	17,262
Device lifetime (CRT-D), $\ln(\lambda), \gamma$	-15.465, 1.935 (7y)	-16.000, 1.863 (13y)	3,841	0.44	8,784
		-14.931, 2.006 (4y)	22,019	0.37	59,421
Device lifetime (ICD), $\ln(\lambda), \gamma$	-15.78 1.94 (~ 8 years)	-16.182 1.889 (~13 years)	14,285	0.41	35,034
		-15.385 1.996 (~5 years)	5,951	0.42	14,218

Table 141 below shows the univariate sensitivity analysis for the CRT-D + OPT versus CRT-P + OPT comparison, with 10 parameters that made the ICER range more than £20,000. As the estimated costs and benefits of these strategies are so similar, the comparison of CRT-D + OPT and CRT-P + OPT is sensitive to the variation of more parameters. Overall, this comparison showed greater sensitivity to parameters related to devices' preventive effect on arrhythmia (baseline risk of hospitalisation for arrhythmia with CRT-D and RR of hospitalisation for arrhythmia of CRT-P), and CRT-D's lifetime.

For the base case analysis, the baseline risk of hospitalisation for arrhythmia with CRT-D (0.0285) was derived from the relevant trials included in the systematic review. As no evidence on the comparison of CRT-P with CRT-D regarding hospitalisation for arrhythmia was found, the risk for CRT-P was assumed to be the same as that of CRT-D, given that clinical advice suggested that Population 3 patients are likely to be hospitalised for arrhythmia irrespective of having a device with defibrillator function implanted. When a lower baseline risk of hospitalisation for arrhythmia is used, the ICER of CRT-D + OPT versus CRT-P + OPT increases significantly as the incremental cost of CRT-D is estimated to increase with no additional benefit. Under this scenario, all strategies show a reduction of the estimated costs; however, strategies without a defibrillator (CRT-P and OPT alone) yield a greater reduction (about £10,000 less) than those with a defibrillator function (CRT-D and ICD), which incur costs of about £5,000 less than in the base case. When the relative risk of

hospitalisation for arrhythmia with CRT-P is assumed less than the baseline risk, the cost of the CRT-P + OPT strategy decreases and this strategy is no longer dominated by CRT-D + OPT.

As for the previous comparison of two strategies both involving initial treatment with a device, CRT-D devices' longevity showed great impact on the ICER for the comparison of CRT-D + OPT with CRT-P + OPT. The incremental cost associated with a 4-year time period for replacement led to an ICER of £58,794/QALY gained.

Table 141. Univariate sensitivity analysis results for CRT-D + OPT vs CRT-P + OPT

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	-	-	-291	0.04	Dominant
Baseline risk of hospitalisation for non-fatal arrhythmia (CRT-D)	0.0285	0.0146	3,993	0.04	93,501
		0.0424	-1,823	0.04	Dominant
Device lifetime (CRT-D), $\ln(\lambda), \gamma$	-15.465, 1.935 (~7y)	-16, 1.863 (~13y)	-866	0.04	Dominant
		-14.931, 2.006 (~4y)	1,840	0.03	58,794
RR of hospitalisation for non-fatal arrhythmia (CRT-P)	1	0.80	1,374	0.04	38,915
		1.20	-1,457	0.04	Dominant
Risk of lead displacement (CRT-D)	0.004	0.0004	-926	0.05	Dominant
		0.0071	313	0.03	9,393
RR of all-cause mortality (OPT)	1.563	1.163	-460	0.02	Dominant
		2.083	-97	0.07	Dominant
Discount rates of costs and benefits	3.5%, 3.5%	0%, 0%	-1,054	0.05	Dominant
		6%, 1.5%	207	0.05	4,370
Risk of surgical mortality with CRT-P	0.0048	0.0015	-450	0.02	Dominant
		0.0081	-131	0.06	Dominant
Risk of lead infections (CRT-D)	0.0006	0	-659	0.04	Dominant
		0.0015	243	0.04	6,432
Risk of lead displacement (CRT-P)	0.0037	0.0004	188	0.03	5,513
		0.0071	-764	0.04	Dominant
Time horizon	Lifetime	CRT-D lifetime	-613	0.02	Dominant

		(7y)			
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The comparison of OPT alone versus ICD+OPT was also sensitive to many parameters (see Table 142 below), given that the estimated costs and QALYs for these strategies were very similar. It showed particular sensitivity to the time horizon, lifetime of CRT-D and ICD devices, baseline risk of hospitalisation for non-fatal arrhythmia (CRT-D) and the respective RRs with OPT and ICD.

Assuming a shorter time horizon made the ICER for the comparison of OPT alone versus ICD + OPT increase substantially as the first strategy showed cost saving associated with a very small reduction of the health benefits accrued. When the 8-year ICD lifetime was assumed as time horizon for the model, OPT alone showed an incremental cost and less benefit compared with ICD + OPT. This incremental cost with OPT alone is mainly a result of the referrals for CRT-D implants due to severe arrhythmic events.

A substantial rise of incremental costs for OPT alone versus ICD + OPT is estimated also when CRT-D devices are assumed to require replacement every 4 years, associated with a small reduction of QALY gain compared with the base case (ICER £123,385). When the ICD's lifetime is assumed to be longer (13 years), the incremental cost of OPT rises but the same incremental benefit is estimated relative to the base case.

The baseline risk of hospitalisation for arrhythmia and the relative effects of the alternative treatments also had noticeable impact on this comparison. With a lower baseline risk, the estimated costs and QALYs for all strategies decreased (strategies without defibrillator yield a greater reduction in costs than those with a defibrillator) compared with the base case. Mainly due to fewer referrals for CRT-D implants, OPT alone (followed by the subsequent implants) was the strategy which saved more costs relative to the base case and also the one with the greatest loss of QALYs accrued; hence the high ICER estimated for it compared with ICD + OPT when a lower baseline risk of hospitalisation due to severe arrhythmia was used. The ICER for OPT alone versus ICD + OPT also rises when the relative risk of hospitalisation for arrhythmia is assumed higher for OPT or lower for ICD + OPT, as the additional cost associated with OPT rises substantially (and the additional benefit rises slightly or does not change, respectively).

Table 142. Univariate sensitivity analysis results for OPT alone versus ICD + OPT

Parameter	Base case value	DSA value	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	-	-	287	0.10	2,824
Time horizon	Lifetime	CRT-D lifetime (7y)	-4,395	-0.05	94,341
Device lifetime (CRT-D), $\ln(\lambda), \gamma$	-15.465, 1.935 (~7y)	-16, 1.863 (~13y)	-6,129	0.12	Dominant
		-14.931, 2.006 (~4y)	8,653	0.07	123,385
Device lifetime (ICD), $\ln(\lambda), \gamma$	-15.78, 1.94 (~8 years)	-16.182, 1.889 (~13 years)	3,505	0.10	35,868
		-15.385, 1.996 (~5 years)	-5,086	0.11	Dominant
Baseline risk of hospitalisation for non-fatal arrhythmia (CRT-D)	0.0285	0.0146	-4,565	-0.09	49,987
		0.0424	2,086	0.19	10,896
RR of hospitalisation for non-fatal arrhythmia (OPT)	1	0.8	-1,978	0.04	Dominant
		1.2	1,923	0.15	13,107
RR of hospitalisation for non-fatal arrhythmia (ICD)	1.11	0.88	2,330	0.10	22,346
		1.41	-2,334	0.10	Dominant
Baseline risk of all-cause mortality (CRT-D), $\ln(\lambda), \gamma$	-6.334, 1.234	-6.467, 1.198	2,047	0.14	14,124
		-6.202, 1.270	-1,092	0.06	Dominant
Lead displacement CRT-D	0.0037	0.0004	-1,083	0.11	Dominant
		0.0071	1,600	0.09	17,916
Discount rates of costs and benefits	3.5%, 3.5%	0%, 0%	3,183	0.22	14,529
		6%, 1.5%	-1,212	0.16	Dominant

Table 143 presents the parameters that have caused a change of the most cost-effective strategy as their value ranged over their 95% CI limits. These relate mainly to the longevity of devices with the defibrillator function (these have shorter estimated lifetimes relative to CRT-P), the relative risk of all-cause mortality of ICD and OPT, and the baseline risk of hospitalisation for arrhythmia (CRT-D) and respective RR with ICD, and discount rates.

Overall, ICD + OPT becomes the most cost-effective strategy at a WTP of £20,000 per QALY gained when 8-year time horizon (the lifetime of an ICD device) is used, or a shorter CRT-D device lifetime (of approximately 4 years), a longer ICD device lifetime (approximately 13 years), a lower RR of all-cause mortality for ICD (RR=1.04), a higher RR of all-cause mortality for OPT (RR=2.08), and a lower RR of hospitalisation for arrhythmia with ICD.

Under a scenario of not discounting future costs and benefits or of discounting future costs at a higher rate (6%) than future benefits (1.5%), CRT-D + OPT would become the most cost-effective strategy at a WTP of £30,000 per QALY gained (ICER £25,602 and £29,650/QALY, respectively, compared with OPT alone). If a higher RR of all-cause mortality for patients being managed with OPT compared to those with CRT-D (RR=2.08) is used, CRT-D becomes the optimal strategy with an ICER just above the WTP of £30,000 per QALY (ICER = £22,240 per QALY).

CRT-P + OPT became the most cost-effective strategy at £30,000/QALY WTP when the lower limit of the baseline risk of hospitalisation for arrhythmia was used (ICER = £26,200 per QALY gained compared with OPT alone).

Table 143. Most cost-effective strategy according to the variation of the most influential parameters

Parameter	Base case value	DSA value	Most CE strategy at £20,000/QALY	Most CE strategy at £30,000/QALY
Base case	-	-	OPT	OPT
Time horizon	Lifetime	8 years (ICD lifetime)	ICD + OPT	ICD + OPT
Device lifetime (CRT-D), $\ln(\lambda), \gamma$	-15.465, 1.935 (~7y)	UL: -14.934, 2.006 (~4y)	ICD + OPT	ICD + OPT
Device lifetime (ICD), $\ln(\lambda), \gamma$	-15.784, 1.943 (~8y)	LL: -16.182, 1.889 (~13 y)	ICD + OPT	ICD + OPT
RR of all-cause mortality (ICD)	1.19	LL= 1.04	ICD + OPT	ICD + OPT
RR of all-cause mortality (OPT)	1.563	UL= 2.08	ICD + OPT	CRT-D + OPT
Costs and Benefits discount rates	3.5%, 3.5%	0%, 0%	OPT	CRT-D + OPT
		6%, 1.5%	OPT	CRT-D + OPT
Baseline risk of hospitalisation for arrhythmia (CRT-D)	0.029	LL= 0.015	OPT	CRT-P + OPT
RR of hospitalisation for arrhythmia with ICD	1.11	LL= 0.88	ICD + OPT	OPT

Scenario analysis

Device longevity

Clinical advice indicated that device longevity estimates for base case analysis could be overestimated. A scenario analysis assuming lower mean estimates of devices' lifetimes used by Fox and colleagues⁴³ (see Table 130 in Section 5.4.5.2.) was conducted and results are presented in Table 144 below. In this scenario, initial management with OPT alone (and subsequent upgrades) was less costly and more effective than with ICD + OPT (i.e. OPT alone dominated ICD + OPT). CRT-P + OPT is more costly and more effective than OPT alone. However, the ICER for CRT-P + OPT versus OPT alone is higher (£43,274 per QALY gained) than that for CRT-D + OPT compared with OPT alone (£39,318 per QALY gained). CRT-P + OPT is therefore extendedly dominated by CRT-D + OPT versus OPT alone. Compared with ICD + OPT, CRT-D + OPT presents an ICER of £23,690/QALY gained and CRT-P + OPT is extendedly dominated in this case as well.

Table 144. Shorter devices' lifetime scenario results (Population 3)

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs next best option ^a	ICER (£/QALY gained) vs ICD + OPT
ICD + OPT	47,068	7.44	5.56	-	-
OPT	44,567	7.57	5.65	Dominant	-
CRT-P + OPT	56,135	7.94	5.92	Extendedly dominated	Extendedly dominated
CRT-D + OPT	56,601	7.99	5.96	39,318	23,690
QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio ^a Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated					

Effect of CRT devices on HF progression

Population 3 base case analysis is based on the conservative assumption of CRT devices having no impact on the distribution of patients by NYHA class over time. A scenario was therefore created to incorporate an eventual beneficial effect of CRT devices on patients' HF progression and consequently on the HRQoL of Population 3, assuming that 50% of patients with a CRT device would improve 1 NYHA class at 6 months of treatment. Table 145 summarises the cost-effectiveness results for this scenario.

Compared with the base case analysis, the improvement of NYHA class introduced in this scenario increased the QALYs estimated for all cohorts. The cost of all cohorts decreased as well due to the improvement in HF. As costs and QALYs gained changed in similar magnitude and direction, the ICERs obtained with this scenario are similar to those of the base case analysis.

Table 145. CRT effect on HF scenario results for Population 3

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs next best option ^a	ICER (£/QALY gained) vs ICD + OPT
ICD + OPT	39,253	7.45	5.91	-	-
OPT	39,528	7.59	5.99	3,165	-
CRT-P + OPT	50,698	7.96	6.27	Extendedly dominated	Extendedly dominated
CRT-D + OPT	50,405	8.01	6.31	34,099	27,483

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio
^aTreatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated

Utilities

A scenario with the utility estimates used by Fox and colleagues⁴³ (presented in Table 132 in Section 5.4.4.4) was explored. Table 146 shows the cost-effectiveness results for this scenario. Using the same utility values as by Fox and colleagues did not impact the model results significantly, a reduction of 0.02 QALYs for OPT alone and of 0.03 for all the strategies beginning with device implant. The ICERs obtained with this scenario are similar to those for the base case analysis.

Table 146. Utilities scenario results for Population 3

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs next best option ^a	ICER (£/QALY gained) vs ICD + OPT
ICD + OPT	39,719	7.45	5.55	-	-
OPT	40,006	7.59	5.64	3,033	-
CRT-P + OPT	51,202	7.96	5.91	Extendedly dominated	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.95	35,515	27,859

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio
^aTreatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated

Costs

All relevant comparisons showed great sensitivity to costs when these were varied as a group between the lower and upper limits of their 95% CI (see Table 111). When all costs were varied, the ICER ranged over £25,000 per QALY for all relevant comparisons except for OPT versus ICD + OPT which showed small variation. The ICER ranged from £22,271 to £50,824 per QALY gained for

CRT-D + OPT compared with ICD + OPT, from £13,829 to £43,853 per QALY gained for CRT-D + OPT versus CRT-P + OPT, and from £28,200 to £60,864 for CRT-D + OPT versus OPT alone.

Under a scenario using the upper limits of all costs, ICD + OPT and OPT alone are the most cost-effective strategies at £20,000 and £30,000/QALY WTP, respectively. When the lower limits of all costs (including device-related costs, health state costs and pharmacological therapy costs) are used, the most cost-effective strategy at £30,000 per QALY gained is CRT-D + OPT.

Probabilistic sensitivity analysis

Table 147 reports the base case probabilistic cost-effectiveness results for Population 3. Appendix 15 reports the variables (mean values and confidence intervals) included in the PSA and the form of distribution used for sampling and the parameters of the distribution. Overall, the probabilistic results are consistent with the deterministic results. PSA results show that an additional QALY gained with OPT alone is estimated to cost £13,053 more than ICD + OPT. The estimated ICER for CRT-D + OPT versus OPT alone is £34,988 per QALY gained. Compared with ICD + OPT, the ICER for CRT-D + OPT is £23,133 per QALY.

Table 147. Base case summary of the probabilistic cost-effectiveness results for Population 3

Strategy	Cost (£)	QALYs	ICER (£/QALY gained) vs next best option ^a	ICER (£/QALY gained) vs ICD + OPT
ICD + OPT	44,310	5.58	-	-
OPT	38,732	5.63	13,053 (-515,869; 471,462)	-
CRT-P + OPT	51,286	5.94	Extendedly dominated	Extendedly dominated
CRT-D + OPT	51,690	5.98	34,988 (-191,681; 264,108)	23,133 (-196,334; 222,149)
QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio ^a Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated				

PSA results of 10,000 iterations are presented on Figure 41 in terms average cost and QALYs, showing their overlap on the scatter plot.

Figure 41 Cost-effectiveness scatter plot for Population 3

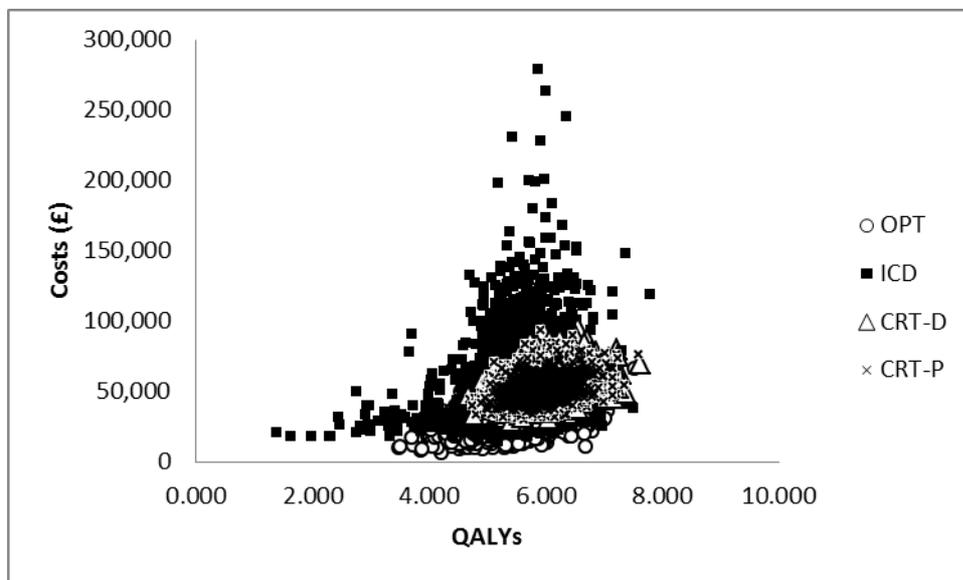
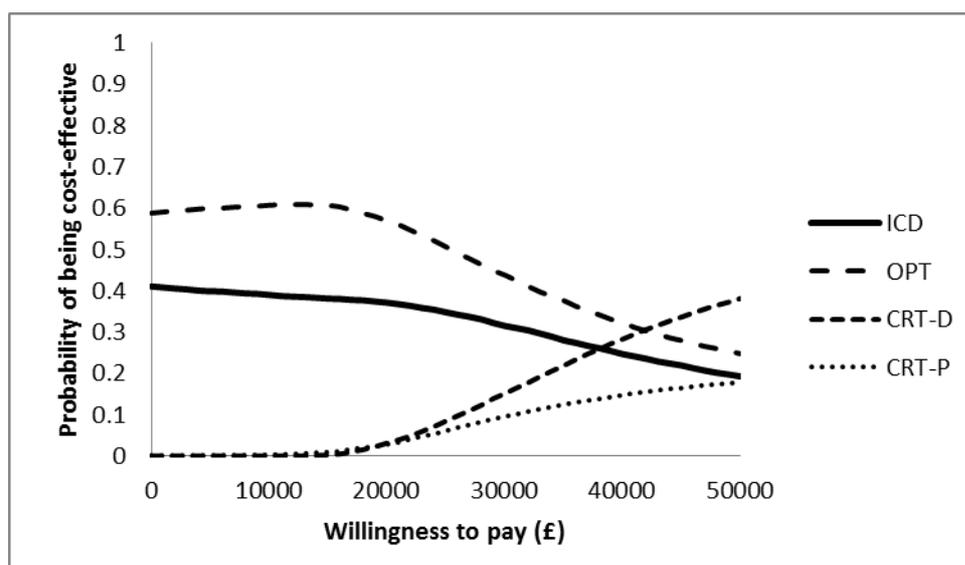


Figure 42 below shows the variation of the probability of being cost-effective for the three treatment strategies as the willingness to pay increases from £0 to £50,000 per QALY gained. At a willingness-to-pay of £20,000 per QALY gained, the probability of OPT alone being cost-effective is 57%, 37% for ICD + OPT, and about 3% for CRT-D + OPT and for CRT-P + OPT. Above a WTP of £42,000 per QALY, the intervention with highest probability of being cost effective is CRT-D + OPT (31%). At £30,000/QALY WTP, OPT alone, ICD + OPT, CRT-D + OPT, and CRT-P + OPT have 44%, 31%, 15%, and 10% probability of being cost-effective, respectively.

Figure 42. Cost-effectiveness acceptability curve for Population 3



5.4.6 Summary of independent economic evaluation

Population 1

- The addition of ICD to OPT for secondary prevention of SCD has an ICER of £19,479 per QALY gained compared with OPT alone. Its probability of being cost-effective at a WTP of £20,000 and £30,000 per QALY gained is 51% and 82%, respectively.
- The ICER for the mixed-age cohort is slightly higher (£24,967/QALY), as it increased with age and 52% of these patients are expected to be over 65 years old.
- Subgroup analysis with MADIT II trial data shows that ICD + OPT is cost-effective (ICER = £14,231/QALY) for primary prevention of SCD in patients with remote myocardial infarction.
- For the SCD-HeFT trial (patients with mild to moderate heart failure), the estimated ICER for ICD + OPT is £29,756 per QALY gained compared with OPT alone.
- For patients with non-ischaemic cardiomyopathy the ICER was £26,028 per QALY gained.
- The parameters with greater impact on the ICER were the time horizon, the HR for all-cause mortality associated with the ICD + OPT arm, the risk of surgical death during ICD implantation, and the lifetime of the device.

Population 2

- The addition of CRT-P to OPT (in the initial stage of management of heart failure) presented an estimated ICER of £27,584 per QALY gained compared with initial management with OPT alone (allowing for the subsequent implants). Similarly, the initial implant of CRT-D

alongside OPT showed an ICER of £27,899 per QALY gained compared with OPT alone. When comparing CRT-D + OPT with CRT-P + OPT, a slightly higher ICER was estimated (£28,420 per QALY gained).

- At a WTP of £20,000 per QALY gained, the initial management with OPT alone followed by the clinically necessary device implants is the strategy with highest probability of being cost-effective (81%). Above a WTP of £28,000 per QALY, the strategy with highest probability of being cost effective is CRT-D + OPT (38%).
- The incremental cost-effectiveness results for the comparisons relevant for Population 2 seem to be sensitive mainly to device-related costs and to parameters that determine the incremental benefit of the devices on patients' survival, such as the RRs of SCD and HF death for CRT-P. CRT-D device's lifetime also showed to be particularly influential due to the incremental costs incurred when it became shorter.
- In a scenario assuming the upper limit estimates of device-related costs or lower estimates for the longevity of all devices, both CRT-P + OPT and CRT-D + OPT became non-cost-effective compared with initial management with OPT alone (followed by the subsequent upgrades).

Population 3

- The base case found that the most cost-effective strategy for people with both conditions at a WTP range of £20,000 to £30,000 per QALY is the initial management with OPT alone (followed by device implantation and subsequent upgrades as necessary). Both strategies with the initial implantation of CRT devices present ICERs over the WTP range of £20,000 to £30,000 per QALY compared with OPT alone (CRT-D £35,193/QALY; CRT-P £41,414/QALY). Costs and QALYs for CRT-D and CRT-P are similar.
- CRT-D + OPT is cost-effective compared with ICD + OPT at a WTP of £30,000 (£27,195/QALY).
- At a WTP of £30,000 per QALY, OPT alone, ICD + OPT, CRT-D + OPT, and CRT-P + OPT have 44%, 31%, 15%, and 10% probability of being cost-effective, respectively. Above the WTP of £42,000 per QALY, the intervention with highest probability of being cost effective is CRT-D + OPT (31%).
- In an alternative scenario using MADIT CRT data, CRT-P and CRT-D are extendedly dominated by ICD + OPT, which is the most cost effective strategy (ICER £154/QALY gained versus OPT).
- Overall, the relative cost-effectiveness of the strategies compared for Population 3 had greater sensitivity to costs and CRT-D device lifetime. The risk of all-cause mortality with OPT relative to CRT-D was the most influential parameter on the comparison of CRT-D + OPT

with OPT alone (followed by the subsequent updates). Similarly, the preventive effect of all-cause mortality estimated for ICD was particularly important for the comparison of CRT-D + OPT with ICD + OPT. The preventive effect of devices on hospitalisation due to arrhythmia was particularly prominent for the comparison of CRT-D + OPT with CRT-P + OPT, as well as CRT-D's longevity. The most influential parameters on the comparison between OPT alone (and subsequent device implantations) and ICD + OPT were CRT-D and ICD devices' lifetime, and the risk of hospitalisation due to arrhythmia of CRT-D, ICD and OPT.

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6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Implications for service provision

The possible extension of indications for ICD and CRT devices is likely to lead to an increase in their use. This will have an impact in terms of cost and service capacity on the provision of services in the UK. Appropriately trained cardiologists, associated clinical staff and technicians, and properly equipped implantation centres will require resources. Access to service provision and location of services are issues for consideration.

Implications for patients and carers

The sudden death of a wage earner results in costs to their relatives that are difficult to quantify but are important nonetheless. With an ICD, individuals and their families feel reassured. The improvements associated with CRT are expected to lessen the impact of heart failure on the lives of individuals and their families.

7 DISCUSSION

7.1 Statement of principal findings

7.1.1 Clinical effectiveness

7.1.1.1 People at risk of sudden cardiac death: ICDs compared with OPT

Thirteen RCTs were included that compared ICDs with medical therapy, four RCTs in people at increased risk of sudden cardiac deaths due to previous ventricular arrhythmias (secondary prevention) and nine RCTs in people who have not suffered a life-threatening arrhythmia but are at risk (primary prevention). Risk of bias was noted in the RCTs, specifically through performance bias due to lack of blinding, detection bias on QoL outcomes and possible selection bias through inadequate reporting. Length of follow-up varied from 18 to 57 months in the four RCTs on secondary prevention and from 20 to 37 months in the nine RCTs on primary prevention. Sample sizes ranged from 66 to 1016 in the four RCTs on secondary prevention and from 103 to 2521 in the nine RCTs on primary prevention. Most participants suffered from congestive heart failure with 50% to 80% of those in secondary prevention RCTs in NYHA I and II and 50% to 66% in primary prevention RCTs in NYHA II or II and III. LVEF varied from 30% to 70% in the secondary prevention RCTs and from 22% to 35% in the primary prevention RCTs. The studies were synthesised according to the criteria they used to identify people at risk of sudden cardiac death.

Ventricular arrhythmia/cardiac arrest (secondary prevention)

Four RCTs compared ICD with AAD. Meta-analysis found that ICDs significantly reduced the risk of all-cause mortality (RR 0.75; 95% CI, 0.61 to 0.93; $p=0.01$; 4 RCTs), sudden cardiac deaths (RR 0.49; 95% CI, 0.34 to 0.69; $p<0.001$; 4 RCTs) and total cardiac deaths (RR 0.74; 95% CI, 0.61 to 0.91; $p=0.004$; 2 RCTs). No significant differences were found between ICDs and AAD for non-arrhythmic cardiac deaths (RR 0.97; 95% CI, 0.72 to 1.31; $p=0.83$; 2 RCTs) or other non-cardiac causes of death (RR 0.79; 95% CI, 0.45 to 1.37; $p=0.40$; 2 RCTs). Two RCTs reported significant benefits for ICDs compared with AAD on overall survival at 3 years (difference 11%, $p<0.02$), survival free of cardiac death at 2 years (difference 4%, $p=0.004$), survival to arrhythmic death at 2 years (difference 5%, $p=0.0002$) and survival free of sudden death at 57 months (HR 0.423, $p=0.005$). One RCT found significant improvements in SF-36 PCS and MCS and PCC for both groups to 1 year follow-up, with no significant between group differences. Another RCT showed benefits on MHI and NHP for the ICDs with no changes for OPT at 1 year follow-up. Both RCTs showed a worsening QoL

increasing numbers of shocks. Pre-specified subgroup analyses for age, LVEF, cause of arrhythmia and qualifying arrhythmia demonstrated no significant difference from each other or the overall population for all-cause mortality.

One RCT (DEBUT) was included in the present review in addition to those included in the previous TAR.⁶⁵ The population in this trial, i.e. SUDS survivors, differed from those of the other RCTs. Despite this difference, the results from the present review concur with those of the previous review.⁶⁵

People with a recent myocardial infarction (within 6 to 41 days, or 31 days or less)

Two RCTs compared ICD plus OPT with OPT. Meta-analysis of two trials found no difference in all-cause mortality (RR 1.04; 95% CI, 0.86 to 1.25; p=0.69), total cardiac deaths (RR 0.97; 95% CI, 0.79 to 1.20; p=0.8) or non-cardiac deaths (RR 1.39; 95% CI, 0.86 to 2.27; p=0.18). People with ICD plus OPT had a lower risk of sudden cardiac death (RR 0.45; 95% CI, 0.31 to 0.64; p<0.0001), but a higher risk of non-arrhythmic cardiac death (RR 1.77; 95% CI, 1.30 to 2.40; p=0.0002). One trial reporting cumulative mortality found no statistically significant difference between groups. QoL was not reported. One trial reported no significant differences for 13 pre-specified subgroups (age, gender, congestive heart failure on admission, criterion of inclusion, ST-elevation MI, early reperfusion for ST-elevation MI, number of vessels, smoking and NYHA class at discharge, diabetes, hypertension, lipid abnormalities, number of risk factors) for all-cause mortality.

These trials were not included in the previous TAR.⁶⁵

People with remote myocardial infarction (more than three weeks or one month previously)

Meta-analysis of the two trials found a reduction in all-cause mortality (RR 0.57; 95% CI, 0.33 to 0.97; p=0.04), total cardiac deaths (RR 0.59; 95% CI, 0.42 to 0.83; p=0.003) and sudden cardiac death (RR 0.36; 95% CI, 0.23 to 0.55; p<0.00001) with ICD plus OPT compared with OPT. There was no difference in non-arrhythmic cardiac death (RR 0.95; 95% CI, 0.41 to 2.18; p=0.1) or non-cardiac death (RR 1.06; 95% CI, 0.58 to 1.95; p=0.84). One trial reporting hospitalisations found higher rates per 1000 months follow-up among people with ICDs (11.3 vs 9.4, p=0.09), with higher heart failure hospitalisations (19.9% vs 14.9%, p=nr). One trial assessed QoL using the HUI3, finding a worsening QoL for both ICD plus OPT and OPT groups annually over 3 years, with no statistically significant differences. One trial reported pre-specified subgroup analyses for all-cause mortality. The hazard ratios in all 12 of the subgroups (age, gender, ejection fraction, NYHA class or QRS interval, hypertension, diabetes, left bundle-branch block, atrial fibrillation, the interval since the most recent MI, type of ICD, and blood urea nitrogen) were similar, with no statistically significant interactions.

Both of these trials were included in the previous TAR,⁶⁵ and no additional RCTs in this population were identified by the present review.

People with non-ischemic or idiopathic dilated cardiomyopathy

Three RCTs compared ICD plus OPT versus OPT, or ICD plus OPT versus amiodarone plus OPT. Meta-analysis found no significant difference in all-cause mortality (RR 0.77; 95% CI, 0.52 to 1.15; $p=0.20$), total cardiac deaths (RR 2.03; 95% CI, 0.17 to 23.62; $p=0.57$), non-arrhythmic cardiac death (RR 1.13; 95% CI, 0.42 to 3.03; $p=0.81$) or non-cardiac death (RR 0.65; 95% CI, 0.13 to 3.29; $p=0.60$). However a statistically significant reduction was found in sudden cardiac deaths (RR 0.26; 95% CI, 0.09 to 0.77; $p=0.02$) with ICD. No statistically significant differences were found on measures of survival or QoL, on the QWBS, STAI, SF-12 MCS or PCS and MLHFQ. One trial reported six pre-specified subgroup analyses for all-cause mortality (age, sex, LVEF, QRS interval, NHYA class and history of atrial fibrillation). None of the differences between subgroups were statistically significant

Additional meta-analysis was undertaken on the advice of clinical experts, combining data on all-cause mortality from the non-ischaeamic congestive heart failure subgroup of SCD-HeFT with data from the three cardiomyopathy trials. The SCD-Heft non-ischemic subgroup strongly influenced the analysis, and a statistically significant effect in favour of ICD with no statistical heterogeneity was found for all-cause mortality (RR 0.74, 95% CI 0.58 to 0.93, $p=0.01$).

Only one of the three cardiomyopathy RCTs was included in the previous TAR⁶⁵ (CAT); the other two RCTs (AMIOVIRT, DEFINITE) were excluded from the previous TAR⁶⁵ due to their population. There were no sudden cardiac deaths in either group in the CAT trial. However the inclusion of the comparatively large DEFINITE trial in the present review strongly influences the results, demonstrating a significant reduction in sudden cardiac death with ICDs in people with non-ischaemic cardiomyopathy and moderate-to-severe left ventricular dysfunction.

People scheduled for CABG surgery

No significant difference was found in all-cause mortality (RR 1.08; 95% CI, 0.85 to 1.38; $p=0.53$), total cardiac deaths (HR 0.97; 95% CI, 0.71 to 1.33; $p=0.84$), non-arrhythmic cardiac death (RR 1.26; 95% CI, 0.87 to 1.82; $p=0.21$), non-cardiac death (RR 1.50; 95% CI, 0.82 to 2.73; $p=0.19$) or actuarial mortality at 4 years follow-up (HR 1.07; 95% CI, 0.81 to 1.42; $p=0.64$) in one trial. Rates of sudden cardiac death were lower with ICD, but this did not reach statistical significance (HR 0.55; 95% CI, 0.29 to 1.03; $p=0.06$). HRQoL was higher among people with OPT for all measures, and this was statistically significant for some perception of health transition, emotional role function, mental health, satisfaction with appearance and satisfaction with scar. Hazard ratios for ICD compared with

control for all-cause mortality were found to be similar among ten pre-specified subgroups (age, gender, heart failure, NYHA class, LVEF, diabetes mellitus, QRS complex duration, use of ACE inhibitors, use of class I or class III antiarrhythmic drugs, and use of beta-adrenergic-blocking drugs).

This trial was included in the previous TAR,⁶⁵ and no additional RCTs in this population were identified by the present review.

People with mild to moderate heart failure

All-cause mortality was significantly lower with ICD plus OPT than placebo plus OPT (HR 0.77; 97.5% CI, 0.62 to 0.96; $p=0.007$) in one trial. A significant reduction in total cardiac death (HR 0.76; 95% CI, 0.27 to 0.59; $p<0.001$) and sudden cardiac death (compared with placebo and amiodarone groups combined, RR 0.44; 95% CI, 0.31 to 0.61; $p<0.00001$) was also found with ICD. There was no statistically significant difference in non-arrhythmic cardiac death (RR 1.14; 95% CI, 0.88 to 1.48; $p=0.32$) or deaths from non-cardiac causes (RR 0.92; 95% CI, 0.66 to 1.27; $p=0.60$) compared with placebo and amiodarone groups combined. QoL was assessed on the DASI, MHI and global health status with either limited difference or no long term difference between the interventions. ICD shock resulted in a significant decrease in QoL. Pre-specified subgroup analyses found no interaction of ICD therapy ($p=0.68$) with the cause of congestive heart failure (ischaemic or non-ischaemic) for all-cause mortality, cardiac deaths, sudden deaths presumed to be ventricular tachyarrhythmic, heart failure deaths or noncardiac deaths. There was a statistically significant interaction between ICD therapy and NYHA class, where ICDs reduced the risk of all-cause mortality, cardiac mortality and sudden death presumed to be ventricular tachyarrhythmic in people with NYHA class II, but not in those with NYHA class III. The interaction between ICD therapy and NYHA class was not statistically significant for heart failure or noncardiac deaths.

This trial was in progress at the time of the previous TAR.⁶⁵

All four RCTs of people with previous ventricular arrhythmias reported adverse events, showing higher rates for ICDs (up to 30%), with most related to the placement and operation of the device. The nine primary prevention RCTs reported adverse event rates between 5% and 61% of people with an ICD, depending on the definition of adverse event and length of follow-up. Adverse event rates for the comparator treatment were between 12% to 55% in the three RCTs reporting this. Lead, electrode or defibrillator generator related problems affected 1.8 to 14% of people in five trials.

7.1.1.2 People with heart failure as a result of LVSD and cardiac dyssynchrony: CRT-P or CRT-D compared with each other or with OPT

Four RCTs were included comparing CRT-P with OPT in people with heart failure as a result of LVSD and cardiac dyssynchrony. One of these RCTs included a third arm with CRT-D. No other RCTs comparing CRT-P with OPT or with CRT-D were identified. There was some risk of bias in the trials, although the risk of bias was unclear in some cases due to inadequate reporting. Length of follow-up in the four RCTs varied: 3 months, 6 months, median 11.9-15.7 months and mean 37.4 months including an extension period. Sample size ranged from 58 to 1520 participants. The majority of participants had NYHA class III symptoms; the remaining few had NYHA class IV symptoms. The eligibility cut-off for LVEF was 35% or less in the trials, with average baseline LVEF 22% to 25% where reported. QRS interval was required to be 120 ms or more (two trials), 130 ms or more, and greater than 150 ms. Average baseline QRS interval was between 160 ms and 175 ms. Where reported the proportion of participants with ischaemic heart disease varied from around 40% to around 60% of participants.

CRT-P vs OPT

Meta-analysis found that CRT-P reduced the risk of all-cause mortality (RR 0.75, 95% CI 0.58 to 0.96, $p=0.02$), heart failure deaths (RR 0.67, 95% CI 0.51 to 0.88, $p=0.004$) and heart failure hospitalisations (RR 0.61, 95% CI 0.44 to 0.83, $p=0.002$). Combining three RCTs in a meta-analysis demonstrated no significant difference in sudden cardiac death (RR 0.97, 95% CI 0.44 to 2.14, $p=0.94$). One RCT (COMPANION) reported no statistically significant difference in total cardiac deaths (CRT-P 17.7% vs OPT 18.8%, $p=0.334$) or non-cardiac deaths (CRT-P 2.3% vs OPT 3.6%, $p=0.122$).

More people with CRT-P had an improvement of one or more NYHA class (RR 1.68, 95% CI 1.52 to 1.86, $p=0.00001$). One RCT reported change in LVEF and reported a statistically significant improvement with CRT-P compared with OPT (4.6% vs -0.2%, $p<0.001$) at 6 months. There was a greater improvement in exercise capacity with CRT-P, as measured by the distance walked in 6 minutes (meta-analysis of three trials, change from baseline or final values, MD 38.14 m, 95% CI 21.74 to 54.54, $p<0.00001$). A statistically significant improvement in peak oxygen consumption was also reported by two of these RCTs. All four RCTs found statistically significant improvements in QoL (MLWHFQ) score with CRT-P (change from baseline or final values, MD -10.33, 95% CI -13.31 to -7.36). One trial (CARE-HF) also reported statistically significant improvements in EQ-5D and QALYs with CRT-P.

One trial reported prespecified subgroup analysis. A significant interaction between CRT-P and aetiology was found, whereby people with non-IHD had a greater change in LVEF. There was little difference in the effect of CRT-P on the composite outcome (death from any cause or unplanned hospitalisation for a major cardiovascular event) for 16 pre-defined subgroups (age, sex, NYHA class, dilated cardiomyopathy, systolic blood pressure, NT-BNP, ejection fraction, end-systolic volume index, QRS interval, interventricular mechanical delay, mitral-regurgitation area, glomerular filtration rate, beta-blocker use, spironolactone use, loop diuretics use, digoxin use).

CRT-D vs OPT

One (three-arm) trial compared CRT-D with OPT. All-cause mortality (HR 0.64, 95% CI 0.48 to 0.86, $p=0.003$), total cardiac deaths (RR 0.68, 95% CI 0.50 to 0.93, $p=0.02$), sudden cardiac deaths (HR 0.44, 95% CI 0.23 to 0.86, $p=0.02$) and heart failure hospitalisations (RR 0.77, 95% CI 0.63 to 0.93, $p=0.008$) were reduced with CRT-D compared with OPT. There were no significant differences in heart failure deaths (HR 0.73, 95% CI 0.47 to 1.11, $p=0.143$) or non-cardiac deaths (CRT-D 2.3% vs OPT 3.6%, $p=0.717$) in those with CRT-D compared to those with OPT. The proportion of people with an improvement of one or more NYHA class (57% vs 38%, $p<0.001$), and improvements in exercise capacity [change in 6-minute walk distance, 46 m (SD 98) vs 1 m (SD 93), $p<0.001$] and QoL (MLWHFQ) score [-26 (SD 28) vs -12 (SD 23), $p<0.001$] were statistically significantly greater with CRT-D.

CRT-P vs CRT-D

One three-arm trial compared both CRT-P and CRT-D with OPT, but the trial was not powered for a statistical comparison of CRT-P with CRT-D. Direct statistical comparisons of CRT-P versus CRT-D have been undertaken for the purposes of this review but should be viewed with caution.

Total cardiac deaths (RR 1.38, 95% CI 1.06 to 1.81, $p=0.02$) and sudden cardiac deaths (RR 2.72, 95% CI 1.58 to 4.68, $p=0.0003$) were higher with CRT-P than CRT-D. All-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, $p=0.12$), heart failure deaths (RR 0.98, 95% CI 0.68 to 1.42, $p=0.93$) and heart failure hospitalisations (28% vs 29%) were similar for those with CRT-P and those with CRT-D. Changes in NYHA class, exercise capacity and QoL were also similar for CRT-P and CRT-D.

Adverse events: two trials randomised people with successful implantation only. The other two trials reported device-related deaths between 0.2% and 0.8% for those with CRT-P and 0.5% for those with CRT-D. Moderate or severe adverse events related to implantation procedure were reported as 10% for those with CRT-P and 8% for those with CRT-D by one trial, with 13% and 9% of CRT-P and CRT-D implantations unsuccessful. Moderate or severe adverse events from any cause were more common among those with CRT-D than OPT (CRT-D 69%, CRT-P 66%, OPT 61%; CRT-D vs OPT

p=0.03, CRT-P vs OPT, p=0.15). Reported complications included lead displacements, infections and coronary-sinus dissections.

No trials in addition to those included in the previous CRT TAR⁴³ were identified. However one trial (CONTAK-CD) that was included in the previous report was not included in this section of the present report, as the population, intervention and comparator were more appropriately considered in the section 'people with both conditions'. Despite this difference, the results from the present review concur with those of the previous review.⁴³

7.1.1.3 People with both conditions: CRT-D compared with OPT, CRT-P or ICD

Nine RCTs were included comparing CRT-D with ICD in people both at risk of sudden cardiac death due to ventricular arrhythmias and with heart failure as a result of LVSD and cardiac dyssynchrony. No RCTs comparing CRT-D with OPT or with CRT-P were identified for this population. The risk of bias was low in some of the included trials, but was unclear in others due to inadequate reporting. Length of follow-up was 6 months in five trials, one year in two trials, and an average of 2.4 years and 3.3 years in the remaining trials. Sample size ranged from 31 to 1820 participants. The trials differed in their eligibility criteria for heart failure; the majority of participants were in NYHA class II in three trials, NYHA class III in four trials, described as 'mild to moderate heart failure' in one trial where NYHA class was not reported, and NYHA class IV in one trial. The eligibility cut-off for LVEF was 35% or less in seven trials and 30% or less in two trials, with mean LVEF at baseline between 21% to 26%. One trial (RethinQ) differed from the others in the criteria used to define cardiac dyssynchrony, recruiting people with a narrow QRS interval (<130 ms) and evidence of mechanical dyssynchrony on echocardiography. Of the other trials, QRS interval was 120 ms or greater (four trials), 130 ms or greater (three trials) or 150 ms or greater (one trial). Mean QRS interval at baseline was 107 ms in RethinQ, and between 156 ms to 169 ms where reported in the remaining trials. The proportion of participants with ischaemic heart disease varied from just over half to 100% of participants.

Meta-analysis found that CRT-D reduced the risk of all-cause mortality (RR 0.84, 95% CI 0.73 to 0.96, p=0.01), total cardiac deaths (RR 0.82, 95% CI 0.67 to 1.00, p=0.05) and heart failure hospitalisations (RR 0.75, 95% CI 0.64 to 0.88, p=0.0005) compared with ICD. Fewer trials reported heart failure deaths or sudden cardiac deaths separately, and zero heart failure or sudden cardiac deaths occurred in some of these trials. Combining three RCTs in a meta-analysis found little difference in sudden cardiac death between CRT-D and ICD (RR 1.45, 95% CI 0.43 to 4.92, p=0.55).

Meta-analysis of four trials found no statistically significant difference in the proportion of people experiencing at least one episode of ventricular tachycardia or ventricular fibrillation (RR 0.90, 95%

CI 0.71 to 1.14, $p=0.38$). An improvement in average NYHA class (MD -0.19, 95% CI -0.34 to -0.05, $p=0.008$) and in the proportion of people improved by one or more NYHA class (RR 1.81, 95% CI 0.91 to 3.60, $p=0.09$), and in average LVEF (MD 2.15, 95% CI 0.45 to 3.86, $p=0.01$), left ventricular end-diastolic volume (MD -19.7 ml, 95% CI -32.1 to -7.3, $p=0.002$) and left ventricular end-systolic volume (MD -20.9 ml, 95% CI -32.9 to -8.8, $p<0.0007$) was found with CRT-D. There was no overall difference in end-diastolic diameter (MD -0.29, 95% CI -1.67 to 1.08, $p=0.67$) or end-systolic diameter (MD -1.88, 95% CI -4.39 to 0.62, $p=0.14$). Substantial statistical heterogeneity was present for these outcomes, and some trials reported median values which may indicate skewed data. One trial of people with moderate to severe heart failure found a significantly greater reduction in QRS interval with CRT-D than with ICD (-20 ms vs 0 ms, $p<0.001$). QRS interval was similar between CRT-D and ICD in two trials of people with mild or mild/moderate heart failure.

There was a greater improvement in exercise capacity (change in peak VO_2 : MD 0.75, 95% CI 0.23 to 1.27, $p=0.005$; change in 6 minute walk distance: MD 14.5 metres, 95% CI 2.9 to 26.1, $p=0.01$) and QoL (change in MLWHFQ score: MD -6.9, 95% CI -10.4 to -3.4, $p=0.0001$) with CRT-D than ICD. One small trial of people with mild to moderate heart failure (Pinter¹⁴⁰) reporting other measures of QoL (Duke Activity Status Index, one item Global Visual Analogue Scale and SF-36) found comparisons of baseline to 6 month changes were statistically significant for the General Health component of the SF-36 only.

Where the large RAFT trial contributed data to meta-analyses, the results were strongly influenced by it. The RAFT trial included people with mild to moderate heart failure despite OPT, LVEF $\leq 30\%$ from ischemic or nonischemic causes, a wide QRS interval, and planned ICD implantation for indicated primary or secondary prevention of sudden cardiac death.

Extent of reporting of adverse events varied between the trials. Some trials reported adverse events for all people undergoing implantation attempts, but only randomised people who had a successful implant. Only three trials reported adverse events according to device received. The large RAFT trial reported adverse events for all implanted participants and found that device or implantation related complications within 30 days of implantation was significantly higher in the CRT-D group than the ICD group (13.3% vs 6.8%, $p<0.001$), as was device-related hospitalisation (20% vs 12.2%, HR 1.68, 95% CI 1.32 to 2.13, $p<0.001$).

Three trials reported pre-specified subgroup analysis. Two trials reported that CRT-D was associated with a greater benefit in people with QRS duration 150 ms or more than in those with a QRS duration of less than 150 ms, and the third trial found significant improvements in the proportion of people with an improvement in peak oxygen uptake in those with QRS ≥ 120 ms but not for those with QRS

<120 ms. CRT-D was associated with greater benefit in women than in men (one trial) and in people with LBBB than in those with nonspecific intraventricular conduction delay (one trial). One trial found a statistically significant improvement with CRT-D distance walked in 6 minutes for those with non-ischemic cardiomyopathy (55.0 m vs 2.5 m, $p=0.01$) but not for those with ischemic cardiomyopathy (4.2 m vs 5.8 m, $p=0.57$). Other evaluated subgroups showed no statistically significant effects.

This evidence (apart from the one trial, CONTAK-CD) has not been previously evaluated in a TAR.^{43,65}

7.1.1.4 Summary of industry-submitted IPD NMA

The MS reported an IPD NMA which assessed the effectiveness of ICDs, CRT-P and CRT-D compared to OPT for people with heart failure. As people with heart failure vary considerably, the NMA aimed to identify sub-groups who may benefit from the different interventions. The NMA assessed the outcomes of all-cause mortality, all-cause hospitalisations and HRQoL, with the findings informing the economic model presented in the MS. The focus of the NMA differed from that specified in the scope for the appraisal, trying to establish which subgroups may benefit from the interventions rather than assessing their effectiveness in the groups identified in the original decision problem.

The NMA was based on a network of evidence identified from a systematic review presented in the MS. It included 13 of 22 trials (95% of patient in the network) from the network for which IPD was available. The network excluded seven RCTs identified in SHTAC's assessment report. The evidence base for the different outcomes varied (all-cause mortality 13 trials, all-cause hospitalisation 11 trials and HRQoL three trials), resulting in limited and, on occasions, skewed data that affected the results of the NMA. The MS outlined the methods followed in the different stages of the NMA, however it did not provide comprehensive results from each stage to allow a full appraisal of the decisions made and their effect on the results. The IPD NMA used meta-regression to assess the effectiveness of the different interventions, allowing the impact of different patient characteristics to be taken into account in the analysis (i.e. baseline risks and treatment modifiers). The NMA followed a two stage process. First, baseline rates were estimated for patients randomised to the comparator treatment of OPT independent of treatment effects. Second, device specific treatment effects were estimated from relevant IPD trials to allow comparison with the baseline rates. Baseline risk and treatment effect modifiers (i.e. patient characteristics) were included in both stages to allow sub-groups to be identified. Where possible, the MS assessed the validity of results against other evidence, making adjustments where considered necessary due to counter-intuitive results or a lack of data.

The results of the NMA showed benefit for people receiving a device compared to OPT on the three outcomes; however the extent of the benefit and the sub-groups most affected remained uncertain. Fixed-effects NMA without the covariables for all-cause mortality estimated hazard ratios that showed statistically significant benefit for all devices compared to OPT [REDACTED]. Hazard ratios showed a statistically significant benefit from CRT-D when compared to CRT-P [REDACTED] and ICD [REDACTED]. NMA models including covariables (treatment modifiers) reported findings that were more equivocal and states that they should be interpreted with caution. Although hazard ratios showed that all devices appeared to have a beneficial effect when compared to OPT, rarely were the differences statistically significant. CRT-D appeared to have a statistically significant effect for people with a QRS ≥ 150 ms. It also had an effect for people with a QRS ≥ 120 to < 150 ms which was statistically significant for women and marginally insignificant for men. ICDs had a statistically significant benefit for men aged < 60 years and men aged ≥ 60 years with a QRS ≥ 120 to < 150 with non-LBBB. CRT-P provided a statistically significant effect for women with a QRS ≥ 150 ms and LBBB. Similar benefits from all devices when compared to OPT were shown on all-cause hospitalisations; although limited data meant that some comparisons were not possible. All-cause hospitalisations were reduced in people in NYHA groups I to III receiving an ICD [REDACTED], in NYHA groups III and IV with CRT-P [REDACTED], and in all NYHA groups with CRT-D [REDACTED]. Results for HRQoL were less clear due to the scarcity of data available for the NMA. Although the use of the devices led to improvements in EQ-5D values, some comparisons could not be made and others resulted in counter-intuitive results. As a consequence, the MS adjusted values to show that ICDs had benefit for people in NYHA I/II and CRT-P and CRT-D had the same effect for people in NYHA III and IV. Given that most utility values were changed and that limited comparisons can be made with other evidence, these should be interpreted with caution.

The IPD NMA provides an opportunity to undertake a more detail analysis of the effectiveness of ICDs, CRT-P and CRT-D in relation to the comparator treatment of OPT, evaluating the benefits for specific groups of people with heart failure. Unfortunately limitations in the data available and lack of detail concerning the methods used, render the findings uncertain. It is clear that all the devices are beneficial compared to OPT for all-cause mortality. They also appear to have benefit for the outcomes of all-cause hospitalisation and HRQoL, although the extent of the effect is less clear. However, the benefits for specific sub-groups remain unclear. Where some benefits are shown, the warnings from the MS concerning the analysis cause some concern. In addition, the sub-groups identified in the NMA differ from those outlined in the scope for the appraisal, making translation of the results between them difficult.

7.1.2 Cost effectiveness

7.1.2.1 Summary of previously published economic evaluations

The systematic review of the cost effectiveness of ICDs for the treatment of arrhythmia and CRT for treatment of heart failure identified 51 studies (36 studies of ICDs and 17 of CRT). Most of the evaluations employed state transition models to estimate long term outcomes extrapolated from short-term outcomes in trials. Almost half the studies reported that ICDs were cost effective, whilst the others found ICDs only cost effective in high risk groups, not cost effective or were uncertain. One high quality study was conducted for a UK setting and perspective and reported a mean ICER for an average UK secondary prevention patient over a 20 year time horizon of £76,139 per QALY gained. However, these results may not be applicable to current UK practice as some data used in the model is now out of date. Almost all studies reported that CRT was cost effective, with only two studies uncertain as to whether CRT was cost effective. One high quality study was conducted for a UK setting and estimated an ICER of £16,735 per QALY gained for CRT-P compared with OPT, and an ICER of £40,160 per QALY gained for CRT-D compared with CRT-P.

7.1.2.2 Summary of systematic review of quality of life studies

The systematic review found six relevant HRQoL studies that measured EQ-5D in heart failure, stratified by NYHA class, or reported on patients who had previously received an ICD. Two studies were conducted in patients who had received an ICD; one study of UK patients who responded to a postal questionnaire found that mean EQ-5D score did not change with time after implant; the other study of volunteers attending a defibrillator clinic in the USA reported no difference between EQ-5D score of primary and secondary prevention patients and that quality of life for ICD patients was similar to the general population. Four cohort studies reported EQ-5D scores in heart failure, with baseline EQ-5D scores ranging from 0.44 to 0.66 depending on NYHA classification. Overall results show decreased EQ-5D scores in heart failure compared with the general population particularly in NYHA Class III and IV.

7.1.2.3 Summary of industry-submitted economic evaluation

One submission was received from ABHI. The general approach taken in the MS seems reasonable with the model structure consistent with the current understanding of heart failure and ventricular arrhythmia. Assumptions over costing are also consistent with current clinical practice. However, there is limited reporting in the MS on some sources of evidence used in the model. Uncertainty is not

comprehensively assessed as the sensitivity analyses presented are limited to few scenarios and the methodology used for PSA is not described in sufficient detail to determine whether joint parameter uncertainty was properly assessed. The cost-effectiveness results presented in ABHI's submission (according to subgroups specified by ABHI) do not directly address questions posed in NICE's scope, as it is unclear how the subgroups selected relate to the groups scoped by NICE. Overall, ABHI's results show that for most subgroups there is at least 1 device with an ICER below £30,000 per QALY gained, and in some cases a different device might be below £20,000 per QALY gained.

7.1.2.4 Summary of independent economic model

We developed an independent state transition model based on that created by Fox and colleagues for the previous TA120.⁴³ The care pathways and assumptions have been adapted according to new evidence and clinical advice to allow for the assessment of the cost-effectiveness of ICDs, CRT-P and CRT-D for people at risk of sudden cardiac death due to ventricular arrhythmias and / or heart failure as a result of LVSD and cardiac dyssynchrony.

People at risk of sudden cardiac death

The current economic model indicates the initial management of patients at increased risk of SCD with ICD alongside OPT is a cost-effective strategy (ICER £19,479/QALY) compared with initial treatment with OPT alone. The use of ICDs for secondary prevention of SCD presented 51% and 82% of probability of being cost-effective at a WTP of £20,000 and £30,000 per QALY gained, respectively. ICDs were also estimated as cost-effective (within the WTP range of £20,000 and £30,000 per QALY gained) for the primary prevention subgroups analysed (people with remote MI, a broad population with mild to moderate heart failure, and non-ischaemic cardiomyopathy patients). The parameters with the greatest impact on the cost effectiveness results were the time horizon, the HR for all-cause mortality associated with the ICD + OPT arm, the risk of surgical death during ICD implantation, and the lifetime of the device.

People with heart failure as a result of LVSD and cardiac dyssynchrony

For patients with heart failure as a result of LVSD and cardiac dyssynchrony, the base case analysis found the addition of either CRT-P or CRT-D to OPT (in the initial stage of management of heart failure) may be considered cost-effective at WTP of £30,000 compared with OPT alone (allowing for subsequent device implantation), with ICERs of £27,584/QALY and £27,899/QALY, respectively. The use of CRT-D + OPT when compared with CRT-P + OPT (ICER £28,420/QALY) was also likely to be cost-effective. At a WTP of £20,000 per QALY gained, initial management with OPT alone (followed by the clinically necessary device implants) was the strategy with highest probability of being cost-effective (81%). Above a WTP of £28,000 per QALY, the strategy with highest

probability of being cost effective was CRT-D + OPT (38%). At £30,000 per QALY, CRT-D + OPT and CRT-P + OPT had a 46% and 31% probability of being cost-effective, respectively, whilst OPT alone had a 23% probability of being cost-effective.

The most influential parameters on the model results for the comparison of CRT-P versus OPT were the risk of hospitalisation for a serious arrhythmic event for patients with CRT-P, risk of HF death for both patients with CRT-P and patients with CRT-D, and risk of SCD for patients with CRT-P. The results of the comparison of CRT-D with OPT were most influenced by the risk of HF death and SCD death in CRT-D patients, and the device lifetime. The results of the comparison of CRT-D with CRT-P were the most sensitive to the variation of individual parameters, with eight parameters ranging the ICER more than £10,000, the most influential being the risk of HF death with CRT-D and the risk of SCD with both CRT-D and CRT-P.

People with both conditions

The base case analysis found that the most cost-effective strategy for people with both conditions at a WTP range of £20,000 to £30,000 per QALY was the initial management with OPT alone (followed by device implantation and subsequent upgrades as necessary), with an ICER of £2,824/QALY compared with ICD + OPT (the least costly and least effective strategy). Costs and QALYs for CRT-D + OPT and CRT-P + OPT were similar. CRT-D had an ICER of less than £30,000 when compared with ICD + OPT (ICER £27,195/QALY), but not when compared with initial management with OPT alone (ICER £35,193/QALY). At a WTP of £30,000 per QALY, OPT alone, ICD + OPT, CRT-D + OPT, and CRT-P + OPT had a 44%, 31%, 15%, and 10% probability of being cost-effective, respectively. Above the WTP of £42,000 per QALY, the intervention with highest probability of being cost effective was CRT-D + OPT (31%).

However, the results differ when using an alternative scenario from the MADIT CRT trial. In this case, ICD + OPT is slightly more costly but yields a greater benefit than OPT alone. As CRT-P + OPT and CRT-D + OPT are less effective than ICD + OPT and much more costly, both CRT strategies are extendedly dominated by ICD + OPT compared with OPT alone. Therefore, the results obtained with MADIT-CRT data indicate ICD + OPT as the most cost-effective strategy, with an ICER of £154 per QALY gained compared with OPT alone.

The cost-effectiveness results for the comparison of CRT-D + OPT versus ICD + OPT were quite robust to the variation of input parameters. The most influential parameters for this comparison were the RR of all-cause mortality with ICD and the lifetime of CRT-D and ICD devices.

7.2 Strengths and limitations of the assessment

This review has the following strengths:

- It is independent of any vested interest.
- It has been undertaken following the principles for conducting a systematic review. The methods were set out in a research protocol (Appendix 2), which defined the research question, inclusion criteria, quality criteria, data extraction process and methods to be employed at different stages of the review.
- A multidisciplinary advisory group has informed the review from its initiation. The research protocol was informed by comments received from the advisory group and the advisory group has reviewed and commented on the final report.
- The review brings together the most up-to-date evidence for the clinical and cost-effectiveness of ICDs, CRT-P and CRT-D for people at risk of sudden cardiac death due to ventricular arrhythmias and / or heart failure as a result of LVSD and cardiac dyssynchrony within one assessment report. This evidence has been critically appraised and presented in a consistent and transparent manner.
- An economic model has been developed de novo following recognised guidelines and systematic searches have been conducted to identify data for the economic model. The main results have been summarised and presented.

In contrast, this assessment also has certain limitations. Limitations of the included trials are as follow:

- Randomised patients with successful implantation may overestimate the benefit and underestimate adverse effects.
- Trials have not been conducted in the UK and may not be generalizable.
- The time horizon of the included trial may be inadequate.
- Blinding of participants and healthcare providers is impossible in trials that compare devices and drugs, however it is important to acknowledge the bias that may occur as a result of this. It would be possible to blind outcome assessors in these trials.
- The definition of OPT has changed over time, therefore the use of pharmacological therapy in some of the included trials would not be considered optimal by current standards.

Limitations of the systematic review of clinical effectiveness are as follows:

- Inclusion of trials where medical therapy not considered optimal by current standards.

- MUSST and MAVERIC trials were excluded from the systematic review as the intervention did not meet the scope of the present review (many participants in the intervention arm did not receive ICD); however, these trials presented subgroup data comparing ICD versus no ICD. These trials did not undergo formal data extraction and quality assessment but were presented for information.
- Significant statistical heterogeneity was shown between trials for some outcomes, therefore the pooled data should be viewed with caution. Some trials reported median values and confidence intervals rather than mean values. Median values are similar to mean values when the distribution of data is symmetrical, so can be used directly in the meta-analyses.⁶⁷ However, means and medians can be very different with each other if the data are skewed. The use of median values in some of the meta-analyses may have contributed to statistical heterogeneity.
- The review only included subgroup analyses specified *a priori* by the trials. However, subgroup analysis lack statistical power and may be misleading, for example due problems of multiplicity. Subgroup analyses should therefore be viewed with caution.

Limitations of the independent economic model:

The independent model for the current appraisal was developed to address the decision problem specified in the NICE scope for the appraisal⁶⁴ and to follow recommended guidance provided in the NICE guide on the methods for technology appraisals. It was based on an adaptation of a model structure used in the previous appraisal of cardiac resynchronisation for heart failure (TA120)⁴⁶ developed by Fox and colleagues,⁴³ providing a consistent approach and comparability. Despite following recognised guidance on developing economic models,^{69;70} the evaluation has some limitations, including:

- As the independent model was based on an adaptation of a model developed by Fox and colleagues,⁴³ it relies on some of the same assumptions made concerning the structure of the model. These relate to the referral of patients receiving particular treatment options, whether the comparator or an intervention, to receive an alternative intervention following occurrence of a particular event (e.g. a non-fatal arrhythmia for a patient on OPT or a serious arrhythmic events for a patient on CRT-P or an unsuccessful CRT-P implantation). As these were validated by clinical advice by Fox and colleagues and considered during previous appraisals, it was felt that they were of limited concern.
- Additional structural assumptions were included concerning the risks and timing of re-implantation of devices, alternative options for those patients who were unsuccessful during device implantation and assumptions concerning perioperative complications, surgical failure,

heart transplantation and death. As with the assumptions in the model by Fox and colleagues,⁴³ these were incorporated following clinical advice.

- Survival estimates over time for the model were derived from relevant trials with the longest follow-up. These were identified in the systematic review of clinical effectiveness produced for this assessment report. Given the heterogeneous nature of the studies included, it is possible that the studies used in the analysis did not encompass the differences in the patient groups. To limit the possible effects, base case and sub-group analyses were estimated to try and encompass the different patients included. Also, follow-up varied (range 18 to 45.5 months) in the different studies used affecting the extent to which survival curves had to be extrapolated.
- Parameter values on the effectiveness of the interventions were sourced, where possible, from the systematic review undertaken for the assessment report. Unfortunately limitations in the evidence base meant that some parameters were either not available for the specific populations being modelled or were presented in a single study that may not have encompassed the inherent variability in heterogeneous patient populations being assessed (e.g. hospitalisation rates, complications). Where necessary, parameter values were obtained from studies in other population groups included within the appraisal or from other studies or sources outside of the systematic review. These were assumed to be representative.
- The evidence base for patients who had both heart failure and an increased risk of SCD (Population 3) was limited, with most studies assessing CRT-D or ICDs. In particular, the lack of a direct comparison of CRT-P with CRT-D meant that evidence had to be used from studies on the clinical effectiveness of CRT-P and CRT-D in patients with heart failure as a result of LVSD and cardiac dyssynchrony (Population 2).
- The availability of HRQoL data varied for the effects of the different devices and for additional procedures or adverse events. Baseline utility values were available by NYHA class. Data were not identified for the effects of transplantation, surgery or infections and assumptions were made following those used by Fox and colleagues.⁴³ Device related utility values were assessed through their effect on changes in the distribution of patients in NYHA classes. Data were only available for patients with CRT-P or OPT alone for Population 2, so effects of CRT-P were assumed to hold only for CRT devices. Robust evidence on HRQoL was not found for population 3 and so CRT and ICD devices were assumed to have no impact on utility and baseline values were maintained. These assumptions may underestimate the benefits of the devices on HRQoL.
- Resource use and costs were obtained from routinely published sources. As some costs were not specifically identified in the routine sources, assumptions were made. These included costs of the implantation of devices, costs of upgrades and routine replacements, operative

complications, device related complications and drug costs. Alternative data were sourced from Fox and colleagues,⁴³, the MS and clinical advice.

Where limitations have arisen in the evaluation, these have been identified in the report. Assumptions made or data identified from alternative sources has been checked through clinical advice and the effects parameters thought to be influential to the results have been assessed through sensitivity analyses.

Comparison of independent economic evaluation with other evaluations

For patients at increased risk of SCD in the UK, Buxton and colleagues estimated an ICER of £76,139 per QALY gained for ICD + OPT compared with OPT for the secondary prevention of SCD over a 20 year time horizon. As some data used in the model is now out of date, these results may not be applicable to current UK practice and not comparable with the results of the current model. Different modelling structures and different data inputs were used in the current model, as well as different approaches to estimate HRQoL. Both models estimated similar utility values among the OPT and the ICD + OPT cohorts. However, the average utility values estimated in the current model for OPT alone (0.81) and ICD + OPT (0.82) are higher than that of 0.75 assumed for both arms by Buxton and colleagues. Scenario analysis using same average utilities as per Buxton and colleagues estimated an ICER of £22,372 per QALY gained for ICD + OPT for secondary prevention of SCD compared with initial management with OPT alone.

For patients with heart failure, Fox and colleagues estimated an ICER of £16,735 per QALY gained for CRT-P compared with OPT, an ICER of £22,231 per QALY gained for CRT-D compared with OPT, and an ICER of £40,160 per QALY gained for CRT-D compared with CRT-P. The current model estimates a slightly higher cost and QALY gain for all strategies. However, the estimated incremental benefit of CRT-P versus OPT is less than that in the previous model and is associated with a higher incremental cost; hence an ICER of £25,779 per QALY gained is estimated for CRT-P compared with OPT. As a greater incremental benefit is estimated with CRT-D versus CRT-P at a similar cost, a smaller ICER (£24,943/QALY) is estimated for CRT-D versus CRT-P. The same incremental benefit is estimated for CRT-D compared with OPT, but the current model estimates a higher incremental cost for CRT-D; thus a higher ICER (£27,899/QALY) is estimated for CRT-D versus OPT.

Using updated costs, different estimates of devices' lifetime, a different set of utilities by NYHA class, and structural differences between models (such as referring patients being managed with OPT alone for CRT-P implantation in case of hospitalisation for HF, instead of ICD, or for CRT-D following

hospitalisation for arrhythmia) explain the differences in results between models. Using the same utility values as the previous model increases the incremental benefit of both CRT-P and CRT-D compared with OPT and with each other, and therefore reduces the ICERs to £22,892 per QALY gained for CRT-P versus OPT; to £24,580 per QALY gained for CRT-D versus OPT; and to £27,893 per QALY gained for CRT-D versus CRT-P. The scenario using the same devices' lifetime estimates as Fox and colleagues estimated higher ICERs for CRT devices compared with OPT, due to higher costs and slightly fewer QALYs estimated for both CRT-D + OPT and CRT-P + OPT.

One joint economic evaluation was submitted by ABHI concluded that for most subgroups there is at least one device with an ICER below £30,000 per QALY gained, and in some cases a different device might be below £20,000 per QALY gained. The general approach taken in the ABHI's submission seems reasonable, as the model structure is consistent with the current understanding of heart failure and ventricular arrhythmia, and the assumptions over costing are also consistent with current clinical practice. However, the cost-effectiveness results presented in ABHI's submission (according to subgroups specified by ABHI) do not directly address questions posed in NICE's scope, as it is unclear how the subgroups selected relate to the groups scoped by NICE. The independent economic model was developed to address the NICE's scope and based on the published clinical evidence and on previously published evaluations. Hence, a different modelling approach was taken and the limited data available did not allow for the analysis of the subgroups defined by ABHI. It is therefore unclear how the cost-effectiveness results of the current model compare with those from the ABHI's submission.

Other recent systematic reviews / meta-analyses

Huang and colleagues²²⁴ presented a meta-analysis comparing CRT-D vs no CRT-D (CRT-P, ICD or OPT) and found that all-cause mortality was reduced in CRT-D patients. However, three of the trials were not RCTs. Subgroup analysis comparing CRT-D vs ICD is also presented, but includes only three of the nine relevant trials identified by the current review. Without the large RAFT trial, the meta-analysis by Huang and colleagues found no significant difference in all-cause mortality between CRT-D and ICD. Al-Majed²²⁵ assessed CRT in people with advanced heart failure and those with less symptomatic disease. The inclusion criteria for their systematic review differed from the present review (eligible comparators were inactive pacing, right or left ventricular pacing alone, ICD), therefore there are some differences in the trials included in the meta-analyses and the results are not directly comparable. The meta-analyses found that CRT-D reduced all-cause mortality and heart failure hospitalisations in subgroups with NYHA class I/II symptoms and with class III/IV symptoms. Functional outcomes were improved in people with NYHA class III/V but not class I/II symptoms. A systematic review and meta-analysis by Wells and colleagues²²⁶ compared CRT-D with ICD or OPT and conducted subgroup analysis for NYHA class. All-cause mortality was reduced with CRT-D

compared with ICD and with OPT. Compared with ICD, CRT-D reduced all-cause mortality for people with NYHA class I or II but not those with class III or IV symptoms. The differences in effects for the NYHA class subgroups between these the two meta-analyses^{225;226} are due to the different comparators and trials included. A meta-analysis by Bertoldi and colleagues²²⁷ also found a significant reduction in all-cause mortality with CRT-P compared with OPT, and with CRT-D compared with ICD, despite including slightly different trials in their meta-analysis.

7.3 Uncertainties

- No new evidence comparing CRT-P and CRT-D devices was identified. Therefore the relative clinical effectiveness and cost-effectiveness of the devices in people with heart failure as a result of LVSD and cardiac dyssynchrony, with or without an established indication for and ICD, remains uncertain.
- No robust evidence was identified on the effect of CRT and ICD devices on heart failure progression in people with both conditions.
- No evidence was found on the relative risk of hospitalisation due to arrhythmia for CRT-P compare with CRT-D in people with both conditions. Hence, CRT devices were assumed to have the same preventive effect on severe arrhythmia. New evidence would reduce the uncertainty associated to this parameter, to which the comparison of CRT-D + OPT with CRT-P + OPT showed particularly sensitivity.
- Utility data were not identified for patients with both conditions or for patients receiving CRT-D or ICDs. Also no utility decrements were found for the effects of transplantation, surgery or infections.
- Routine cost data was not available for costs of implantation of devices, upgrades and routine device replacements, and operative complications.

8 CONCLUSIONS

8.1 Implications for service provision

ICDs were found to reduce all-cause mortality in people who were at increased risk of SCD as a result of ventricular arrhythmias, where increased risk was defined as previous ventricular arrhythmias/cardiac arrest, myocardial infarction more than 3 weeks previously, non-ischaemic cardiomyopathy (depending on the data included), or ischaemic or non-ischaemic congestive heart failure and LVEF 35% or less. No benefit from ICD was found in people who were scheduled for CABG surgery. A significant reduction in SCD was found in people with a recent MI, but there was no difference in all-cause mortality. No significant differences between pre-specified subgroups were reported by most of the trials reporting these. The addition of ICD to OPT was cost-effective at a WTP threshold of £30,000 for all of the scenarios modelled, and in some cases at a WTP threshold of £20,000.

CRT-P and CRT-D both reduced mortality and heart failure hospitalisations in people with heart failure as a result of LVSD and cardiac dyssynchrony, when compared with OPT. Improvements in NYHA class, exercise capacity and QoL were also found with both devices. SCD was lower with CRT-D compared with CRT-P, but other outcomes, including all-cause mortality, were similar between devices. Both CRT-P and CRT-D presented ICERs below £30,000 per QALY gained compared with OPT, as did the comparison of CRT-D versus CRT-P.

Compared with ICD, CRT-D reduced the risk of all-cause mortality and heart failure hospitalisation in people with both conditions. An improvement in LVEF, exercise capacity and QoL was also found with CRT-D compared with ICD. Device or implantation complications were more common with CRT-D. The costs and QALYs for CRT-D and CRT-P were similar. The ICER for the comparison of CRT-D + OPT with ICD + OPT was below £30,000 per QALY (unless no difference in all-cause mortality was assumed) but not for the comparison with initial management with OPT alone.

8.2 Suggested research priorities

- An RCT comparing CRT-D and CRT-P in people with heart failure due to LVSD and cardiac dyssynchrony is required, for both those with and without an ICD indication.
- A trial is needed into the benefits of ICD in non-ischaemic cardiomyopathy in the absence of dyssynchrony.

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10 APPENDICES

Appendix 1: Comparison of inclusion criteria in previous and present TARs

Appendix 2: Review methods from the research protocol

Appendix 3: Sources of information, including databases searched and search terms

Appendix 4: Economic evaluation checklist

Appendix 5: List of excluded clinical effectiveness studies and recent abstracts

Appendix 6: Ongoing trials

Appendix 7: Hospitalisations: total, cardiac and non-cardiac

Appendix 8: Data extraction: people at risk of sudden cardiac death due to ventricular arrhythmias

Appendix 9: Data extraction: people with heart failure as a result of LVSD and cardiac dyssynchrony

Appendix 10: Data extraction: people with both conditions

Appendix 11: SHTAC peer review of manufacturers' submission

Appendix 12: List of excluded economic evaluations

Appendix 13: Data extraction: cost-effectiveness

Appendix 14: List of excluded QoL studies

Appendix 15 Parameters included in the probabilistic sensitivity analyses

Appendix 16 Regression analyses for deriving model parameters

Appendix 17 Validation of the independent economic model

**Technology Assessment Report commissioned by the NIHR HTA
Programme on behalf of the National Institute for Health and
Clinical Excellence**

**Implantable cardioverter defibrillators for the treatment of
arrhythmias and cardiac resynchronisation therapy for the
treatment of heart failure: systematic review and economic
evaluation**

Appendices

List of Appendices

Appendix 1: Comparison of inclusion criteria in previous and present TARs	3
Appendix 2: Review methods from the research protocol.....	4
Appendix 3: Sources of information, including databases searched and search terms	10
Appendix 4: Economic evaluation checklist.....	20
Appendix 5: List of excluded clinical effectiveness studies and recent abstracts.....	21
Appendix 6: Ongoing trials.....	41
Appendix 7: Hospitalisations: total, cardiac and non-cardiac.....	43
Appendix 8: Data extraction: people at risk of sudden cardiac death due to ventricular arrhythmias..	49
Appendix 9: Data extraction: people with heart failure as a result of LVSD and cardiac dyssynchrony	129
Appendix 10: Data extraction: people with both conditions.....	151
Appendix 11: SHTAC peer review of manufacturers' submission	189
Appendix 12: List of excluded economic evaluations	210
Appendix 13: Data extraction: cost-effectiveness.....	212
Appendix 14: List of excluded QoL studies	215
Appendix 15 Parameters included in the probabilistic sensitivity analyses.....	217
Appendix 16 Regression analyses for deriving model parameters	221
Appendix 17 Validation of the independent economic model.....	229

Appendix 1: Comparison of inclusion criteria in previous and present TARs

	ICD TAR ¹	CRT TAR ²	Present TAR
Population	<p>Adults at high risk of SCD due to arrhythmia:</p> <p>(a) ‘Secondary prevention’</p> <p>(i) Cardiac arrest due to either VT or VF.</p> <p>(ii) Spontaneous sustained VT causing syncope or significant haemodynamic compromise.</p> <p>(iii) Sustained VT without syncope/cardiac arrest, and who have an associated reduction in EF (<35%) but are no worse than NYHA class III.</p> <p>(b) ‘Primary prevention’</p> <p>(i) A history of previous MI and</p> <ul style="list-style-type: none"> – non-sustained VT on Holter (24-hour ECG) monitoring: – inducible VT on electrophysiological testing: – LV dysfunction with an EF <35% and no worse than NYHA class III. <p>(ii) A history of previous MI and depressed heart function (EF ≤0.30).</p> <p>(iii) Non-ischaemic (dilated) cardiomyopathy with arrhythmia at high risk of SCD and depressed heart function (EF ≤0.30).</p>	<p>People with heart failure (any NYHA class) due to LVSD with evidence of cardiac dyssynchrony (QRS >120 ms) and LVSD (LVEF ≤ 35%)</p>	<p>People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT;</p> <p>People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite OPT;</p> <p>People with both conditions described above.</p>
Intervention	ICD	CRT-P or CRT-D	ICD, CRT-P, CRT-D
Comparator	AAD or placebo/control	OPT alone, CRT-P vs CRT-D	OPT CRT-P vs CRT-D CRT-D vs ICD
Outcomes	Mortality, QoL, adverse effects	Mortality Number of people with heart failure hospitalisations Exercise capacity NYHA class Number with adverse effects QoL	Mortality Adverse effects QoL Symptoms and complications related to tachyarrhythmias and/or heart failure Heart failure hospitalisations Change in NYHA class Change in LVEF

Appendix 2: Review methods from the research protocol

Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify: (i) clinical-effectiveness studies of ICDs for arrhythmias and CRT for the treatment of heart failure; (ii) studies reporting on the cost-effectiveness of ICDs and CRT. Additional search strategies will also identify studies reporting resource use and costs, epidemiology and natural history of arrhythmias and heart failure.

The following electronic databases will be searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); Medline In-Process and Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); NIHR-Clinical Research Network Portfolio; Zetoc (Mimas); Clinical Trials.gov and Current Controlled Trials. The draft clinical-effectiveness search strategy for Medline is shown in Appendix 9.1. This will be adapted for other databases.

Bibliographies of related papers will be assessed for relevant studies where possible. The manufacturers' submissions to NICE will be assessed for any additional studies that meet the inclusion criteria. Experts in the field will be contacted to identify additional published and unpublished evidence.

Literature searches will be carried out from database inception to the present for studies in the English language and will be limited to randomised controlled trials (RCTs) for the assessment of clinical effectiveness and to full economic evaluations for the assessment of cost effectiveness. Searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 6) and may include a wider range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report to NICE.

Inclusion and exclusion criteria for systematic review of clinical effectiveness and cost-effectiveness

Population

- People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment
- People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment
- People with both conditions described above

Interventions

The interventions under consideration for each patient group are:

- For people at increased risk of sudden cardiac death:
 - ICDs in addition to optimal pharmacological treatment
- For people with heart failure:
 - CRT-P or CRT-D in addition to optimal pharmacological treatment
- For people with both conditions:
 - CRT-D in addition to optimal pharmacological treatment

Comparators

The comparators for each patient group are:

- For people at increased risk of sudden cardiac death:
 - Standard care (optimal pharmacological treatment without ICD)
- For people with heart failure:
 - CRT-P or CRT-D will be compared with each other
 - Standard care (optimal pharmacological treatment without CRT)
- For people with both conditions:
 - ICD
 - CRT-P
 - Standard care (optimal pharmacological treatment alone)

Outcomes

Studies must include one or more of the following outcome measures to be eligible for inclusion in this review:

- Mortality (including progressive heart failure mortality, non heart failure mortality, all cause mortality and sudden cardiac death)
- Adverse effects of treatment
- Health related quality of life
- Symptoms and complications related to tachyarrhythmias and/or heart failure
- Heart failure hospitalisations
- Change in NYHA class
- Change in left ventricular ejection fraction

Types of studies

- Only RCTs will be included for the assessment of clinical effectiveness.
- Studies published as abstracts or conference presentations from 2010 onwards will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- Systematic reviews of the clinical-effectiveness of ICDs and CRT will be used as a source of references.

- For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations [cost-effectiveness analyses (reporting cost per life year gained), cost-utility analyses or cost-benefit analyses].
- Non-English language studies will be excluded.

Screening and data extraction process

Reference screening

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. This will be performed by two reviewers. Full papers of studies which appear potentially relevant will be requested for further assessment. These will be screened by two reviewers and a final decision regarding inclusion will be agreed. At each stage, any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

Data extraction

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 9.2). Extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with recourse to a third reviewer when necessary.

Quality assessment strategy

The quality of the clinical-effectiveness studies will be assessed according to criteria based on that devised by the Centre for Reviews and Dissemination (CRD, University of York)³ and the Cochrane Collaboration.⁴ Economic evaluations will be appraised using criteria based on those recommended by Drummond and colleagues,⁵ and the checklist for assessing good practice in decision analytic modelling by Philips and colleagues⁶ (Appendix 9.3). Published studies carried out from the UK NHS and Personal Social Services (PSS) perspective will be examined in more detail.

The quality of the individual studies will be assessed by one reviewer and checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted.

Methods of data analysis/synthesis of clinical-effectiveness data

Clinical-effectiveness data will be synthesised through a narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate, it will be performed using specialised software such as Cochrane Review Manager 5 (RevMan). Where direct evidence is lacking, we will consider appropriate methods of indirect comparisons.⁷ If considered appropriate by clinical experts and only

where data allow, clinical- and cost-effectiveness will be assessed according to patient sub-groups. Possible subgroups that could be examined include age, degree of LVSD, QRS duration, ischaemic and non-ischaemic heart failure, effect of atrial fibrillation, NYHA class, and renal dysfunction.

Report methods for synthesising evidence of cost-effectiveness

Published and submitted economic evaluations

A systematic review of the literature will be conducted in order to identify published economic evaluations of the treatment of arrhythmias and heart failure, relevant to the UK NHS. The inclusion and exclusion criteria will be the same as for the clinical-effectiveness review, apart from study design as described in section 5.2. The quality assessment criteria are described in Section 5.3.3. The results of this review will include a narrative synthesis of the included economic evaluations alongside the data extraction tables.

Any economic evaluation included in sponsor submissions to NICE will be critically appraised using the same quality criteria as for published economic evaluations, but will be reported separately.

An additional systematic search of the literature will be conducted specifically for studies reporting HRQoL of adults with ventricular arrhythmias and/or heart failure. Useful HRQoL data may also be available in studies found in the clinical and cost-effectiveness reviews, and will be extracted if relevant. In the absence of evidence meeting our criteria, evidence from alternative sources may be used in the model.

Economic Modelling

Where appropriate, a decision analytic model will be built *de novo* for the current project, or developed through adaptation and update of one of the existing models from the previous NICE appraisal and published literature. The perspective will be that of the NHS and PSS. The incremental cost-effectiveness of the interventions will be estimated in terms of cost per QALY gained, as well as the cost per life year gained, if data permit. Both cost and outcomes will be discounted at 3.5%.

The appropriate model structure will be determined on the basis of the biological disease process, the main care pathways for patients in the UK NHS context and the disease states or events which are most important in determining patients' clinical outcomes, QoL and consumption of NHS or PSS resources. This will be informed by published clinical research evidence and expert opinion, as well as methods adopted in previously published economic evaluations and sponsor submissions to NICE. Parameter values will be derived from the best available evidence in the relevant research literature, including our own systematic review of clinical-effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group, we may use data from

sponsor submissions to NICE or experts' clinical opinion. Searches for additional information regarding model parameters, patient preferences and other topics will be conducted as required. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

The modelled population will be defined on the basis of both the published evidence about the characteristics of the UK population of people with ventricular arrhythmias, heart failure or both, and the populations for which good quality clinical-effectiveness is available. The base case results will be presented for adult populations with: (1) risk of sudden death due to ventricular arrhythmias; (2) heart failure (3) both risk of sudden death due to ventricular arrhythmias and heart failure.

The time horizon for our analysis will initially be governed by follow-up data available from included clinical trials. We will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

Methods for estimating quality of life

HRQoL data will be extracted from studies included in the clinical- and cost-effectiveness systematic reviews. Where available, the impact of treatment adverse effects on patients will also be incorporated. Where QoL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. In accordance with the NICE methodological guide for technology appraisals,⁸ the utility values used in the model will be elicited where possible from the general population using a preference-based method. Where these are not available, utility estimates will be derived from alternative sources and the assumptions made will be explicitly stated.

Analysis of uncertainty

Assuming that the health gains from treatment can be expressed in QALYs, a cost-utility analysis will be conducted. The results of the analysis will be provided as incremental cost-effectiveness ratios (ICERs), i.e. the incremental cost per QALY gained.

Uncertainty in the model concerning the parameters and the structure used will be investigated through deterministic sensitivity analyses. If the data and modelling approach permit, joint parameter uncertainty will be explored by probabilistic sensitivity analysis, with the results presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the assessment team no later than 13th July 2012. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with the NICE methodological guide for technology appraisals, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any [REDACTED] data taken from a company submission, and specified as confidential in the check list, will be highlighted in [REDACTED] in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any

[REDACTED] material used in the assessment report will be highlighted

[REDACTED].

Appendix 3: Sources of information, including databases searched and search terms

TOTAL BEFORE DE-DUPLICATION N=7997 N=4225 AFTER DE-DUPLICATION

Database, Host Date Searched	Search Strategy	Results
Ovid MEDLINE 1946-2012 FINAL STRATEGY 11/01/2012 KEYWORDS: MEDLINE CLINICAL EFFECTIVENESS KW	<ol style="list-style-type: none"> 1 Defibrillators, Implantable/ (9092) 2 (implant* adj2 (defibrilat* or defibrillat*)).tw. (7371) 3 ICDs.tw. (1750) 4 (S-ICD or S-ICDS).mp. (10) 5 subcutaneous ICD*1.tw. (14) 6 (implant* adj5 ICD*1).tw. (3365) 7 (CRT or CRT-D or CRT-P).mp. (5381) 8 dual chamber ICD.tw. (100) 9 single chamber ICD.tw. (33) 10 resynch* therap*.tw. (2776) 11 ((heart or cardiac or myocardial or coronary) adj2 (resynch* or depolari* or repolari*)).tw. (4300) 12 (atriobiventricular adj10 pac*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (13) 13 (atriobiventricular adj10 stimulat*).mp. (1) 14 BVP.tw. (166) 15 (biventricular adj10 pac*).mp. (1222) 16 (biventricular adj10 stimulat*).mp. (149) 17 (cardiover* or "cardio-ver*" or cardioconver* or "cardio-conver*" or "cardio conver*").tw. (10472) 18 or/1-17 (23443) 19 exp arrhythmia/ (149057) 20 Tachycardia, Ventricular/ or Arrhythmias, Cardiac/ or Tachycardia/ or Ventricular Fibrillation/ (79877) 21 Atrial Fibrillation/ (27947) 22 Heart Ventricles/bs, in [Blood Supply, Injuries] (878) 23 exp Ventricular Dysfunction, Left/ (18010) 24 exp cardiomyopathy, dilated/ (11764) 25 ventricula* remodel*.tw. (2958) 26 bundle-branch block/ (6995) 27 Heart Failure/ (73266) 28 exp heart failure, congestive/ (74453) 	2433

29	Death, Sudden, Cardiac/ (9241)	
30	Heart Arrest/ (20135)	
31	(ventricul* adj2 (tachycardia* or fibril* or arrhythmia*)).tw. (34555)	
32	((heart or cardiac or myocardial or coronary) adj2 (failur* or arrest* or sudden)).tw. (116912)	
33	((cardiac or ventricular or intraventricular) adj5 asynchron*).tw. (438)	
34	((cardiac or ventricular or intraventricular) adj5 dyssynchron*).tw. (844)	
35	tachyarrhythmia*.tw. (6663)	
36	"abnormal heart rhythm*".tw. (37)	
37	("unexpected death" or "sudden death").tw. (16602)	
38	(cardiomyopathy or cardiomyopathies).tw. (38422)	
39	Myocardial Infarction/ (128452)	
40	"heart attack*".tw. (3218)	
41	Long QT Syndrome/ (4998)	
42	Syncope/ (8267)	
43	(syncope adj2 (cardiogenic or heart or cardiac or myocardial)).tw. (519)	
44	(atrial adj2 (fibril* or flutter*)).tw. (30606)	
45	("sudden cardiac death" or "sudden arrhythmic death").tw. (7232)	
46	"unstable heart rhythm*".tw. (2)	
47	"left ventricular systolic dysfunction".tw. (1601)	
48	((reduced or reduction or impair*) adj2 left ventricular ejection fraction).tw. (572)	
49	LVSD.tw. (238)	
50	((heart or cardiac or myocardial) adj2 dysfunction*).tw. (10374)	
51	exp cardiomyopathies/ (64726)	
52	Brugada syndrome.tw. (1352)	
53	arrhythmogenic right ventricular dysplasia.tw. (777)	
54	ARVD.tw. (378)	
55	(surg* adj5 "congenital heart disease").tw. (1327)	
56	((familial or genetic or inherited) adj "heart disease").tw. (53)	
57	("heart failure" or "cardiac failure" or "ventricula*1 failure").tw. (93943)	
58	Heart Defects, Congenital/su [Surgery] (12194)	
59	Heart Conduction System/ (26125)	
60	exp Cardiac Pacing, Artificial/ (18111)	
61	exp Pacemaker, Artificial/ (21156)	
62	exp Heart-Assist Devices/ (6947)	
63	or/19-62 (502075)	
64	18 and 63 (17567)	

	<p>65 Randomized Controlled Trials as Topic/ (75979) 66 randomized controlled trial.pt. (315877) 67 controlled clinical trial.pt. (83182) 68 Controlled Clinical Trial/ (83182) 69 random allocation/ (72622) 70 Double-Blind Method/ (111942) 71 Single-Blind Method/ (15496) 72 (random* adj2 allocat*).tw. (16697) 73 placebo*.tw. (131568) 74 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (109548) 75 Research Design/ (64180) 76 ((random* or control*) adj5 (trial* or stud*)).tw. (414902) 77 random*.tw. (534613) 78 exp Placebos/ (30269) 79 Meta-Analysis/ (30726) 80 meta analysis.pt. (30726) 81 meta analys*.tw. (34905) 82 (systematic adj2 (review* or overview*)).tw. (30123) 83 Technology Assessment, Biomedical/ (7447) 84 or/65-83 (1030489) 85 64 and 84 (2873) 86 (comment or editorial or letter).pt. (1090861) 87 85 not 86 (2728) 88 limit 87 to english language (2501) 89 limit 88 to (cats or cattle or chick embryo or dogs or goats or guinea pigs or hamsters or horses or mice or rabbits or rats or sheep or swine) (94) 90 patient*.tw. (3739049) 91 89 not 90 (68) 92 88 not 91 (2433)</p>	
<p>Ovid MEDLINE(R) In- Process & Other Non-Indexed Citations Searched 11/01/2012</p>	<p>As per medline</p>	<p>77</p>

KEYWORDS: MEIP CLINICAL EFFECTIVENESS KW		
Ovid EMBASE Searched 11/01/2012 KEYWORDS: EMBASE CLINICAL EFFECTIVENESS KW	1 Defibrillator/ and (implant* or subcutaneous*).tw. (10227) 2 (implant* adj2 (defibrilat* or defibrillat*)).tw. (10068) 3 ICDs.tw. (2725) 4 (S-ICD or S-ICDS).mp. (29) 5 (subcutaneous adj2 ICD*1).tw. (43) 6 (implant* adj2 ICD*1).tw. (2770) 7 (CRT or CRT-D or CRT-P).mp. (10003) 8 dual chamber ICD.tw. (166) 9 single chamber ICD.tw. (74) 10 resynch* therap*.tw. (5086) 11 ((heart or cardiac or myocardial or coronary) adj2 (resynch* or depolari* or repolari*)).tw. (7021) 12 ((atriobiventricula* or atrio-biventricula* or "atrio biventricula*") adj10 (pacing or pacemaker*1)).tw. (51) 13 ((atriobiventricula* or atrio-biventricula* or "atrio biventricula*") adj10 stimulat*).mp. (7) 14 BVP.tw. (228) 15 ((biventricula* or bi-ventricula* or "bi ventricula*") adj10 (pacing or pacemaker*1)).tw. (1891) 16 ((biventricula* or bi-ventricula* or "bi ventricula*") adj10 stimulat*).tw. (253) 17 (cardiover* or "cardio-ver*" or cardioconver* or "cardio-conver*" or "cardio conver*").tw. (14287) 18 or/1-17 (32069) 19 exp heart arrhythmia/ (287154) 20 Heart Ventricle Tachycardia/ (22817) 21 Heart Atrium Fibrillation/ (56280) 22 Heart Ventricle Fibrillation/ (21002) 23 heart left ventricle failure/ or heart ventricle remodeling/ (21418) 24 exp cardiomyopathy, dilated/ (15329) 25 ventricula* remodel*.tw. (4156) 26 heart bundle branch block/ (4458) 27 Heart Failure/ (101143) 28 exp heart failure, congestive/ (66402) 29 Sudden Death/ (31517) 30 Heart Arrest/ (34638) 31 (ventricul* adj2 (tachycardia* or fibril* or arrhythmia*)).tw. (44251) 32 ((heart or cardiac or myocardial or coronary) adj2 (failur* or arrest* or sudden)).tw. (162727)	2899

33	((cardiac or ventricular or intraventricular) adj5 asynchron*).tw. (598)	
34	((cardiac or ventricular or intraventricular) adj5 dyssynchron*).tw. (1522)	
35	tachyarrhythmia*.tw. (8770)	
36	"abnormal heart rhythm*".tw. (51)	
37	("unexpected death" or "sudden death").tw. (21577)	
38	(cardiomyopathy or cardiomyopathies).tw. (51851)	
39	heart infarction/ (181694)	
40	"heart attack*".tw. (4253)	
41	Long QT Syndrome/ (6550)	
42	Syncope/ (21589)	
43	(syncope adj2 (cardiogenic or heart or cardiac or myocardial)).tw. (739)	
44	(atrial adj2 (fibril* or flutter*)).tw. (45450)	
45	("sudden cardiac death" or "sudden arrhythmic death").tw. (10167)	
46	"unstable heart rhythm*".tw. (2)	
47	"left ventricular systolic dysfunction".tw. (2264)	
48	((reduced or reduction or impair*) adj2 left ventricular ejection fraction).tw. (806)	
49	LVSD.tw. (460)	
50	((heart or cardiac or myocardial) adj2 dysfunction*).tw. (13985)	
51	exp cardiomyopathies/ (76269)	
52	Brugada Syndrome/ or "Brugada syndrome".tw. (2864)	
53	arrhythmogenic right ventricular dysplasia.tw. (1004)	
54	ARVD.tw. (551)	
55	(surg* adj5 "congenital heart disease").tw. (1785)	
56	((familial or genetic or inherited) adj "heart disease").tw. (88)	
57	("heart failure" or "cardiac failure" or "ventricula*1 failure").tw. (131999)	
58	congenital heart malformation/ (29438)	
59	atrioventricular conduction/ or heart muscle conduction system/ or heart conduction/ (20024)	
60	heart pacing/ (12688)	
61	artificial heart pacemaker/ (27811)	
62	exp heart assist device/ (5781)	
63	or/19-62 (764662)	
64	18 and 63 (23240)	
65	randomized controlled trial/ (297819)	
66	controlled clinical trial/ (173820)	
67	randomization/ (55443)	
68	(random* or placebo*).tw. (761478)	

	<p>69 Double Blind Procedure/ (104980) 70 Single Blind Procedure/ (14650) 71 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*).tw. (140490) 72 "systematic review"/ (46550) 73 "systematic review*".tw. (38228) 74 meta analysis/ (58442) 75 meta analy*.tw. (49352) 76 or/65-75 (970577) 77 64 and 76 (3010) 78 (comment or editorial or letter).pt. (1152313) 79 77 not 78 (2962) 80 limit 79 to animal studies (63) 81 79 not 80 (2899) 82 from 81 keep 1001-2000 (1000) 83 from 81 keep 2001-2899 (899)</p>	
<p>Web of Science Science Citation Index Expanded (SCI-EXPANDED) -- 1970-present Conference Proceedings Citation Index- Science (CPCI-S) --1990- present Keywords WOS CLINICAL EFFECTIVENESS KW</p>	<p># 1 10,116 (TS=(implant* NEAR (cardiover or defibril* or ICD*))) AND Language=(English) # 2 9,845 (TS=(ICDs or S-ICD or S-ICDS or CRT or CRT-D or CRT-P)) AND Language=(English) # 3 191 ((TS=("single chamber ICD*" or "dual chamber ICD*")) AND Language=(English) # 4 3,343 (TS=(implant* NEAR ICD*)) AND Language=(English) # 5 11,399 (TS=((heart or cardiac or myocardial or coronary) NEAR (resynch* or depolari* or repolari*))) AND Language=(English) # 6 12 (TS=(atriobiventricula* NEAR (pace* or pacing or stimulat*))) AND Language=(English) # 7 1,689 (TS=(biventricula* NEAR (pace* or pacing or stimulat*))) AND Language=(English) # 8 7,996 (TS=(implant* NEAR (cardiover* or "cardio-ver*" or cardioconver* or "cardio-conver*" or "cardio conver*"))) AND Language=(English) # 9 28,032 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 # 10 182,051 (TS=(arrhythmia* or tachycardia* or tachyarrhythmia* or "heart failure" or "sudden cardiac death" or "sudden arrhythmic death")) AND Language=(English) # 11 48,202 (TS=(fibril* NEAR (atrial or heart or ventricula*))) AND Language=(English) # 12 5,494 (TS=("long QT syndrome")) AND Language=(English) # 13 1,969 (TS=("brundle branch block" or "brugada syndrome")) AND Language=(English) # 14 2,075 (TS=(surg* NEAR ("congenital heart disease"))) AND Language=(English) # 15 813 (TS=(ARVD or "arrhythmogenic right ventricular dysplasia")) AND Language=(English) # 16 2,315 (TS=(syncope NEAR (cardiogenic or heart or cardiac or myocardial))) AND Language=(English) # 17 216,898 #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 # 18 13,910 #17 AND #9</p>	<p>783</p>

	<p># 19 77,723 (TS=("randomised controlled trial" or "randomized controlled trial")) AND Language=(English)</p> <p># 20 2,213 (TS=(random NEAR allocat*)) AND Language=(English)</p> <p># 21 252,439 (TS=(random* NEAR trial*)) AND Language=(English)</p> <p># 22 253,954 #21 OR #20 OR #19</p> <p># 23 1,080 #22 AND #18</p> <p>Refined by: Document Type=(ARTICLE OR PROCEEDINGS PAPER OR MEETING ABSTRACT)</p> <p># 24 790 #22 AND #18 (6 chapters in books taken out 784)</p>	
<p>Biosis</p> <p>All years searched</p> <p>Searched</p> <p>17/01/2012</p> <p>Keywords:</p> <p>BIOSIS</p> <p>CLINICAL</p> <p>EFFECTIVENESS KW</p>	<p>Strategy as per Web of Science above.</p>	<p>63</p>
<p>Cochrane</p> <p>Issue 1 of 12 Jan</p> <p>2012</p> <p>All years searched</p> <p>Searched</p> <p>18/01/2012</p>	<p>#1 MeSH descriptor Defibrillators, Implantable, this term only 708 edit delete</p> <p>#2 (implant* NEAR (defibrilat* or defibrillat*)) 939 edit delete</p> <p>#3 (ICDs or "S-ICD" or S-ICDs) 230 edit delete</p> <p>#4 subcutaneous NEAR ICD* 2 edit delete</p> <p>#5 implant* NEAR ICD* 455 edit delete</p> <p>#6 (CRT or "CRT-D" or "CRT-P") 744 edit delete</p> <p>#7 ("dualchamber*" AND ICD*) 15 edit delete</p> <p>#8 ("dual chamber*" AND ICD*) 46 edit delete</p> <p>#9 "singlechamber" AND ICD* 8 edit delete</p> <p>#10 "single chamber" AND ICD* 25 edit delete</p> <p>#11 resynch* NEAR therapy 290 edit delete</p> <p>#12 ((heart or cardiac or myocardial or coronary) NEAR (resynch* or depolari* or repolari*)) 468 edit delete</p> <p>#13 (atriobiventricular NEAR pacing) 3 edit delete</p> <p>#14 (atriobiventricular NEAR stimulat*) 0 edit delete</p> <p>#15 BVP 17 edit delete</p> <p>#16 biventricular NEAR pac* 137 edit delete</p> <p>#17 biventricular NEAR stimulat* 18 edit delete</p> <p>#18 (cardiover* or "cardio-ver*" or cardioconver* or "cardio-conver*" or "cardio conver*") 1241 edit delete</p> <p>#19 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR</p>	<p>Total 1577</p> <p>(CENTRAL</p> <p>1465</p> <p>CDSR 37</p> <p>DARE 75)</p>

	<p>#18) 2517 edit</p> <p>#20 MeSH descriptor Arrhythmias, Cardiac explode all trees 5728 edit delete</p> <p>#21 MeSH descriptor Cardiomyopathy, Dilated explode all trees 410 edit delete</p> <p>#22 ventricula* remodel* 655 edit delete</p> <p>#23 MeSH descriptor Bundle-Branch Block explode all trees 82 edit delete</p> <p>#24 MeSH descriptor Heart Failure explode all trees 4620 edit delete</p> <p>#25 "congestive heart failure" 3269 edit delete</p> <p>#26 MeSH descriptor Death, Sudden, Cardiac explode all trees 444 edit delete</p> <p>#27 MeSH descriptor Heart Arrest, this term only 533 edit delete</p> <p>#28 (ventricul* NEAR (tachycardia* or fibril* or arrhythmia*)) 2774 edit delete</p> <p>#29 ((heart or cardiac or myocardial or coronary) NEAR (failur* or arrest* or sudden)) 12656 edit delete</p> <p>#30 ((cardiac or ventricular or intraventricular) NEAR asynchron*) 28 edit delete</p> <p>#31 ((cardiac or ventricular or intraventricular) NEAR dyssynchron*) 66 edit delete</p> <p>#32 tachyarrhythmia* 576 edit delete</p> <p>#33 ("unexpected death" or "sudden death") 837 edit delete</p> <p>#34 (cardiomyopathy or cardiomyopathies) 1494 edit delete</p> <p>#35 "heart infarction" 1098 edit delete</p> <p>#36 "heart attack*" 418 edit delete</p> <p>#37 "long QT syndrome" 156 edit delete</p> <p>#38 (syncope NEAR (heart or cardiac or cardio* or myocardial)) 120 edit delete</p> <p>#39 (atrial NEAR (fibril* or flutter*)) 3572 edit delete</p> <p>#40 ("sudden cardiac death" or "sudden arrhythmic death") 436 edit delete</p> <p>#41 abnormal* NEAR "heart rhythm*" 14 edit delete</p> <p>#42 (unstable NEAR ("heart rhythm*)) 1 edit delete</p> <p>#43 "left ventricular systolic dysfunction" 231 edit delete</p> <p>#44 ((reduced or reduction or impair*) NEAR ("left ventricular ejection fraction")) 142 edit delete</p> <p>#45 (LVEF NEAR (reduced or reduction or impair*)) 96 edit delete</p> <p>#46 LVSD 36 edit delete</p> <p>#47 ((heart or cardiac or myocardial) NEAR dysfunction*) 1209 edit delete</p> <p>#48 MeSH descriptor Cardiomyopathies explode all trees 1181 edit delete</p> <p>#49 "brugada syndrome" 21 edit delete</p> <p>#50 "arrhythmogenic right ventricular dysplasia" 10 edit delete</p> <p>#51 ARVD 12 edit delete</p> <p>#52 (surg* NEAR ("congenital heart disease")) 79 edit delete</p> <p>#53 ((familial or genetic or inherited) NEAR "heart disease") 28 edit delete</p> <p>#54 ("heart failure" or "cardiac failure" or "ventricular failure") 9933 edit delete</p>	
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	<p>#55 MeSH descriptor Heart Defects, Congenital explode all trees 1233 edit delete #56 MeSH descriptor Heart Conduction System explode all trees 628 edit delete #57 MeSH descriptor Cardiac Pacing, Artificial explode all trees 964 edit delete #58 MeSH descriptor Pacemaker, Artificial explode all trees 552 edit delete #59 MeSH descriptor Heart-Assist Devices explode all trees 129 edit delete #60 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59) 23347 edit delete #61 (#19 AND #60) 1748 1465 Central 37 CDSR</p>	
<p>CRD DARE AND HTA Searched 18/12/2012</p>	<p>Dare results downloaded via Cochrane as filter works better 1 implant* NEAR cardiover* 139 Delete 2 implant* NEAR defibril* 165 Delete 3 "S-ICD" or "S-ICDs" 239 Delete 4 subcutaneous NEAR ICD* 1 Delete 5 implant* NEAR ICD* 103 Delete 6 CRT OR "CRT-D" or "CRT-P" 57 Delete 7 "dual chamber" and ICD* 1 Delete 8 "single chamber" AND ICD* 3 Delete 9 resynch* and cardi* and therapy 67 Delete 10 ((heart or cardiac or myocardial or coronary) NEAR (resynch* or depolari* or repolari*)) 69 Delete 11 biventricula* pac* 23 Delete 12 biventricula* stimulat* 1 Delete 13 (cardiover* or "cardio-ver*" or cardioconver* or "cardio-conver*" or "cardio conver*") 186 Delete 14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 442 Delete 15 random* NEAR trial* 22702 Delete 16 (random* NEAR (study or studies)) 7141 Delete 17 random* NEAR allocat* 2535 Delete 18 "controlled trial*" 4054 Delete 19 "systematic review*" 21591 Delete 20 meta analy* 207 Delete 21 "technology assessment" 12557 Delete 22 "double blind*" OR "single blind*" 325 Delete 23 placebo NEAR trial* 2370 Delete 24 "controlled clinical trial*" 184 Delete</p>	<p>CRD HTA 89 CRD DARE 76</p>

	25 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 39834 Delete 26 #14 AND #25 382	
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Appendix 4: Economic evaluation checklist

	Item	StudyID	Comments
1	Is there a clear statement of the decision problem?		
2	Is the comparator routinely used in UK NHS?		
3	Is the patient group in the study similar to those of interest in UK NHS?		
4	Is the health care system comparable to UK?		
5	Is the setting comparable to the UK?		
6	Is the perspective of the model clearly stated?		
7	Is the study type appropriate?		
8	Is the modelling methodology appropriate?		
9	Is the model structure described and does it reflect the disease process?		
10	Are assumptions about model structure listed and justified?		
11	Are the data inputs for the model described and justified?		
12	Is the effectiveness of the intervention established based on a systematic review?		
13	Are health benefits measured in QALYs?		
14	Are health benefits measured using a standardised and validated generic instrument?		
15	Are the resource costs described and justified?		
16	Have the costs and outcomes been discounted?		
17	Has uncertainty been assessed?		
18	Has the model been validated?		

Yes / No / ? (unclear)

Appendix 5: List of excluded clinical effectiveness studies and recent abstracts

Are implantable cardioverter-defibrillators or drugs more effective in prolonging life? The Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial Executive Committee. *The American journal of cardiology* 1997;**79(5)**:661-3.

Reason for exclusion: Patient group, intervention, outcomes and study design

Adamson PB, Kleckner KJ, VanHout WL, Srinivasan S, Abraham WT. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* 2003;**108(3)**:266-9.

Reason for exclusion: Outcomes

Alonso C, Ritter P, Leclercq C, Mabo P, Bailleul C, Daubert JC *et al.* Effects of cardiac resynchronization therapy on heart rate variability in patients with chronic systolic heart failure and intraventricular conduction delay. *American Journal of Cardiology* 2003;**91(9)**:1144-7.

Reason for exclusion: Outcomes and study design

Aranda JM, Jr., Conti JB, Johnson JW, Petersen-Stejskal S, Curtis AB. Cardiac resynchronization therapy in patients with heart failure and conduction abnormalities other than left bundle-branch block: analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Clinical Cardiology* 2004;**27(12)**:678-82.

Reason for exclusion: Study design

Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P *et al.* Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *Journal of the American College of Cardiology* 2002;**39(12)**:2026-33.

Reason for exclusion: Comparator

Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR *et al.* Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *Journal of the American College of Cardiology* 2003;**42(12)** :2109-16.

Reason for exclusion: Comparator

Auricchio A, Metra M, Gasparini M, Lamp B, Klersy C, Curnis A *et al.* Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. *American Journal of Cardiology* 2007;**99(2)**:232-8.

Reason for exclusion: Population, comparator and study design

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Reason for exclusion: Intervention and comparator (while the study is excluded, some details of the study are discussed in the report)

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Reason for exclusion: Study design (review)

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Reason for exclusion: Comparator and study design

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Reason for exclusion: Population and design

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Reason for exclusion: Population

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Reason for exclusion: Study design

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Reason for exclusion: Outcomes

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Reason for exclusion: Comparator and study design

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Reason for exclusion: Population, intervention and outcomes

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Reason for exclusion: Population and intervention

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Reason for exclusion: Population, intervention and outcomes

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Reason for exclusion: Population, intervention and outcomes

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Reason for exclusion: Population and intervention

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Reason for exclusion: Intervention and comparator

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Reason for exclusion: Comparator and study design

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Reason for exclusion: Study design

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Reason for exclusion: Study design

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Reason for exclusion: Study design

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Reason for exclusion: Comparator, outcomes and study design

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Reason for exclusion: Study design

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Reason for exclusion: Outcomes

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Reason for exclusion: Study design

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Reason for exclusion: Study design

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Reason for exclusion: Study design

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Reason for exclusion: Comparator, outcomes and study design

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Reason for exclusion: Comparator

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Reason for exclusion: Outcomes and study design

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Reason for exclusion: Study design

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Reason for exclusion: Abstract (insufficient details)

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Reason for exclusion: Comparator and study design

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Reason for exclusion: Comparator

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Reason for exclusion: Study design

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Reason for exclusion: Population and intervention

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Reason for exclusion: Study design

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Reason for exclusion: Outcomes

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Reason for exclusion: Study design

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Reason for exclusion: Study design

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Reason for exclusion: Study design

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Reason for exclusion: Study design

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Appendix 6: Ongoing trials

Five relevant trials in progress were identified by the searches:

- ICD2–trial: ‘A prospective randomised controlled trial to evaluate the prevention of sudden cardiac death using Implantable Cardioverter Defibrillators in dialysis patients’ (ISRCTN20479861). The trial aims to determine whether the ICD therapy in dialysis patients aged 55 to 80 years will result in significant reduction in sudden cardiac (arrhythmic) death rates when compared to no ICD therapy. This is a multi-centre RCT in the Netherlands, start date: 01/04/2007, end date: 01/04/2017. Funded by Biotronik Nederland B.V.
- The DANISH Study. Danish ICD Study in Patients With Dilated Cardiomyopathy: ‘A DANish Randomized, Controlled, Multicenter Study to Assess the Efficacy of Implantable Cardioverter Defibrillator in Patients With Non-ischemic Systolic Heart Failure on Mortality’ (NCT00542945 and NCT00541268). The comparator is OPT only. This is a multi-centre RCT in Denmark, start date: December 2007, end date: December 2012. Funding not stated.
- REFINE-ICD: ‘Efficacy of Implantable Defibrillator Therapy After a Myocardial Infarction (official title ‘Risk Estimation Following Infarction Noninvasive Evaluation - ICD Efficacy)’ (NCT00673842). The trial aims to determine whether prophylactic ICD therapy reduces mortality in MI survivors with better-preserved LV function compared with standard medical care and standard post-MI treatment. This is a multi-centre RCT in Canada, start date: March 2011, end date: February 2018. Funding: not stated, but collaborators are Alberta Innovation and Science, Medtronic and GE Healthcare.
- EchoCRT: ‘Echocardiography Guided Cardiac Resynchronization Therapy’ (NCT00683696). The trial aims to evaluate the effects of CRT-D on mortality and morbidity of patients with heart failure due to LVSD already receiving OPT, a narrow QRS width and echocardiographic evidence of ventricular dyssynchrony compared with OPT only and CRT-D off. This is an international multi-centre RCT (including Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Spain, Switzerland, United Kingdom and United States), start date: August 2008, end date: December 2012. Funded by Biotronik, Inc.

- ADOPT Trial: ‘Assessment of Efficacies of Cardiac Resynchronization Therapies (CRT-P/D) for Heart Failure Patients in China’ (ChiCTR-TRC-09000574). The trial aims to evaluate whether CRT-P/D can further reduce mortality, improve CHF symptoms and enhance QoL on top of OPT compared with OPT alone in Chinese CHF patients. This is a multi-centre RCT in China, start date: October 2008, end date: December 2012. Funded by Medtronic, Inc.

Appendix 7: Hospitalisations: total, cardiac and non-cardiac

People with heart failure as a result of LVSD and cardiac dyssynchrony

Number of patients hospitalised

The CARE-HF trial⁹ reported unplanned hospitalisations for a major cardiovascular event and this was the primary outcome of the study. In addition, the study reported mean number of days in hospital by 3 months, days in hospital after 3 months and mean days in hospital overall during the entire study (median 29.6 months). The COMPANION trial¹⁰ reported data for all hospital admissions, cardiac admissions and non-cardiac admissions.

CRT-P vs OPT

There were statistically significantly fewer unplanned hospitalisations for a major cardiovascular event with CRT-P compared with OPT (31% vs 46% respectively; HR 0.61, 95% CI, 0.49 to 0.77, $p<0.001$) in CARE-HF.⁹ Mean number of days in hospital overall was also lower with CRT-P compared with OPT, but no statistical comparisons for these outcomes were reported (Table 1). Similarly, all hospital admissions (63% vs 65% respectively, $p=0.02$) and cardiac admissions (49% vs 53% respectively, $p<0.01$) were both statistically significantly lower with CRT-P compared with OPT in COMPANION.¹⁰ However, non-cardiac hospital admission were higher in those with CRT-P (36% vs 27% OPT), but no statistical comparison was reported.

CRT-D vs OPT

All hospital admissions (CRT-D 63% vs OPT 65%, $p=0.03$) and cardiac hospital admissions (CRT-D 48% vs OPT 53%, $p<0.01$) were statistically significantly lower with CRT-D compared with OPT in COMPANION.¹⁰ However, non-cardiac hospital admissions were higher with CRT-D (35% vs 27% OPT), but no statistical comparison was reported.

CRT-P vs CRT-D

The authors of the COMPANION trial¹⁰ state that no significant differences were found in any of the hospital endpoints for CRT-P vs CRT-D, but no statistics were reported (Table 1).

Number of events / days of admission

CRT-P vs OPT

CARE-HF⁹ reported 222 unplanned hospitalisations for a major cardiovascular event in the CRT-P group ($n=409$) and 384 in the OPT group ($n=404$) (Table 2). COMPANION¹⁰ found statistically significantly fewer admissions per patient year for cardiac procedure for those with CRT-P (0.13 vs 0.24 OPT; $p<0.01$). The number of average admissions per patient year of follow-up was lower for those with CRT-P (1.25 vs 1.59 OPT). The average number of hospital days per patient year of

follow-up was also lower with CRT-P (8.3 vs 11.0 OPT), with the average length of hospital stay per admission similar for both treatment groups (CRT-P 6.7 vs OPT 6.9 days). Average hospital admissions per patient year of follow-up for cardiac (CRT-P 0.79 vs OPT 1.20) and non-cardiac (CRT-P 0.46 vs OPT 0.39 admissions) causes were lower in those with CRT-P. Average hospital days per patient year of follow-up for cardiac (CRT-P 5.2 vs OPT 8.1) and non-cardiac (CRT-P 3.2 vs OPT 2.8) causes, and average length of stay per hospital admission for cardiac (CRT-P 6.5 vs OPT 6.8 days) and non-cardiac (CRT-P 6.9 vs OPT 7.1 days) causes were similar between both treatment groups.

CRT-D vs OPT

COMPANION¹⁰ reported statistically significantly fewer hospital admissions per patient year for cardiac procedure in those with CRT-D (0.09 vs 0.24 OPT, $p < 0.01$). The number of average admissions per patient year of follow-up in those with CRT-D (1.20 vs 1.59 OPT). The average number of hospital days per patient year of follow-up were lower in those with CRT-D was also lower (8.6 vs 11.0 OPT), with the average length of hospital stay per admission similar for both treatment groups (CRT-D 7.2 vs OPT 6.9). Those with CRT-D had fewer average hospital admissions per patient year of follow-up for cardiac causes (CRT-D 0.76 vs OPT 1.20), but more admissions for non-cardiac causes (CRT-D 0.44 vs OPT 0.39). Average hospital days per patient year of follow-up for cardiac (CRT-D 5.5 vs OPT 8.1) and non-cardiac (CRT-D 3.8 vs OPT 2.8) causes, and average length of stay per hospital admission for cardiac (CRT-D 7.2 vs OPT 6.8) and non-cardiac (CRT-D 8.8 vs OPT 7.1) causes were similar for both treatment groups.

CRT-P vs CRT-D

The authors of COMPANION¹⁰ state that no significant differences were found in any of the hospitalisation endpoints for CRT-P vs CRT-D, but statistics were not reported.

Table 1: All hospitalisations: number of patients

Study	Outcome; follow-up, months	CRT-P, n/N (%) ^c	OPT, n/N (%)	Effect	95% CI, p value
CARE-HF ⁹	Major cardiovascular event; 29.4 ^a	125/409 (31)	184/404 (46)	HR 0.61	0.49 to 0.77, <0.001
	Mean days in hospital by 3 months	7.5, median 4 (IQR 2-8)	3.4, median 0 (IQR 0-1)		
	Days in hospital after 3 months	222	384		
	Mean days in hospital overall during entire study (reported as median 29.6 months)	20.7 median 9 (IQR 4-26)	22.4 median 9 (IQR 0-31)		
MIRACLE ¹¹	Hospitalisations unrelated to HF or function of left ventricular lead, n	37/228 (16.2)	33/225 (14.7)		
COMPANION ^{10b}	All admissions, CRT-P 16.2, OPT 11.9 ^c	388/617(63)	199/308 (65)		0.02
	Cardiac	301/617 (49)	164/308 (53)		<0.01
	Non-cardiac	222/617 (36)	84/308 (27)		
		CRT-D, n/N (%)	OPT, n/N (%)		
	All admissions, CRT-D 15.7, OPT 11.9 ^c	372/595 (63)	199/308 (65)		0.03
Cardiac	284/595 (48)	164/308 (53)		<0.01	
Non-cardiac	207/595 (35)	84/308 (27)			

^a Mean. ^b COMPANION¹² states that no significant difference were found in any of the end-points for CRT-P vs CRT-D (no p values reported).

^c Median.

Table 2: All hospitalisations: number of events and/or of days of admission

Study	Outcomes; median follow-up, months	CRT-P	OPT	Effect	95% CI, p value
CARE-HF ⁹	No. of unplanned hospitalisations for a major cardiovascular event, 29.4	222	384		
COMPANION ^{10a}	No. of admissions (% of total admissions), no. of average admissions per patient year of follow-up; CRT-P 16.2, OPT 11.9				
	- All admissions	993 (n/a) 1.25	516 (n/a) 1.59		
	- Cardiac	628 (63) 0.79	338 (75) 1.20		
	- Non-cardiac	365 (37) 0.46	126 (24) 0.39		
	Average days per patient year of F-up (av. length of stay per admission)				
	- All admissions	8.3 (6.7)	11.0 (6.9)		
- Cardiac	5.2 (6.5)	8.1 (6.8)			
- Non-cardiac	3.2 (6.9)	2.8 (7.1)			
	No. of admissions per patient year for cardiac procedure	0.13	0.24		<0.01
		CRT-D	OPT		
	No. of admissions (% of total admissions), no. of average admissions per patient year of follow-up; CRT-D 15.7, OPT 11.9				
	- All admissions	919 (n/a) 1.20	516 (n/a) 1.59		
	- Cardiac	580 (63) 0.76	338 (75) 1.20		
	- Non-cardiac	339 (37) 0.44	126 (24) 0.39		ns

	Average days per patient year of follow-up (av. length of stay per admission):				
	- All admissions	8.6 (7.2)	11.0 (6.9)		
	- Cardiac	5.5 (7.2)	8.1 (6.8)		
	- Non-cardiac	3.8 (8.8)	2.8 (7.1)		
	No. of admissions per patient year for cardiac procedure	0.09	0.24		<0.01

^a COMPANION¹² states that no significant difference were found in any of the end-points for CRT-P vs CRT-D (no p values reported).

People with both conditions

The RAFT study¹³ reported that a similar proportion of participants (about 56%) in each group were hospitalised at least once (Table 3), and the majority were hospitalised for a cardiac cause (CRT-D 47.3%, ICD 44.7%, p=0.56). All-cause hospitalisations were also similar in the MIRACLE ICD study,¹⁴ although the mean length of stay was slightly reduced with CRT-D [mean 4.8 days (SD 4.9) vs mean 5.4 days (SD 4.7), p=0.06]. All-cause hospitalisations were slightly lower with CRT-D in the Pinter study¹⁵ (30.6% vs 36.1%).

Table 3 All hospitalisations

Study	Outcome; follow-up, months	CRT-D n/N (%)	ICD n/N (%)	Effect	95% CI, p value
MIRACLE ICD ¹⁴	Hospitalisations, 6	85/187 (45.5)	78/182 (42.9)		
	Length of hospital stay days, mean (SD)	mean 4.8 (SD 4.9)	mean 5.4 (SD 4.7)		0.06
Pinter ¹⁵	Patients hospitalised, 6	11/36 ^a (30.6)	13/36 ^a (36.1)		
RAFT ¹³	Hospitalisation ≥ 1 during follow-up (mostly cardiovascular), mean 40 (SD 20)	509/894 (56.9)	509/904 (56.3)		
	Hospitalisation: cardiac cause, n	423/894 (47.3)	404/904 (44.7)	HR 1.04	0.56

^aNumerator calculated by reviewer.

Appendix 8: Data extraction: people at risk of sudden cardiac death due to ventricular arrhythmias

AMIOVIRT

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Strickberger <i>et al.</i>, 2003¹⁶ Wijetunga and Strickberger, 2003¹⁷</p> <p>AMIOVIRT</p> <p>Study design: RCT</p> <p>USA</p> <p>Number of centres: 10</p> <p>Funding: unrestricted research grant from the Guidant Corporation</p>	<p><i>Intervention:</i> ICD + OPT (ICD were inserted using conventional non-thoracotomy techniques)</p> <p><i>Comparator:</i> Amiodarone + OPT (dose: 800 mg/day for first week, 400 mg/day for one year and then 300 mg/day)</p> <p><i>Other interventions used:</i> OPT with angiotensin-converting enzyme inhibitors, beta-blockers, and potassium-sparing diuretics was strongly encouraged and attempted throughout the duration of the study for both groups.</p>	<p><i>Indication for treatment:</i> Non-ischemic dilated cardiomyopathy (NIDCM) and asymptomatic non-sustained ventricular tachycardia (NSVT)</p> <p><i>Number of randomised participants:</i> n = 103 ICD, n=51 OPT, n=52</p> <p><i>Inclusion criteria:</i> Age ≥ 18years; NIDCM (left ventricular dysfunction in the absence of, or disproportionate to the severity of, coronary artery disease); LVEF ≤0.35; Asymptomatic NSVT (≥3 consecutive ventricular premature depolarization with a rate of >100bpm, lasting <30s and not associated with symptoms of cerebral hypofusion); NYHA class I to III.</p> <p><i>Exclusion criteria:</i> Syncope; Pregnancy; A contraindication to amiodarone or defibrillator therapy or concomitant therapy with a Class I antiarrhythmic drug</p>	<p><i>Primary outcomes:</i> total mortality</p> <p><i>Secondary outcomes:</i> Sudden cardiac death (SCD), non-SCD, non-cardiac death, syncope, arrhythmia-free survival, QoL and costs</p> <p><i>Method of assessing outcomes:</i> Stored electrograms and all available clinical data were used to determine the appropriateness of ICD therapies. Causes of death were determined by an events committee, with each of the 3 members independently evaluating all information available regarding each death. Differences in the cause of death were adjudicated and a consensus reached.</p> <p>QoL: both completed by patients at the time of randomisation and during follow-up visits.</p> <ul style="list-style-type: none"> • Quality of Well Being Schedule - score range 0 – 110 (higher level of general well-being associated with a greater value) • State Trait Anxiety - score range 40 – 160 (greater value associated with lower level of anxiety) <p>Cost analysis: In- and outpatient costs for the 24 patients based on University of Michigan Health System for 1 year starting at the study entry (not data extracted)</p> <p>Amiodarone group: assessed for thyroid function studies, aspartate and alanine transaminase plasma levels, and a chest X-ray obtained at baseline and every 4 months during follow-up. Serum concentrations of Amiodarone and Desethylamiodarone were obtained 4 months and 1 year after initiation of</p>

		or NIDCM diagnosed within 6 months. ¹⁷	<p>treatment (until 30-6-2001).</p> <p>ICD: defibrillator follow-up was performed every 4 months, including evaluation of stored electrograms, and sensing and pacing functions.</p> <p><i>Definitions:</i></p> <ul style="list-style-type: none"> • Arrhythmia-free survival: freedom from death, syncope, appropriate ICD therapy, and sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). <p><i>Length of follow-up:</i> mean duration 2.0 years (SD 1.3; range 0.1 to 4.8 years); ICD 2.2yrs (SD 1.2); Amiodarone 1.8yrs (SD 1.4) p = 0.4</p> <p><i>Recruitment:</i> August 1996 - September 2000</p>	
Participant characteristics		ICD, n=51	Amiodarone, n=52	p value
Age years, mean (SD)		58 (11)	60 (12)	0.5
Gender, M %		67	74	0.3
Ethnicity		Not reported	Not reported	
NYHA classification				0.9
I		18	13	
II		64	63	
III		16	24	
LVEF		0.22 (0.10)	0.23 (0.08)	0.5
Heart rate (bpm), mean (SD)		80 (17)	78 (14)	0.7
Right bundle branch block, %		16	8	0.2
Left bundle branch block, %		42	53	0.3
Electrophysiology findings				
No. of beats of non-sustained ventricular tachycardia (NSVT) (SD)		8 (7)	12 (21)	0.2
NSVT, beats/min (SD)		160 (27)	151 (20)	0.4
NSVT identified, %				0.7
ECG		6	8	
Event monitor		26	29	
Holter monitor		6	2	
Hospital telemetry		62	61	
Current pharmacological therapy		Not reported	Not reported	
Duration of NIDCM, mean years (SD)		2.9 (4.0)	3.5 (3.9)	0.6
CAD >70%, ^a n/N (%)		2/41 (4.9)	3/27 (11.0)	0.3
Cardiac history				
Previous treatment		Not reported	Not reported	
Comorbidities				
Diabetes mellitus, %		31	36	0.6
Hypertension, %		58	67	0.4
Quality of Well-Being Schedule, mean (SD)		67 (15)	70 (17)	0.5
State Trait Anxiety Inventory, mean (SD)		75 (25)	79 (21)	0.5

Comments: ^a CAD >70%, 1 major epicardial coronary artery with a 70% or greater stenosis;

RESULTS

Outcomes	ICD, n=51	Amiodarone n=52	p value
Primary outcome total mortality, n (%)	6 (11.8)	7 (13.5)	0.8
Secondary outcomes			
Cardiac deaths, n (%)	4 (67)	5 (71)	0.9
SCD, n (%)	1 (25)	2 (40)	0.7
Non-SCD, n (%)	3 (75)	3 (60)	0.7
Survival rates at 1 and 3 years			0.8
Survival rates 1 year, %	96	90	
Survival rates 3 year, %	88	87	
Arrhythmia-free survival rates at 1 and 3 years			p= 0.1
Arrhythmia-free survival rates 1 year, %	78	82	
Arrhythmia-free survival rates 3 year, %	63	73	
Non-cardiac, n (%)	2 (33)	2 (29)	0.9
Cardiac transplant, n (%)	1 (2)	2 (4)	0.8
Syncope, %	3.9 ^a	5.8	0.7
Health related quality of life			
Quality of Well Being Schedule 1 year, mean (SD)	74 (19)	70 (22)	0.5 ^b
State Trait Anxiety Inventory 1 year, mean (SD)	61 (17)	67 (20)	0.4 ^b

Comments: ^a ventricular tachycardia or VF was the cause of syncope in each ICD patient in whom it occurred; ^b p values were also reported within groups (not data extracted).

- Kaplan Meier estimate of cumulative survival and arrhythmia-free survival also displayed in figures for 0 to 55 months.
- At 1 year, the Quality of Well Being Schedule and the State Trait Anxiety Inventory scores were not significantly different between patients treated with an ICD who did (67 (SD15) and 73 (SD 22), respectively) and did not (68 (SD 16) and 82 (SD 31) respectively; both p=0.05) receive appropriate ICD therapies.
- Cost of medical care reported, but not data extracted.

Concomitant drug therapy at last follow up	ICD, n=51	Amiodarone, n=52	p value
Beta-blocker, %	53	50	0.5
ACE inhibitor, %	90	81	0.4
Digoxin, %	71	67	0.5
Diuretic, %	71	67	0.5
Spirolactone, %	20	19	0.9

Comments: Amiodarone group: mean dose at the conclusion of the study 303 mg/day (SD 93). The serum concentrations of Amiodarone and Desethylamiodarone at 4 and 12 months were also reported (not data extracted).

Adverse effects of treatment	25 patients discontinued Amiodarone due to adverse side effects (mean 17.8 months, SD 13.3; range 1.2 to 43.8 months) ^c
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Comments: ^c states in the discussion that Amiodarone was discontinued in a third of patients, but data not reported per treatment group.

- All ICD implants were successful.
- An appropriate ICD therapy was delivered in 16 patients for ventricular arrhythmias that had a mean rate of 218 beats/min (SD 40; range 170 to 284).

Methodological comments

- *Allocation to treatment groups*: Randomisation was stratified by centre (patients who refused study participation were followed in a voluntary registry).
- *Blinding*: un-blinded trial. Assessors for causes of death were blinded (independent events review

committee) and all references to Amiodarone or ICD therapy were removed from the reviewed documents (including the death certificate, other relevant medical records, and interviews with family members).

- *Comparability of treatment groups:* there were no statistically significant differences at baseline between the treatment groups.
- *Method of data analysis:* Patients who underwent cardiac transplantation were censored from data analysis beginning on the day of transplantation. All analyses were based on ITT. Primary and secondary endpoints were compared between the 2 groups with a log-rank test, and survival curves were constructed using Kaplan-Meier methods. Continuous variables are expressed as mean \pm 1 SD and were compared using Student t test, except for comparisons between baseline and 1-year QoL scores within the 2 study groups, which were compared with a paired t-test. A chi-squared or Fisher's exact test was used to compare nominal variables. A $p < 0.05$ was considered statistically significant. A data safety monitoring board evaluated the results every 10 deaths. Prospectively determined stopping rules consisted of a mortality difference at a significance level of < 0.025 , or a significance level of > 0.025 (90% power) based on a power calculation conditional on holding outcomes stable and assuming enrolment of 600 patients. At the first interim analysis in September 2000, the study enrolment was discontinued because the prospective stopping rule for the inability to demonstrate statistical significance was reached.
- *Sample size/power calculation:* During the anticipated follow-up duration of 2 years, the expected total mortality rates were 20% in the Amiodarone group and 10% in the ICD group. An 80% power to identify a reduction in total mortality from 20% to 10% was calculated to require 219 patients in each group ($p < 0.05$, two-sided t test).
- *Attrition/drop-out:* states that no patients were lost at follow-up. Amiodarone: Crossover from Amiodarone to ICD (n=8): near-syncope with documented VT (n=2), cardiac arrest (n=2) or Amiodarone intolerance (n=4), ICD insertion, mean months: 26.1 (SD 16.9) after study entry. ICD patients also receiving Amiodarone (n=11): frequent appropriate defibrillator therapies (n=1; 200mg/day, SD 0), atrial fibrillation (n=8; 200 mg/day, SD 0), other reasons (n=2; 150 mg/day, SD 71).

General comments

- *Generalisability:* only to patients with NIDCM and asymptomatic NSVT.
- *Outcome measures:* appear appropriate.
- *Inter-centre variability:* not reported.
- *Conflict of interests:* none reported, but supported by grant from Guidant Corporation.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Randomly assigned and stratified by centre, but no details of sequence generation.
Allocation concealment	Unclear	Not reported
Performance bias		
Blinding of participants and personnel		
- Mortality	High risk	No blinding
- QoL	High risk	May be influenced by lack of blinding.
Detection bias		
Blinding of outcome assessment		
- Mortality	Low risk	Independent events review committee assessing causes of death were blinded.
- QoL	High risk	May be influenced by lack of blinding.
Attrition bias		
Incomplete outcome data addressed	Low risk	States that all analyses were based on ITT, no patients lost to follow-up.
Reporting bias		

Selective reporting	Low risk	No study protocol available, but results for specified primary and secondary outcomes were reported.
Other bias		
Other sources of bias	Low risk	

^a 'Low risk', 'high risk' or 'unclear risk' of bias

AVID

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>AVID investigators, 1997,¹⁸ AVID Investigators 1999,¹⁹ Hallstrom 1995²⁰ & Schron et al. 2002²¹</p> <p>AVID (Antiarrhythmics Versus Implantable Defibrillators)</p> <p><i>Study design:</i> RCT</p> <p>Country or countries: USA, Canada & New Mexico¹⁸</p> <p><i>Number of centres:</i> 56 (52 USA, 3 Canada, 1 New Mexico).¹⁸</p> <p><i>Funding:</i> National Heart, Lung, and Blood Institute, Bethesda, Md. Contract N01-HC-25117.</p>	<p><i>Intervention:</i> ICDs. Investigators chose any 'state-of-the-art' ICD meeting pre-specified criteria.</p> <p><i>Comparator:</i> Best contemporary antiarrhythmic drugs (AADs)</p> <p>Consideration of the use of sotalol left to physician judgement. If patients eligible for sotalol a second randomisation assigned them to either amiodarone (doses determined empirically) or sotalol (guided by electrophysiologic testing, Holter monitoring, or both).</p> <p><i>Other interventions used:</i> aspirin, beta-blockers, and ACE inhibitors when clinically appropriate.</p>	<p><i>Indication for treatment:</i> resuscitated from near-fatal ventricular fibrillation; or symptomatic sustained ventricular tachycardia with hemodynamic compromise.</p> <p><i>Number of randomised participants:</i> n = 1016 ICD, n= 507 (93% non-thoracotomy lead system, 5% epicardial system, 2% no device implanted) AAD, n= 509 n=356 began immediate treatment with amiodarone. Remaining n=153 randomised to amiodarone n=79, or sotalol n=74.</p> <p>QoL substudy²¹: n=800. ICD n=416, AAD n=384</p> <p><i>Inclusion criteria:</i> Ventricular fibrillation, ventricular tachycardia with syncope or ventricular tachycardia without syncope but with ejection fraction ≤ 0.40 and systolic blood pressure < 80mm Hg, chest pain, or near syncope.²⁰ If patients underwent revascularisation their ejection fraction had to be ≤ 0.40</p> <p><i>Exclusion criteria:</i> contra-indication to amiodarone or ICD</p>	<p><i>Primary outcome:</i> Overall mortality</p> <p><i>Secondary outcomes:</i> cost and quality of life</p> <p><i>Other:</i> ICD shock, sustained arrhythmia, syncope</p> <p><i>Method of assessing outcomes:</i> Patients evaluated every 3 months and at the time of events.</p> <p>Cause of death reviewed by Events Committee.</p> <p>QoL substudy²¹ - baseline (before randomisation), 3, 6 and 12 months after randomisation.</p> <p>- Medical Outcomes Short Form 36-item questionnaire (SF-36). Overall score, physical component summary (PCS) and mental component summary (MCS) range from 0 to 100 points with higher scores indicating superior QoL.</p> <p>- the 46 item patient concerns checklist (disease-specific) score range 0-46, higher scores indicate</p>

		<p>therapy, transient or correctable cause identified for the arrhythmia, CABG or percutaneous transluminal coronary angioplasty planned and ejection fraction >0.40, left ventricular aneurysm surgery planned or performed since index event, recent amiodarone exposure (definition provided), long QT syndrome, atrial fibrillation or other supraventricular arrhythmia requiring class I or III antiarrhythmic agents, bradycardia or heart block without permanent pacemaker. NYHA class IV heart failure. Life expectancy < 1 year.²⁰</p>	<p>increased concern and poorer QoL - cardiac version of the QoL index (QL index). Score range 0 to 30 points, higher score indicates superior QoL (this measure administered at baseline and 12 months only).</p> <p>Defibrillator shocks categorized as appropriate or inappropriate on the basis of clinical presentation, RR intervals, and electrograms.</p> <p><i>Length of follow-up:</i> Mean 18.2 months (SD 12.2)¹⁸ For QoL sub-study follow-up was 1 year.²¹</p> <p><i>Recruitment:</i> June 1st 1993, to April 7th 1997.</p>
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Participant characteristics	ICD, n=507	AAD, n=509	p value
Age years, mean (SD)	65 (11)	65 (10)	
Gender, % male	78	81	
Ethnicity, % white	87	86	
Index arrhythmia ventricular fibrillation, n	226	229	
Index arrhythmia sustained ventricular tachycardia, n	281	280	
Congestive heart failure at enrolment, %			
- no congestive heart failure	45	40	
- NYHA class I or II	48	48	
- NYHA class III	7	12	a
Angina at enrolment, %			
- no angina	64	65	
- Canadian Cardiovascular Society (CCS) class I or II	34	33	
- CCS class III	2	2	
LVEF, mean (SD)	0.32 (0.13)	0.31 (0.13)	
- Median time from index event to measurement, days	3	3	
Findings on base-line electrocardiogram ^b			
- heart rate beats/min, mean (SD)	77 (18)	78 (17)	
- PR interval msec, mean (SD)	178 (37)	183 (37)	
- QRS complex msec, mean (SD)	116 (26)	117 (26)	

Participant characteristics	ICD, n=507	AAD, n=509	p value
- corrected QT interval msec, mean SD	441 (40)	445 (39)	
- paced, %	3	4	
- bundle-branch block, %	23	25	
Clinical history before index arrhythmia, %			a
- atrial fibrillation or flutter	21	26	
- ventricular fibrillation	5	5	
- ventricular tachycardia	14	15	
- unexplained syncope	11	15	
- coronary artery disease	81	81	
- myocardial infarction	67	67	
- congestive heart failure	46	47	
- hypertension	55	56	
- diabetes	25	24	
- angina	48	50	
- peripheral vascular disease	16	15	
- antiarrhythmic-drug therapy	16	15	
Coronary revascularisation during hospitalisation for the index arrhythmia, %	10	12	
Therapy at discharge, % ^c	ICD, n=497	AAD, n=496	
- ICD	98.6	1.4	
- amiodarone	1.8	95.8	
- sotalol	0.2	2.8	
- beta-blocker	42.3	16.5	<0.001 ^d
- calcium-channel blocker	18.4	12.1	
- both beta-blocker and calcium channel blocker	5.3	2.4	
- digitalis	46.8	40.6	=0.04 ^d
- diuretic agent	48.2	50.7	
- other antiarrhythmic drug	4.2	1.2	
- ACE inhibitor	68.8	68.2	
- nitrate	36.4	37.0	
- other antihypertensive agent	7.6	8.8	
- lipid lowering agent	13.2	11.5	
- aspirin	60.7	59.2	
- warfarin	21.9	34.8	
Comments: ^a Paper stated baseline characteristic similar in the two groups except for NYHA class III heart failure and history of atrial fibrillation or flutter. ^b Recorded when patients were taking no antiarrhythmic drugs and without cardiac pacing. ^c 23 patients are excluded: 19 who died while in hospital after the index event and 4 who were still in hospital at the termination of the study. ^d Unclear in paper when these p-values apply, discharge, 12 months or 24 months follow up, or overall.			

RESULTS

Outcomes	ICD, n=507	AAD, n=509	p value
Deaths, n	80/507	122/509	<0.012
Cause of death, n ¹⁹			
- Cardiac death	63	94	
- arrhythmic	24	55	
- nonarrhythmic	39	39	
- Non cardiac death	17	28 (3 attributed to pulmonary toxicity due to amiodarone)	0.053; RR 1.78 (95% CI 0.98 to 3.26)
Crude death rate (± 95% CI) over mean follow-up of 18.2 (SD 12.2) months	15.8% (±3.2)	24.0% (±3.7)	

RESULTS					
Outcomes	ICD, n=507		AAD, n=509		p value
Survival free of cardiac death ¹⁹ (non-cardiac deaths censored) - at one year - at two years	90.9% 85.0%		85.1% 81.2%		0.0042
Survival to arrhythmic death ¹⁹ (non-cardiac & non-arrhythmic deaths censored) - at one year - at two years	96.6% 94.2%		91.9% 89.1%		0.0002
Survival free of non-arrhythmic cardiac death (non-cardiac and arrhythmic deaths censored)	presented in figure only		presented in figure only		0.8039
Overall survival through the course of study - patients surviving at 1 year, % - patients surviving at 2 year, % - patients surviving at 3 year, %	89.3 81.6 75.4		82.3 74.7 64.1		<0.02 in favour of ICD
Cumulative % of patients with any activation of the ICD (antitachycardia pacing or shock) - at 3 months - at 1 year - at 2 years - at 3 years	numbers not reported^e Index VF Index VT 15 36 39 68 53 81 69 85				<0.001 for VT vs VF
% of patients rehospitalised (denominator n=1011) - at 1 year - at 2 years - at 3 years	ICD 59.5 74.8 83.3		AAD 55.6 64.7 75.5		=0.04
Change in NYHA class	Not reported		Not reported		
Change in LVEF	Not reported		Not reported		
Exercise capacity outcomes	Not reported		Not reported		
Crossover rate, % - 1 year - 2 years - 3 years	ICD, n=507 17.7 25.7 33.7		AAD, n=509 12.6 18.9 24.3		<0.001
Therapy at follow-up, %	ICD		AAD		
	12 mo n=338	24 mo n=171	12 mo n=306	24 mo n=162	
- ICD	97.9	95.7	9.5	9.8	
- amiodarone	8.3	9.3	84.7	82.4	
- sotalol	1.8	3.1	5.8	8.5	
- beta-blocker	38.1	39.4	11.0	10.1	
- calcium-channel blocker	22.9	19.4	16.6	14.1	
- both beta-blocker and calcium channel blocker	6.8	5.6	2.1	0.7	
- digitalis	45.8	44.4	37.9	32.3	
- diuretic agent	56.0	56.9	59.3	56.4	
- other antiarrhythmic drug	7.1	10.0	3.8	4.0	
- ACE inhibitor	68.4	68.1	65.5	63.1	

RESULTS					
Outcomes	ICD, n=507		AAD, n=509		p value
- nitrate	29.1	28.1	27.9	29.5	
- other antihypertensive agent	9.0	10.0	9.4	6.1	
- lipid lowering agent	19.5	23.1	17.2	19.5	
- aspirin	55.4	62.5	55.4	56.4	
- warfarin	24.8	22.5	35.4	30.2	
<p>Comments: ^e For % of patients with activation of the ICD - it is not clear whether events reported are for the ICD group only or for the whole trial population (i.e. including participants in the AAD group who received an ICD during the course of the study.)</p> <ul style="list-style-type: none"> • A Kaplan-Meier plot of overall survival is presented. The survival figures represent a decrease in death rates ($\pm 95\%$ CI) of $39\pm 20\%$, $27\pm 21\%$, and $31\pm 21\%$ at 1, 2 and 3 years respectively. The study authors note that the accuracy of long-term data is limited because few patients had been followed beyond 2 years at the time the study ended. The average unadjusted length of additional life with ICD (not clear if just those in the ICD group, or all those with ICD in the study) was 2.7 months at 3 years. • The location of deaths (in hospital or out of hospital) and whether or not death was witnessed was also reported but has not been data extracted. Causes of non-cardiac death were also reported but have not been data extracted. • A plot of time to first rehospitalisation is presented but has not been data extracted. Five patients are excluded (baseline overall n=1011) because they were still hospitalised for the index arrhythmia at the time the study was stopped. The group these patients were in is not reported. • The paper reports the daily maintenance doses of amiodarone and sotalol received by participants during follow-up however it is not clear whether these data are reported only for those in the ADD group or for the whole trial population. The mean (SD) daily dose of amiodarone decreased during the study [389 (112) mg at 3 months, 331 (99) mg at 1 year, 294 (94) mg at 2 years, 256 (95) mg at 3 years]. Of the patients receiving amiodarone at discharge 87% continued it at 1 year and 85% at 2 years. These percentages differ from those given above (therapy at follow-up). The mean (SD) daily dose of sotalol was stable during the study [258 (81) mg at 3 months, 248 (88) mg at 1 year, 280 (121) mg at 2 years, 240 (113) mg at 3 years]. 					
Adverse effects of treatment	ICD	Amiodarone	Sotalol	p value	
Non-fatal torsade-de-pointes ventricular tachycardia, n		1			
Suspected pulmonary toxicity in patients treated with amiodarone, %					
- at 1 year		3			
- at 2 years		5			
Death due to pulmonary toxicity, n		1			
Thyroid replacement medication, %					
- at 1 year	1	10			
- at 2 years	1	16			
Death within 30 days of initiation of therapy, n (%) ^f	12/507 (2.4)	18/509 (3.5)		=0.27	
Bleeding requiring reoperation or transfusion, n patients	6				
Serious haematoma, n patients	13				
Infection, n patients	10				
Pneumothorax, n patients	8				
Cardiac perforation, n patients	1				
Early dislodgment or migration of leads, n patients	3				
Unsuccessful first attempt at ICD implantation without thoracotomy	5 ^g				
Overall rate of nonfatal complications of	5.7				

implantation, % (reported in discussion)			
<p>Comments: ^f Or by the time of hospital discharge if discharge occurred later than 30 days after therapy began. ^g Unsuccessful in four patients because of an excessively high defibrillation threshold and in one because of cardiac perforation. Three of the five patients subsequently underwent successful implantation.</p> <ul style="list-style-type: none"> Two linked excluded studies, Kron et al.^{22;23} provide data on lead and device-related complications, including time to event data with Kaplan-Meier curves, but have not been data extracted. A linked excluded study, Klein et al.²⁴ provides data on events triggering ICD or antitachycardia pacing, reviewing whether therapy was appropriate and what the results were. This has not been data extracted. 			

Subgroup data ¹⁸	HR	95% CI	p value
Age			
<60 years	0.57	0.31 to 1.05	
60-69 years	0.63	0.38 to 1.04	
≥70 years	0.67	0.44 to 1.00	
LVEF			
>0.35	0.86	0.47 to 1.61	
≤0.35	0.57	0.41 to 0.79	
Cause of arrhythmia			
- coronary artery disease	0.62	0.46 to 0.86	
- other	0.62	0.28 to 1.35	
Rhythm			
- ventricular fibrillation	0.57	0.38 to 0.86	
- ventricular tachycardia	0.68	0.46 to 1.02	
Overall	0.62	0.47 to 0.83	

<p>Comments:</p> <ul style="list-style-type: none"> Hazard ratios and 95% CIs estimated from a figure in the paper using Engauge digitising software. Numbers in each subgroup were not reported. No subgroup differed significantly from the entire population. The early termination of the study diminished its power to detect differences between the subgroups. Multivariate analysis showed that the beneficial effect of the implantation of an ICD persisted after adjustment for other factors (e.g. age, beta-blockers, congestive heart failure, ejection fraction). Revascularisation after the index arrhythmia did not alter survival (data not reported in paper). When the Cox model was used to adjust for baseline difference in the presence or absence of heart failure, the ejection fraction, and history of atrial fibrillation the estimates indicated that reductions in mortality (\pm 95% CIs) attributable to the ICD were 37\pm22% at 1 year, 24\pm22% at 2 years, and 29\pm33% at 3 years. Estimates adjusted for the use of beta-blockers were unchanged from the unadjusted values (data not reported in paper). 			
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Subgroup data ¹⁹			
Outcomes	Index arrhythmia VF n=455 at baseline	Index arrhythmia VT, n=561 at baseline	p value
Survival free of arrhythmic death	Improved by the ICD for patients whose presenting arrhythmia was VT (p = 0.025) or VF where there were twice as many deaths in the AAD group (p = 0.0019). Survival curves presented but not extracted.		
Nonarrhythmic cardiac death	No difference in survival between ICD and AAD groups in patients with either VT (p=0.72) or VF (p=0.98)		

Participant characteristics QoL substudy ²¹	ICD n=416	AAD n=384	p-value
Age years, mean (SD)	64.3 (10.5)	64.7 (10.1)	0.5
Gender, % male	81.3	80.5	0.8
Ethnicity, % white	89.7	88.0	0.5
Live with spouse partner, %	72.6	70.6	0.5
High school graduate, %	74.0	74.5	0.9

Participant characteristics QoL substudy²¹	ICD n=416	AAD n=384	p-value
Index arrhythmia ventricular fibrillation, %	43.5	42.4	0.8
LVEF, mean (SD)	0.33 (0.13)	0.32 (0.14)	0.6
History of heart failure, %	44.5	41.1	0.3
Discharge beta-blocker use, %	43.0	16.4	<0.001
RESULTS QoL substudy²¹			
Outcomes	ICD, n=416	AAD, n=384	p value
SF-36 PCS score, mean (SD)			
- baseline	37.4 (10.9)	36.5 (11.2)	= 0.3
- 12 months	40 (10.5)	38 (17)	
SF-36 MCS score, mean (SD)			
- baseline	45.9 (11.8)	47.5 (11.5)	=0.006
- 12 months	49 (16.5)	48 (17)	
Patient concerns checklist			
baseline	15.9 (8.6)	16.2 (8.9)	=0.06
- follow-up	nr	nr	=0.1
QL index baseline	22.1 (4.9)	21.9 (5.0)	Similar at baseline & follow-up
Impact of adverse symptoms on quality of life ^h			
- SF-36 PCS score	-2.25 (-3.32, -1.18) p<0.001	-1.64 (-2.89, -0.41) p=0.009	
- SF-36 MCS score	-2.32 (-3.76, -0.88) p=0.002	-0.51 (-1.97, 0.94) p=0.5	
- Patient concerns	1.84 (0.91, 2.76) p<0.001	0.91 (0.07, 1.75) p=0.03	
Impact of ICD shocks on quality of life ⁱ			
- SF-36 PCS score	-1.45 (-2.74, -0.18) p=0.03		
- SF-36 MCS score	-1.82 (-3.56, -0.08) p=0.04		
- Patient concerns	2.15 (1.07, 3.23) p<0.001		
ICD shocks	ICD, n=373 ⁱ		
- experienced ≥1 shock during 1 st year of follow up, n/N (%)	144/373 (39%)		
experienced 1 or 2 shocks	71/144 (49%)		
experienced ≥3 shocks	73/144 (51%)		
- proportion of shocks considered appropriate	94%		
<p>Comments: Values in italics obtained from Figure in paper using Engauge software. Subgroup analysis of patients discharged with and without beta-blockers not data extracted. ^h Multivariate analysis with model comparing any adverse events/ICD shock versus none. Model includes age, sex, race, index arrhythmia, ejection fraction, history of heart failure and use of beta-blockers at hospital discharge. Unit for outcome not given, assumed to be mean impact (change) in QoL score with 95% CI. ⁱ Complete data on shocks available for 373/416 (90%) ICD recipients in the QoL substudy.</p> <ul style="list-style-type: none"> The occurrence of ≥1 versus no shocks was independently associated with significant reductions in mental well-being and physical functioning and an increase in patient concerns. The development of more frequent shocks (≥3 versus <3) was associated with similar alterations in self-perceived QoL (numerical data not presented in paper). 			
Methodological comments			
<ul style="list-style-type: none"> <i>Allocation to treatment groups:</i> Stratified by clinical site and index arrhythmia²⁰ AAD group sub-randomised to empiric amiodarone or Holter/EP guided sotalol (if no contraindications to 			

sotalol, otherwise assigned to amiodarone).¹⁸

- *Blinding*: not stated but presume unblinded because only one group received an ICD and implantation of this requires an operation. The primary end point of overall mortality not likely to be affected by bias. Cause of death analysis was blinded. All references to therapy with either ICD or AAD were removed from medical records sent to the Clinical Trial Centre. In addition, 'sham blinding' was performed to try and mimic the removal of items that would have been deleted if the patient had been randomised to the alternative arm. The committee judging cause of death knew that sham blinding could occur.
- *Comparability of treatment groups*: Described as similar except for a history of atrial fibrillation or flutter and NYHA class III heart failure. Also more patients were taking beta-blockers ($p < 0.001$) and slightly more were taking digitalis ($p = 0.04$) in the ICD group at discharge than in the AAD group (see comment d in baseline characteristics). Adjusting for the difference in beta-blocker use in the Cox-regression analysis slightly reduced the estimated beneficial effect of ICD on survival (unadjusted HR for ICD vs AAD 0.62, adjusted HR 0.67). In the QoL substudy baseline characteristics similar except that patients in the ICD group were more often discharged with beta-blocker therapy.
- *Method of data analysis*: The null hypothesis was that there was no difference in overall mortality between therapy with an ICD and AAD therapy. Analysis was by ITT for overall mortality, quality of life and costs²⁰ however it is clear from the numbers reported that for other outcomes analysis was not by ITT. Significance was based on a two-sided alpha level of 0.05 for comparisons of survival distributions. At the end of the pilot phase sequential data monitoring was performed every six months. Criteria for termination of the study were based on an O'Brien-Fleming spending function, which requires a substantial difference between treatment groups to stop the study early (referenced). Subgroup analyses were to be specified early in the course of the second phase (after the pilot phase with first 200 participants), and that the intention was to limit severely the numbers of a priori subgroup analyses.²⁰ Two subgroup analyses are specified: index arrhythmia (VF vs VT) and cardiac substrate (coronary artery disease vs cardiomyopathy). In the QoL substudy²¹ both appropriate and inappropriate shocks were included in the analysis. Because follow-up QoL values cannot be reliably defined for patients who die before reassessment the primary analyses were limited to patients who survived 1 year after randomisation. Secondary sensitivity analyses included all QoL substudy participants. A chi-squared test or t test was used for pairwise comparisons. Generalised estimating equations were used to model change in QoL scores over time to account for correlation of individual values and to deal with missing follow-up data. Separate models were used for PCS, MCS, and patient concerns checklist scores. Models were adjusted for baseline characteristics of age, sex, race, living alone versus with a spouse or partner, index arrhythmia, ejection fraction, history of heart failure, and beta-blocker use to assess the independent relationship of variables with QoL. All analyses were ITT and $p \leq 0.05$ was considered significant.
- *Sample size/power calculation*: A sample size of 1200 patients was estimated, assuming average follow-up of 2.6 years and an event rate of 40% in the AAD group at 4 years to detect a 30% decrease in mortality. The Data and Safety Monitoring board recommended stopping the trial on April 7th 1997 when analysis revealed that the difference in the primary outcome variable between the two groups had crossed the statistical boundary for early termination of the study (1016 patients had been randomised).
- *Attrition/drop-out*: In 2% of the ICD group no device was implanted. In the AAD group 13/74 patients assigned to sotalol had adequate suppression of arrhythmia and were receiving sotalol at discharge. The remaining 61/74 patients randomised to sotalol received amiodarone ($n = 58$), another antiarrhythmic drug ($n = 1$), or an ICD ($n = 2$). ICD 25.7%, AAD 18.9% crossed over to the other therapy by 24 months. The crossover rate was higher among those initially assigned to therapy with an ICD ($p < 0.001$). States that rates of crossover did not compromise the power of the study and that most crossovers occurred because arrhythmia recurred, rather than because of intolerance to either drugs or devices.

QoL substudy²¹: of the 1016 participants randomised in the main study, 905 (89%) completed at least one QoL assessment in the first year of follow-up, and most of these (800/905, 88%) survived for 1

year and were included in the analyses of QoL (n=416 in the ICD group, and n=384 in the AAD group). Complete QoL data were available for most patients at each timepoint, more data were missing at later compared with earlier assessments. Most (49%) incomplete data were missing because collection fell outside the specified time period. Details reported (not extracted) for whole study (but not for treatment groups).

General comments

- *Generalisability:* In the discussion of the paper it is noted that data in the AVID registry show that the clinical characteristics of patients included in the trial were similar to those who were not included and therefore the AVID study authors believed that the population studied was representative of the general population of patients who are resuscitated from ventricular fibrillation or who have symptomatic, sustained ventricular tachycardia.
- QoL substudy²¹: There were differences between the 905 participants who completed at least one QoL assessment and those in the trial as a whole. QoL substudy participants were younger on average (65 vs 68 years), more likely to be male (81% vs 70%), be white (88% vs 70%), be living with a spouse or partner (71% vs 51%), to have graduated from high school (73% vs 42 %) compared to 111 non-participants. Also reports differences between those who died in the first year versus those who survived.
- *Outcome measures:* Appear appropriate. For the QoL substudy²¹ definitions and categorisation of symptoms provided.
 - *Inter-centre variability:* not discussed
 - *Conflict of interests:* no conflicts of interest statement made.
 - *Other:* A registry was maintained for all patients who qualified for the study but did not undergo randomisation in order to compare the randomised and nonrandomised patients. The registry also followed patients with ventricular fibrillation or ventricular tachycardia who were not eligible for randomisation. Data on long-term mortality among the nonrandomised patients could be obtained from the National Death Index.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^j	Support for Judgement
Selection bias		
Random sequence generation	Unclear	“Allocation is stratified by clinical site and index arrhythmia (ventricular fibrillation or ventricular tachycardia).” ²⁰ No other information provided
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	High risk	Not explicitly stated but presume unblinded (because only one of the two groups received an ICD). QoL self-assessment by participants at risk of bias due to knowledge of intervention received.
Detection bias		
Blinding of outcome assessment - Overall mortality & cause of death	Low risk	For overall mortality outcome risk of bias likely to be low in an unblinded study. Committee judging causes of death were blinded to the participant group.
- QoL	High risk	
Attrition bias		
Incomplete outcome data addressed - overall mortality	Low risk	“Analysis was performed according to the intention-to-treat principle.” Although there were cross-overs between groups no drop outs are recorded in the paper.
Incomplete outcome data addressed -	High risk	The QoL sub study did not include all

QoL		randomised participants and there were some differences between those completing the QoL sub-study and the whole trial population. In addition data from those who completed baseline QoL assessment but died within a year could not be included in the QoL assessment which may be another source of bias.
Reporting bias		
Selective reporting	Low risk	Paper available describing rationale, design and methods for the study.
Other bias		
Other sources of bias	Low risk	

^J 'Low risk', 'high risk' or 'unclear risk' of bias

CABG Patch

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Bigger <i>et al.</i>, 1997²⁵⁻²⁸; Namerow <i>et al.</i>, 1999²⁹ Spotnitz <i>et al.</i>, 1998³⁰</p> <p>CABG Patch (Coronary Artery Bypass Graft Patch trial)</p> <p><i>Study design:</i> RCT</p> <p>United States and Germany</p> <p><i>Number of centres:</i> 37 (35 in USA, 2 in Germany)</p> <p><i>Funding:</i> NHLBI grants HL-48120 and HL-48159, and a grant from Guidant/CPI, St. Paul, Minn.</p>	<p><i>Intervention:</i> ICD: epicardial defibrillator. Leads and pulse generators provided by Guidant/CPI (St. Paul, Minn). Most were committed devices (i.e. deliver a shock even if the arrhythmia stops before the end of charging) that were not capable of storing electrograms.</p> <p><i>Comparator:</i> control group, OPT (subject to caveats described below). No defibrillator therapy²⁵ and no specific therapy for ventricular arrhythmias.³¹</p> <p><i>Other interventions used:</i> ICD group: The protocol prohibited the use of antiarrhythmic drugs for asymptomatic ventricular</p>	<p><i>Indication for treatment:</i> Patients scheduled for CABG surgery and at risk for sudden death (LVEF < 0.36 and abnormalities on an ECG). Prophylactic.</p> <p><i>Number of randomised participants:</i> n = 900 ICD, n= 446 Control, n= 454</p> <p><i>Inclusion criteria:</i> Scheduled for CABG surgery, <80 years old, LVEF <0.36, marker of arrhythmia: abnormalities on an ECG (duration filtered QRS complex \geq 114 msec; root-mean-square voltage in the terminal 40 msec of the QRS complex <20μV; or duration of the terminal filtered QRS complex at <40μV >38 msec).</p> <p><i>Exclusion criteria:</i> history of sustained ventricular tachycardia or fibrillation, diabetes</p>	<p><i>Primary outcomes:</i> mortality</p> <p><i>Secondary outcomes:</i> Not explicitly stated but quality of life and adverse events reported.</p> <p><i>Method of assessing outcomes:</i> Follow-up visits every 3 months</p> <p><i>QoL study²⁹:</i> Single assessment at 6 months included 1) 7 of the subscales of the SF-36: - general health - physical functioning - physical role functioning - bodily pain - social functioning - emotional role functioning - mental health For each subscale a raw score is transformed to a 0-100 scale. 2) Health transition variable with five response categories (higher score represents</p>

	<p>arrhythmias and specified that patients without contraindications should be treated with aspirin.</p> <p>Clinical advice has indicated that although drug therapy received was lower than current standards (especially for statin use) for a trial conducted at this time it would have been considered OPT.</p>	<p>mellitus with poor blood glucose control or recurrent infections, previous or concomitant aortic-or mitral-valve surgery, concomitant cerebrovascular surgery, serum creatinine > 3mg/decilitre (265 mmol/L), emergency coronary bypass surgery, non-cardiovascular condition with expected survival <2 years, inability to attend follow-up visits.</p>	<p>perception that health status has become worse)</p> <p>3) Items on employment status, and body image (two two-item scales: satisfaction with appearance and satisfaction with scar). Higher scores = greater satisfaction.</p> <p><i>Length of follow-up:</i> Mean of 32 months</p> <p><i>Recruitment:</i> Pilot study from 14 August 1990, full-scale study from 1993. Final enrolment February 5th 1996.²⁹ Study data reported on April 30th 1997 for main trial publication.²⁵</p>
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Participant characteristics	ICD, n= 446	Control, n= 454	p value
Age years, mean (SD)	64 (9)	63 (9)	
Gender, M/F	386/60	373/81	
Ethnicity, ^a % ²⁹			ns
- White	88	86	
- African-American	7	10	
- other	5	4	
LVEF, mean (SD)	0.27 (0.06)	0.27 (0.06)	
Heart rate bpm, mean (SD)	79 (15)	79 (14)	
Findings on 12-lead ECG, %			
- duration of QRS complex >100 msec	71	74	
- left bundle-branch block	10	12	
- Q-wave myocardial infarction	52	53	
Cardiovascular history, %			
- cigarette smoking at any time	79	76	
- angina pectoris	76	76	
- myocardial infarction	83	82	
- ≥2 prior myocardial infarctions	30	33	
- heart failure	51	49	
- treatment for heart failure	49	47	
-NYHA functional class II or III	71	74	
- treatment for hypertension	54	52	
- diabetes mellitus	36	40	
- diabetes treated with insulin	17	20	
- treatment for ventricular arrhythmias	7	7	
- PTCA or atherectomy	11	11	
- CABG surgery	12	10	
- electronic cardiac pacemaker	2	2	
Systolic blood pressure mm Hg, mean (SD)	126 (19)	123 (19)	
Pulmonary rales, %	20	25	

S ₃ gallop, %	14	11	
Left ventricular end-diastolic pressure mmHg, mean (SD)	21 (10)	22 (10)	
Findings on coronary angiography, %			
- one-vessel disease	8	9	
- two-vessel disease	36	36	
- three-vessel disease	55	55	
Drug therapy at hospital discharge, % of patients ^b	ICD, n= 430	Control, n= 442	
- oral antiarrhythmic drugs			
none	63.3	65.2	
class I drugs	16.7	12.0	
amiodarone	3.7	3.2	
sotalol	0.5	0.2	
beta-blockers (not sotalol)	17.9	24.0	
- angiotensin-converting-enzyme inhibitors	54.7	53.8	
- diuretics	57.2	47.1	
- digitalis	68.6	64.5	
- nitrates	8.1	8.1	
-calcium-channel blockers	10.5	7.0	
- antiplatelet drugs	82.8	85.1	
- oral anticoagulants	15.3	14.7	
- lipid-lowering drugs	9.5	8.4	
Comments: ^a baseline data for marital status, educational attainment, employment status and occupational status are reported in the paper describing QoL outcomes ²⁹ these characteristics did not differ between the groups and have not been data extracted. ^b data were not available for all patients.			
<ul style="list-style-type: none"> • States there was no significant difference between the two groups for the variables listed. States the use of cardiac drugs was similar at the time of discharge. 			

RESULTS

Outcomes	ICD, n= 446	Control, n= 454	p value
Deaths in the first 30 days after randomisation, n (% - calculated by reviewer)	24 (5.4%)	20 (4.4%)	=0.60
Deaths during mean (SD) follow-up of 32 (16) months ^{27 c}	102	96	
Mechanisms of death, ²⁷ n (%)			
- Cardiac	76/102 (74.5)	79/96 (82.3)	
primary arrhythmic	13/102 (12.7)	22/96 (22.9)	arrhythmic deaths 15% vs 29%, $\chi^2= 5.10$, p= 0.024
secondary arrhythmic	2/102 (2)	6/96 (6.3)	
nonarrhythmic, cardiac	57/102 (55.9)	46/96 (47.9)	
myocardial pump failure	30/102 (29.4)	23/96 (24.0)	$\chi^2= 0.75$, p= 0.358
cardiac procedure	27/102 (26.5)	23/96 (24.0)	
unwitnessed, cardiac	0	2/96 (2.1)	
uncertain, cardiac	4/102 (3.9)	3/96 (3.1)	
- Non cardiac	25/102 (24.5)	17/96 (17.7)	
- Unknown	1/102 (1.0)	0	
Relative risk of cause specific death by treatment assignment ²⁷	Relative risk (95% CI)		p value
- Cardiac	0.97 (0.71 to 1.33)		0.84
arrhythmic	0.55 (0.29 to 1.03)		0.06
nonarrhythmic, cardiac	1.24 (0.84 to 1.84)		0.28
myocardial pump failure	1.28 (0.74 to 2.22)		0.37

RESULTS					
Outcomes	ICD, n= 446		Control, n= 454		p value
procedure death	1.20 (0.69 to 2.10)				0.52
- Non-cardiac	1.49 (0.80 to 2.76)				0.21
- Total	1.07 (0.81 to 1.42)				0.63
Actuarial mortality by 4 years follow-up	27%		24%		=0.64
Hazard ratio for death per unit time	1.07 (95% CI 0.81 to 1.42)				
Hazard ratio from Cox regression model stratified by clinical centre and LVEF	1.02 (95% CI 0.76 to 1.35)				
Hazard ratio from Cox model beginning 30 days after randomisation	1.03 (95% CI 0.75 to 1.41)				
Received a shock within 1 year of ICD implantation (actuarial incidence [fig 2])	50%				
Received a shock within 2 years of ICD implantation (actuarial incidence [fig 2])	57%				
Symptoms and complications related to tachyarrhythmias and/or heart failure	Not reported		Not reported		
Heart failure hospitalisations	Not reported		Not reported		
Change in NYHA class	Not reported		Not reported		
Change in LVEF	Not reported		Not reported		
Exercise capacity outcomes (e.g. 6 minute walk distance, total exercise time, peak oxygen uptake)	Not reported		Not reported		
Drug therapy after CABG, % ^d	ICD		Control		
	3 mo n= 403	1 yr n= 374	3 mo n= 411	1 yr n= 373	
- oral antiarrhythmic drugs					
none	70.7	70.3	70.1	72.9	
class I drugs	8.2	7.5	5.8	4.8	
amiodarone	4.2	6.1	3.6	2.9	
sotalol	1.0	0.8	0.5	0.5	
beta-blockers (not sotalol)	16.4	16.0	21.7	19.8	
- angiotensin-converting-enzyme inhibitors	60.3	64.2	63.7	67.8	
- diuretics	61.3	64.7	57.2	55.2	
- digitalis	70.7	70.6	62.5	60.1	
- nitrates	10.9	15.8	12.2	16.9	
-calcium-channel blockers	9.2	12.0	7.1	9.7	
- antiplatelet drugs	78.2	79.1	83.7	82.6	
- oral anticoagulants	20.6	20.1	16.8	16.6	
- lipid-lowering drugs	12.9	23.0	13.4	23.3	
<p>Comments: ^c Total number of deaths and number of cardiac deaths reported differs slightly between the main trial publication²⁵ and that specifically reporting mechanism of death.²⁷ Results from the latter paper are reported above (main trial publication²⁵ reported 101 (71 from cardiac causes) in the ICD group and 95 (72 from cardiac causes) in the control group). ^d drug therapy - data were not available for all patients.</p> <ul style="list-style-type: none"> • The hazard ratio (95% CI) derived from a Cox model after adjustment for the 10 pre-specified covariates was stated to be similar to the value obtained without adjustment but data are not reported in the paper. • Separate Cox regression analyses for each of the 10 pre-specified covariates showed no significant interaction with ICD therapy (i.e. hazard ratios for ICD group compared to control group were similar among the predefined subgroups). 					

RESULTS			
Outcomes	ICD, n= 446	Control, n= 454	p value
<ul style="list-style-type: none"> • Kaplan-Meier figures for analysis of the probability of death and analysis of the probability of the discharge of first shock from the ICD in the ICD group are presented but have not been data extracted. • States use of cardiac drugs was similar in the two groups at three months and at 1 year after hospital discharge. Rates of use of class I or III antiarrhythmic drugs and beta-blockers were similar in the two groups throughout the trial. 			

QoL RESULTS

Outcomes	ICD, n=262	Control, n= 228	p value^c
Health related quality of life at 6 months, mean (SD) ²⁹			
Perception of health			
- general health status	54.8 (22.9)	58.3 (23.6)	NS
- perception of health transition ^f	2.4 (1.2)	2.1 (1.2)	0.030
- physical limitations	41.7 (42.3)	49.2 (42.8)	0.055
- bodily pain	57.4 (24.6)	58.8 (24.8)	NS
Ability to Function			
- employment status	0.25 (0.4)	0.29 (0.5)	NS
- physical role functioning	58.3 (27.5)	61.8 (28.3)	NS
- emotional role functioning	55.4 (43.4)	67.3 (39.9)	0.003
- social functioning	70.5 (27.2)	70.8 (26.4)	NS
Psychological well-being			
- mental health	72.5 (18.3)	77.2 (17.0)	0.004
- satisfaction with appearance	6.0 (1.3)	6.3 (1.1)	0.008
- satisfaction with scar	7.0 (1.2)	7.2 (1.1)	0.040
Received a shock prior to completing the 6-month QoL instrument, n/N (%)	101/262 (38.5%)		

Health related quality of life at 6 months, mean (SD) ²⁹	ICD device did not fire, n=161	ICD device fired, n=101	Control, n=228	Control vs ICD fired 95% CI^g
Perception of health				
- general health status	56.6 (23.3)	52.1 (22.1)	58.3 (23.6)	NS
- perception of health transition ^f	2.3 (1.2)	2.5 (1.3)	2.1 (1.2)	(-0.73 to -0.01) ^h
- physical limitations	44.8 (42.9)	36.8 (41.1)	49.2 (42.8)	(0.31 to 24.6) ⁱ
- bodily pain	57.8 (24.1)	56.8 (25.3)	58.8 (24.8)	NS
Ability to Function				
- employment status	0.30 (0.5)	0.18 (0.4)	0.29 (0.5)	NS
- physical role functioning	61.5 (27.5)	53.2 (27.0)	61.8 (28.3)	(0.7 to 16.6)
- emotional role functioning	59.5 (43.4)	49.1 (42.8)	67.3 (39.9)	(6.2 to 30.1)
- social functioning	71.6 (26.9)	68.8 (27.7)	70.8 (26.4)	NS
Psychological well-being				
- mental health	73.6 (43.4)	70.6 (18.5)	77.2 (17.0)	(1.5 to 11.6)
- satisfaction with appearance	6.0 (1.3)	6.0 (1.4)	6.3 (1.1)	(-0.01 to 0.71)
- satisfaction with scar	7.0 (1.2)	7.1 (1.2)	7.2 (1.1)	NS
Rate of rehospitalisation prior to date of 6-month QoL	36.0%	55.5%	33.8%	
ICDs explanted prior to completing 6-month QoL	12/262			
- at patient request	1			

QoL RESULTS			
- because of infection	8		
- other reasons	3		
<p>Comments: ^e p-values for QoL outcomes represent significance of t-tests comparing mean scores of control versus ICD patients. ^f lower score reflects a tendency to rate health as better now relative to 1 year ago. For all other QoL measures higher scores represent a more favourable score. ^g 95% CIs control the experiment-wise Type 1 error rate to be 0.5 using Tukey's method. ^h F test for analysis of variance (ANOVA) has p value of 0.0507. ⁱ F test for ANOVA has p value of 0.0549.</p> <ul style="list-style-type: none"> • QoL outcomes grouped into three categories: perception of health status; ability to function; and psychological wellbeing. • Paper states that control group and ICD group patients whose devices had not fired did not differ on any of the reported QoL measures. ICD group patients whose devices had not fired and ICD group patients who had received a shock from their ICD did not differ significantly from each other. • A graph showing cumulative incidence of ICD discharges is presented but has not been data extracted. • In discussion states that although hospitalisation affects perceived QoL, the differences in QoL scores between controls and ICD patients whose devices had fired persisted even when rehospitalisation was controlled for in regression analyses. 			
Adverse effects of treatment	ICD, n= 446	Control, n= 454	p value
Postoperative complications, %			
- myocardial infarction	4.0	3.5	
- sustained ventricular tachycardia	5.8	6.8	
- ventricular fibrillation	3.4	5.3	
- bradycardia	2.9	4.4	
- atrial fibrillation	22.9	20.7	
- shock	9.2	7.5	
- new or more severe heart failure	15.7	12.6	
- conduction defect	14.1	14.5	
- residual central nervous system deficit	3.6	2.0	
- bleeding treated with surgery	4.9	3.1	
- post-pericardiotomy syndrome	0.9	0.7	
- deep sternal-wound infection	2.7	0.4	0.01<p<0.05
- infection at wound or catheter site	12.3	5.9	0.01<p<0.05
- pneumonia	8.5	4.0	0.01<p<0.05
- other infection	6.3	3.3	
- renal failure	6.7	4.8	
Events during long-term follow-up, %			
- angina pectoris	27.0	27.5	
- myocardial infarction	0.5	4.2	0.01<p<0.05
- new or worsening heart failure	42.5	42.5	
- ventricular arrhythmias	19.4	14.3	
- atrial fibrillation	14.7	10.1	
- hospitalisation	61.4	55.2	
- repeat CABG surgery	0.0	0.7	
- PTCA or atherectomy	2.9	2.1	
- permanent cardiac pacemaker	2.9	4.9	
ICD removed, n patients	40		
- infection	19		
- ICD reached end of service period and not replaced	5		
- patient request	5		
Comments:			

- p-values have no adjustment for multiple comparisons
- Reasons for every ICD removal not reported.

Methodological comments

- *Allocation to treatment groups:* Two independent randomisation schedules were set up for each hospital, one for patients with LVEF ≤ 20 , another for those with LVEF 0.21 to 0.35. Randomisation therefore stratified by LVEF and also by centre.²⁶ Patients randomly assigned to ICD or control within randomly permuted blocks. Randomisation took place in the operating room after completion of CABG and patients were on partial cardiopulmonary bypass. The attending surgeon had the option not to have the patient randomly assigned if they thought that implanting and testing an ICD in the patient was too risky. Assignment supplied by data coordinating centre in opaque envelopes sealed with a validating label.
- *Blinding:* No blinding, states that the nature of the intervention precluded the blinding of investigators or patients.
- *Comparability of treatment groups:* States that baseline characteristics of the two study groups were similar. There was no baseline assessment of QoL because informed consent was obtained just hours prior to surgery which made it impossible to obtain preoperative QoL data.
- *Method of data analysis:* Data were reviewed by an independent Data and Safety Monitoring Board. Four interim analyses were scheduled and performed. These were based on sequential-monitoring procedures for the groups, with prospective stopping rules defined by a Lan-DeMets boundary with an O'Brien-Fleming spending function. Cumulative survival curves were estimated by the Kaplan-Meier method. Cox proportional-hazards regression models were used to estimate hazard ratios. Log-rank tests, stratified according to LVEF and clinical centre were used to test hypotheses about between group differences. Secondary analyses (also based on Cox models) examined survival after surgery and treatment interactions for pre-specified subgroups. Ten prospectively selected covariates [age, sex, presence/absence of heart failure, NYHA functional class, LVEF, presence/absence diabetes, duration of QRS complex (>100 msec or ≤ 100 msec), use of ACE inhibitors, use of class I or class III antiarrhythmic drugs, and use of beta-adrenergic-blocking drugs] were evaluated for their interaction with the effect of ICD on risk of death. All analyses used the ITT principle. The last of the four interim looks at mortality data was on April 2nd 1997. 76% of the anticipated information was available. This fourth analysis showed no difference between the ICD and control groups and a negligible chance that a difference would ever be found. The Board therefore recommended that the data on the primary end point be reported as of April 30th 1997, while the trial continued to pursue its secondary objectives.
QoL substudy:²⁹ comparisons of scales based on t-tests. Analysis of variance models were used to test for differences in QoL scales between 3 groups: i) control, ii) ICD - device did not fire, iii) ICD - device did fire. If a significant difference was found between the three groups based on an F-test, subsequent pairwise comparisons of each group to the others were made adopting Tukey's method to maintain an overall 0.05 Type 1 error probability. There was no correction or testing the several scales from the QoL instrument. All tests were two tailed.
- *Sample size/power calculation:* Design ensured that the study had a power of $> 80\%$ to detect a difference of 26% in mortality between the groups, a difference that corresponded to a 40% reduction in the hazard rate for death from all causes in the ICD group compared with the control group (allowing for anticipated crossovers). Originally the protocol was for 800 patients to be recruited and monitored for a minimum of 2 years. Many would have needed their ICD pulse generators to be replaced during follow-up. However, a clarification of the Medicare reimbursement policy for investigational use of devices caused a protocol change which meant that ICDs would not be replaced at the end of service life because of battery depletion. This change would have decreased average follow-up time and statistical power. Mortality was also lower than expected in the control group. Therefore in October 1994 the Data and Safety Monitoring Board recommended that power be restored by increasing recruitment from 800 to 900 patients and lengthening the minimum follow up to 42 months (which is the average service time of a Ventak P pulse generator). ICDs with battery depletion before 39 months were replaced.²⁸

- *Attrition/drop-out*: Of 1422 eligible patients 1055 (74%) signed a consent form. Of these, 155 were not randomised (n=67 found to meet one or more criteria for exclusion between enrolment and randomisation, n=88 not randomised because surgeon decided intraoperative events made ICD implantation too risky). There were 70 crossovers during follow-up: 18 control group patients had an ICD implanted; 12 patients assigned to ICD did not receive one because of death or hemodynamic instability in the operating room; 40 ICD group patients had the ICD removed (see adverse events). At 42 months the cumulative rate of crossover to the control group was 10%, the cumulative rate of cross over to the ICD group was <5%.

QoL substudy²⁹: of the 900 participants randomised in the main study, only 719 were expected to complete the 6-months QoL instrument [study authors presumed that death 43%, language difficulties 19% (those whose first language was not English were not expected to complete the instrument), and completing 6 months of follow-up 38%, prior to the development of the QoL instrument would cause some participants to be unable to contribute data]. Of the 719 expected to have completed the instrument 490 did so (68% of those expected, 54% of total trial population). A comparison of the characteristics of those who completed versus those who did not complete the instrument is presented (not data extracted). This showed that completers differed by race, educational attainment, occupational attainment, and randomisation group (higher rate of completion in ICD group).

- *Other*: QoL substudy²⁹: ICD patients were recommended NOT to participate in the enrolling centre's ICD support group meetings because their ICDs had been placed prophylactically and therefore they differed to those getting ICDs for conventional reasons. It was anticipated that the meeting might cause trial participants to become confused and anxious.

General comments

- *Generalisability*: This study found that their population did not benefit from an ICD. In the discussion section of the paper²⁵ the authors indicate that they enrolled a high proportion of eligible patients from a well characterised population. However mortality in this population differed from that in the AVID and MADIT trials and this leads the study authors to conclude there must be differences between the enrolled populations. The authors speculate that the indicator for arrhythmia used may be the important factor and that occurrence of either natural or induced sustained ventricular arrhythmias is a better marker for an at risk population than abnormalities on a signal-averaged ECG as was used in this study. Revascularisation may be another factor contributing to differences between this and other studies. The QoL part of the study²⁹ notes that the ICDs in this study were older generation which were larger and more intrusive than current devices. Thus outcomes on satisfaction with appearance may not apply to new generation devices. In addition the QoL findings are based on English speaking, predominantly white, male participants and so the results may not be generalisable to other groups, and other differences between those who did and did not complete the QoL study may also impact generalisability.
- *Outcome measures*: Appear appropriate although not all (e.g. QoL outcomes) were ITT.
- *Inter-centre variability*: Not discussed.
- *Conflict of interests*: Not explicitly stated. The leads and pulse generators were provided by the device manufacturer Guidant/CPI who also provided part of the grant funding for the study.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ¹	Support for Judgement
Selection bias		
Random sequence generation	Unclear	States 'randomised' and also 'randomly permuted blocks' mentioned but no detail about how randomisation schedule was set up.
Allocation concealment	Low	Central allocation, opaque sealed envelopes.
Performance bias		
Blinding of participants and personnel	High risk	"The nature of the intervention precluded the blinding of investigators or patients"
Detection bias		
Blinding of outcome assessment	Low –	"The nature of the intervention precluded the

	mortality High - QoL	blinding of investigators or patients.” Death which is unlikely to be influenced by lack of blinding
Attrition bias		
Mortality outcomes	Low risk	States analyses ITT. Methods for handling censored data not described but bias unlikely, particularly as no significant difference between groups and trial was expecting to find one.
QoL outcomes	High risk	Not all participants contributed data, those that did differed from those that did not and there was a higher rate of completion in the ICD group.
Reporting bias		
Selective reporting	Unclear	Protocol ²⁶ states primary outcome and lists 11 of the secondary outcomes but does not indicate how many secondary outcomes there would be overall. Most outcomes appear to have been reported.
Other bias		
Other sources of bias	Low risk	

^j ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias

CASH

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Kuck <i>et al.</i>, 2000³²</p> <p>CASH (Cardiac Arrest Study Hamburg)</p> <p><i>Study design:</i> RCT</p> <p>Germany</p> <p><i>Number of centres:</i> multicentre but number of centres not reported.</p> <p><i>Funding:</i> supported by a grant from CPI/Guidant Corporation and ASTRA GmbH.</p>	<p><i>Intervention:</i> ICD Cardiac Pacemakers, Inc. devices were used (Ventak AID, Ventak AICD, Ventak P, Ventak PRx, Ventak Mini)</p> <p>From recruitment start to June 1991 participants received an epicardial device (n=55). From July 1991 participants received an endocardial device (n=44).</p> <p>If patients required surgical revascularisation, implantation of epicardial and endocardial devices was performed at the time of or 7 to 15 (mean 10±3) days after coronary artery bypass grafting, respectively.</p> <p><i>Comparator:</i> Antiarrhythmic drugs (AAD) either amiodarone or metoprolol (propafenone arm originally included but eliminated).</p> <p>Amiodarone oral loading dose of 1000mg/day for 7 days, followed by maintenance dose of 200 to 600mg/day.</p>	<p><i>Indication for treatment:</i> Patients resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias. Index arrhythmia ventricular fibrillation in 293/349 (84%) of patients and ventricular tachycardia in 56/349 (16%) (entire group before termination of propafenone arm)</p> <p><i>Number of randomised participants:</i> n =349, but this dropped to 288 after termination of the propafenone arm. ICD, n= 99 Amiodarone, n= 92 metoprolol, n= 97</p> <p>Some evidence for error in participant numbers &/or missing data. Details in methodological comments.</p>	<p><i>Primary outcomes:</i> All-cause mortality</p> <p><i>Secondary outcomes:</i> Sudden death Recurrence of cardiac arrest at 2-year follow-up</p> <p><i>Method of assessing outcomes:</i> Evaluations at 2, 4, 6, 12, 18, and 24 months then every 12 months thereafter.</p> <p>Sudden death defined as death within 1 hour after the onset of symptoms or an unwitnessed death.</p> <p>Cardiac arrest defined as sudden circulatory collapse requiring resuscitation.</p> <p><i>Length of follow-up:</i> Minimum of 2 years, study terminated March 1998. Mean 57 (SD 34) months.</p>

	<p>Metoprolol initiated at 12.5 to 25 mg/day and increased within 7 to 14 days to a maximum of 200mg/day if tolerated.</p> <p>Details reported for propafenone (study arm terminated early due to interim analysis) in other publications³³⁻³⁵ – excluded comparator).</p> <p><i>Other interventions used:</i> concurrent therapies at discharge reported (see below) but doses not provided.</p>	<p><i>Inclusion criteria:</i> not reported. Rate was the only criterion selected for detection of a sustained ventricular arrhythmia.</p> <p><i>Exclusion criteria:</i> cardiac arrest occurred within 72 hours of an acute myocardial infarction, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect.</p>	<p><i>Recruitment:</i> March 1987 to March 1992 (propafenone arm terminated early) or to 1996 (remaining study arms)</p>
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Participant characteristics	ICD, n=99	Amiodarone, n=92	Metoprolol, n=97	p value
Age years, mean (SD)	58 (11)	59 (10)	56 (11)	
Gender, % male	79	82	79	
Ethnicity	Not reported	Not reported	Not reported	
Underlying disease, %				
Coronary artery disease	73	77	70	
Dilated cardiomyopathy	12	10	14	
Others	6	2	5	
No heart disease	9	11	11	
Congestive heart failure at enrolment, %				
NYHA class I	23	25	32	
NYHA class II	59	57	55	
NYHA class II (drug arms combined)		56		
NYHA class III	18	18	13	
LVEF, mean (SD)	0.46 (0.19)	0.44 (0.17)	0.47 (0.17)	
		0.46 (0.17)		
Heart rate bpm, mean (SD)	81 (17)	80 (17)	76 (16)	
Findings on baseline ECG				
Corrected QT interval ms, mean (SD)	437 (42)	430 (51)	430 (48)	
Bundle-branch block, % of patients	17	23	19	
Concurrent therapies at discharge, n				
ICD	99	0	0	
Amiodarone	0	90	0	
Metoprolol	0	0	96	
Digitalis	26	23	15	
Diuretic agents	33	25	30	
Nitrates	29	27	24	
Calcium channel blockers	26	15	12	
ACE inhibitors	45	40	40	
Aspirin	57	41	40	
Warfarin	9	6	9	
Coronary revascularisation during hospitalisation after index event, %	19	21		
Cardiac history	Not reported	Not reported	Not reported	
Previous treatment	Not reported	Not reported	Not reported	
Comorbidities	Not reported	Not reported	Not reported	
Exposure time to primary events, months	4,767.36	4,169.41	5,078.40	

Comments:

- Daily maintenance doses throughout the study were amiodarone 225±75 mg and metoprolol 85±73mg.

RESULTS

Outcomes	ICD, n=99	Amiodarone, n=92	Metoprolol, n=97	p value
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RESULTS				
Outcomes	ICD, n=99	Amiodarone, n=92	Metoprolol, n=97	p value
Crude death rates during mean follow up 57±34 months (CI ^a)	36.4% (26.9 to 46.6)	44.4% (37.2 to 51.8)		0.845 ^b
		43.5% (33.2 to 54.2)	45.4% (35.2 to 55.8)	
Overall survival (ICD vs antiarrhythmic therapy)	HR 0.766 (97.5% CI upper bound 1.112) ^c Survival curve presented but not data extracted			0.081 ^d
Crude sudden death rates (CI ^a)	13.0% (7.9 to 19.6)	33.0% (27.2 to 41.8)		0.467 ^b
		29.5% (19.4 to 40.8)	35.1% (25.2 to 48.8)	
Survival free of sudden death (ICD vs antiarrhythmic therapy)	HR 0.423 (97.5% CI upper bound 0.721) Survival curve presented but not data extracted			0.005 ^d
Crude rates of nonfatal cardiac arrest (CI ^a)	11.1% (6.9 to 16.5)	19.5% (12.2 to 25.6)		
Survival free of cardiac arrest (ICD vs antiarrhythmic therapy)	HR 0.481 (97.5% CI upper bound 1.338) No survival curve presented			0.072 ^d
Symptoms and complications related to tachyarrhythmias and/or heart failure	Not reported	Not reported	Not reported	
Health related quality of life	Not reported	Not reported	Not reported	
Heart failure hospitalisations	Not reported	Not reported	Not reported	
Change in NYHA class	Not reported	Not reported	Not reported	
Change in LVEF fraction	Not reported	Not reported	Not reported	
Exercise capacity outcomes	Not reported	Not reported	Not reported	
<p>Comments: ^a level of the CI not reported. ^b For the comparison between amiodarone and metoprolol. ^c a 23% non-significant reduction in all-cause mortality in ICD patients. ^d 1-sided p value unadjusted for multiple looks for survival or survival free of the event for the comparison ICD vs antiarrhythmic therapy.</p> <ul style="list-style-type: none"> Survival curves presented for <ul style="list-style-type: none"> Long-term overall survival in ICD and AAD groups Long-term overall survival in amiodarone and metoprolol groups Long-term survival free of sudden death in ICD and AAD groups Long-term survival free of sudden death in amiodarone and metoprolol groups Kaplan-Maier estimates of the decrease in death rates at years 1 to 9 of follow up were 41.9%, 39.3%, 28.4%, 27.7%, 22.8%, 11.4%, 9.1%, 10.6%, 24.7%. The Kaplan-Maier estimates of the % reduction in sudden death of ICD patients at years 1 to 9 of follow up were 81.8%, 86.7%, 76.2%, 78.3%, 80.8%, 73.1%, 64.3%, 56.7%, 60.6%. The decrease in cardiac arrest rates of patients assigned to ICD were 61.8%, 65.5%, 59.2%, 53.8%, 50.4%, 58.6%, 49.2%, 52.8%, 42.1% at years 1 to 9 of follow up. Death rates for the subgroups of patients with either inducible sustained ventricular arrhythmia at baseline or non-inducible ventricular arrhythmia at baseline are reported but have not been data extracted. Over a mean follow-up of 37±26 months a similar outcome (data not reported) was observed between the ICD arm patients who received an epicardial device and those who received an endocardial device (p=0.189). States that there were no significant differences in the hazard ratios for death from any cause for subgroups defined by LVEF, NYHA class, and presence of organic heart disease. Data presented but not extracted. A trend towards higher benefit from ICD for subgroups with lower ejection fraction and higher NYHA function class is reported. 				
Adverse effects of treatment				
Number of patients (%)				
- Drug related pulmonary toxicity		0	nr	
- Hyperthyroidism,		3 (3.3%)		
- Drug discontinuation required		9 (9.8%)	10 (10.3%)	
- Perioperative deaths, or for drug arms deaths within the same time frame.	5 (5.1%)	2 (1.1%)		p=0.029
	3 (5.4%) epicardial ICD, 2 (4.5%)	2	0	

RESULTS				
Outcomes	ICD, n=99	Amiodarone, n=92	Metoprolol, n=97	p value
	endocardial ICD			
Other complications				
- Infection	3 (explantation required for 2)			
- Haematoma or seroma	6			
- Pericardial effusion	1			
- Pleural effusion	3			
- Pneumothorax	1			
- Dislodgement or migration of system leads	3			
- Device dysfunction	5			
Overall complication rate	23.0% (including an explantation rate of 2.1%)			
Comments:				
Methodological comments				
<ul style="list-style-type: none"> • <i>Allocation to treatment groups:</i> Randomisation ratio ICD:AAD = 1:3 (ICD:amiodarone:metoprolol:propafenone = 1:1:1:1). All patients assigned to the antiarrhythmic drug arm underwent repeat pre-discharge 24-hour Holter monitoring, programmed electrical stimulation, and exercise testing. Response to serial drug testing did not affect the therapy assignment obtained by randomisation. • <i>Blinding:</i> Not reported • <i>Comparability of treatment groups:</i> Described as similar in the two treatment groups (ICD & AAD), but data presented separately for amiodarone and metoprolol groups. Baseline characteristics were not reported for the suspended propafenone arm. • <i>Method of data analysis:</i> Analysis by intention to treat. An interim analysis was required by the Safety Monitoring Board in March 1992 because of the unexpectedly long recruitment time and subsequent data in the literature showing life-threatening proarrhythmic effects by class Ic antiarrhythmic agents. The aim of this analysis was to prevent further patients being assigned to a possibly harmful treatment. However, since no precautions had been stated concerning multiple group comparisons and multiple looks into the data at the study start the interim analysis meant that the overall significance level for comparisons of the ICD group with each of the 3 drug groups was adjusted according to Bonferroni inequality. Time to clinical events (i.e. mortality, sudden death, cardiac arrest recurrence) for ICD vs antiarrhythmic drug agents was analysed by the Kaplan-Meier method. Cumulative survival functions were compared by the log-rank (Mantel-Cox) test. The Cox proportional regression model was used for calculation of hazard ratios with the patients groups as randomised (ITT). • <i>Sample size/power calculation:</i> Based on an assumption that ICDs would in the worst case be as effective as antiarrhythmic drugs. The α-level for comparison of survival distributions between the ICD and drug arms was based on a 1-sided test, the significance test was at a 0.025 level. Design had a power of 80% to detect a difference of 19 percentage points in 2-year mortality rates between the 2 arms (50% expected mortality rate in patients assigned to the drug arm, 31% in the ICD arm). Sample size of 390 with a 1:3 (ICD:drug therapy) ratio for randomisation estimated to be sufficient. States that the 19.6% 2-year all-cause mortality rate observed in the amiodarone and metoprolol groups was less than half the mortality rate used to calculate trial sample size, thus rendering the trial underpowered to test the working hypothesis. Note that data were presented and analysed separately for the 2 drugs and it is unclear whether the study was powered for this. • <i>Attrition/drop-out:</i> Three participants are unaccounted for from the description of numbers of participants. Overall 349 included (293 ventricular fibrillation + 56 ventricular tachycardia) but 58 receiving propafenone were eliminated from the trial after an interim analysis found a higher all-cause mortality rate in this arm. This should leave 291 participants, however it is stated that 288 remained in the continuing 3 study arms. Two in the amiodarone group refused to start drug therapy (Table 2 in the paper indicates these are included among the 92 in the amiodarone group). During follow-up six (6.1%) of patients in the ICD arm and 11 (5.8%) in the drug arm crossed over or added the other therapy by 24 months. Three (3.0%) patients in the ICD arm and none of those assigned to amiodarone received β-blockers during follow-up. 				
General comments				
<ul style="list-style-type: none"> • <i>Generalisability:</i> The study authors suggest that the mean ejection fraction for the whole study population (0.46) suggests that there may have been disproportionate representation of relatively healthy patients in 				

their trial. The effect of this on the generalisability of the results to more typical patients is unclear but the authors suggest that the benefit of ICD therapy may have been underestimated in their trial.

- *Outcome measures*: Appear appropriate.
- *Inter-centre variability*: unclear since number of centres and their characteristics not reported. The discussion section of the paper does note as a limitation the small number of participating centres and their reluctance to enrol patients for potential ICD therapy in the early phase of the study, and to deny ICD therapy in the late phase of the study.
- *Conflict of interests*: Not stated

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	No information provided
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	High	No information provided, assume none
Detection bias		
Blinding of outcome assessment	Low	No information provided, but mortality unlikely to be influenced by lack of blinding.
Attrition bias		
Incomplete outcome data addressed	Low risk	“For calculation of hazard ratios, the Cox proportional regression model was used with the patients grouped as randomised (intention to treat).” Cross overs or addition of the other treatment was similar in the two groups (ICD 6.1%, AAD 5.8%).
Reporting bias		
Selective reporting	Low risk	The study protocol is not available but primary and secondary outcomes are specified and defined. The outcomes are the outcomes expected.
Other bias		
Other sources of bias	Unclear	Study authors note that centres were reluctant to enrol patients for potential ICD therapy in the early phase of the study and to deny ICD therapy in the late phase of the study. It is not clear whether this could have introduced any bias.

^a ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias

CAT

Reference and design	Intervention and Comparator	Participants	Outcome measures
Bänsch <i>et al.</i> , 2002 ³⁶ The German dilated cardiomyopathy study investigators 1992 ³⁷	<i>Intervention</i> : ICD + OPT. Transvenous electrode systems (Endotak, Cardiac Pacemakers, Inc). Pulse generators Ventak P2, P3, PrX II, CPI.	<i>Indication for treatment</i> : recent onset idiopathic dilated cardiomyopathy (DCM) and impaired LVEF & without documented symptomatic VT.	<i>Primary outcomes</i> : all-cause mortality at 1 year <i>Secondary outcomes</i> : Heart transplantation, cardiac mortality (sudden and non-sudden cardiac death), sustained VT (adequate ICD therapy), symptomatic ventricular
CAT (Cardiomyopathy Trial) <i>Study design</i> : RCT	Defibrillation threshold of < 20J mandatory. VT zone with detection rate of 200 bpm programmed for all	<i>Number of randomised participants</i> : n = 104 ICD, n= 50 Control, n= 54	

(pilot phase) Germany Number of centres: 15 Funding: Grant from Guidant, Giessen, Germany	patients. All shocks programmed to maximum output 30J. Pacemaker rate 40 bpm. Comparator: OPT Other interventions used: both groups received pharmacological treatment throughout the trial (details in participant characteristics). No changes in ACE inhibitor, digitalis and diuretic medications between baseline and 2-year follow-up were documented.	<i>Inclusion criteria:</i> NYHA class II or III LVEF \leq 30% LVEDD not reported QRS interval not reported Aged 18-70 years symptomatic DCM \leq 9 months. <i>Exclusion criteria:</i> Coronary artery disease (coronary stenosis $>$ 70%), prior history of myocardial infarction, myocarditis, or excessive alcohol consumption. Symptomatic bradycardia, ventricular tachycardia, ventricular fibrillation, on heart transplant list. Significant valvular disease, hypertrophic or restricted cardiomyopathy, NYHA class I or IV. Mentally unable to understand protocol.	tachyarrhythmias requiring antiarrhythmic treatment. Complications. <i>Method of assessing outcomes:</i> Visits every 3 months & encouraged to make additional visit if the first shock, cluster of shocks or syncope had occurred. Electrograms stored on devices. <i>Length of follow-up:</i> 2 years <i>Recruitment:</i> 1991 to 1997
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Participant characteristics	ICD, n= 50	Control, n= 54	p value
Age years, mean (SD)	52 (12)	52 (10)	ns
Gender male/female	43/7	40/14	ns
Ethnicity	not reported	not reported	
NYHA class II, %	66.7	64.1	ns
NYHA class III, %	33.3	35.8	
Duration of symptoms, months median	3.0	2.5	ns
LVEF %, mean (SD)	24 (6)	25 (8)	ns
Heart rate	not reported	not reported	
Echocardiography ^a LV diastolic mm, Mean (SD)	69 (7)	69 (8)	ns
Echocardiography ^a LV systolic mm, Mean (SD)	58 (9)	59 (10)	ns
ECG rhythm - sinus %	79.6	86.8	ns
atrial fibrillation/flutter ^b %	20.4	11.3	
paced %	0	1.9	
QRS morphology normal %	72.9	55.1	ns
not normal %	27.1	44.9	
left bundle-branch block %	84.6	81.8	
right bundle-branch block %	7.7	0	
other or undefined BB %	7.7	18.2	
QRS width ^c ms, mean (SD)	102 (29)	114 (29)	ns
Patients with non-sustained VT (nsVT) %	53.1	58.0	ns
Median duration of nsVT seconds (25%/75%)	5 (3.0/6.5)	3.5 (2.3/6.0)	ns
Rate of nsVTs bpm, mean (SD)	175 (39)	157 (23)	ns
Bradycardias, % of patients	2.1	18.8	0.015
- SA block %	0	4.2	

Participant characteristics	ICD, n= 50	Control, n= 54	p value
- AV block %	2.1	14.6	ns
Inducible VT %	6.1	0	ns
Inducible VF %	16.0	3.7	ns
Current pharmacological therapy, %			
- beta-blocker	4.0	3.7	ns
- calcium antagonist	16.0	7.4	ns
- digitalis	86.0	75.9	ns
- diuretics	88.0	85.2	ns
- nitrates	32.0	25.9	ns
- ACE inhibitor	94.0	98.1	ns
- warfarin	24.0	35.2	ns
Cardiac history	not reported	not reported	
Previous treatment	not reported	not reported	
Comorbidities	not reported	not reported	
Follow- up, months (per protocol) mean (SD)	22.7 (4.5)	22.9 (4.2)	ns
Follow -up, years (per August 2000) mean (SD)	5.7 (2.2)	5.2 (2.1)	ns
<p>Comments: ^a states echocardiographic M-mode data only available for 70 patients, not asterisk in table to indicate which characteristics this relates to but believed to be these. ^b chronic or intermittent, ^c patients with pacemakers not included.</p> <ul style="list-style-type: none"> The following baseline characteristics were reported but not extracted: baseline violators, Orthopnoe, Edema, LVED pressure, QT duration, baseline AH interval and HV interval. 			

RESULTS

Outcomes	ICD, n= 50	Control, n= 54	p value
All-cause mortality after 1-year (primary endpoint) ^d	4 patients (all cardiac)	2 patients (both non-cardiac) ^e	0.3672
All- cause mortality after mean 5.5 (SD 2.2) years follow-up	13 patients	17 patients	
2-year cumulative survival	92%	93%	0.554
4-year cumulative survival	86%	80%	
6-year cumulative survival	73%	68%	
Health related quality of life	not reported	not reported	
Symptoms and complications related to tachyarrhythmias and/or heart failure	not reported	not reported	
Heart failure hospitalisations	not reported	not reported	
Change in NYHA class	not reported	not reported	
Change in LVEF	not reported	not reported	
Exercise capacity outcomes (e.g. 6 minute walk distance, total exercise time, peak oxygen uptake)	not reported	not reported	
Received adequate therapy from ICD for VTs > 200 bpm	11 patients	n/a	
Syncope during VTs	6 patients		
<p>Comments: ^d no sudden death occurred in either group. ^e states both control group deaths are non-cardiac in text but Table 1 shows 1 cardiac death.</p> <ul style="list-style-type: none"> A Kaplan-Meier plot of cumulative survival is presented but has not been extracted. Predictors of mortality (based on baseline characteristics) have not been data extracted as this analysis is not defined a priori in the study design paper³⁷ All-cause mortality for subgroups of patients with and without adequate therapies in the ICD group reported but not extracted. 			
Adverse effects of treatment	ICD, n= 50	Control, n= 54	p value
Complications caused by ICD therapy			

RESULTS			
Outcomes	ICD, n= 50	Control, n= 54	p value
- deaths within 30 days of ICD implantation	0		
- device dislocation & bleeding requiring revision	2		
- electrode dislocation requiring revision	2		
Complications in 24 months of follow-up	10 in 7 patients		
- electrode dislocation & sensing/isolation defects	7		
- infection with total device replacement	2		
- perforation	1		

Methodological comments

- *Allocation to treatment groups:* Random assignment performed centrally. Closed envelopes with the assigned study group were sent to each centre. Envelopes opened when a patient was enrolled.
- *Blinding:* None reported so presume no blinding.
- *Comparability of treatment groups:* Did not differ between groups except for bradycardias caused by sinus arrest and atrioventricular block I and II (Wenckebach) which were more common in the control group (18.8%) than the ICD group (2.1%) $p=0.015$ during Holter monitoring. Any other differences observed between groups were not statistically significant.
- *Method of data analysis:* No statement made regarding whether analysis ITT or not. Blind interim analysis after inclusion of 100 patients at 1 year follow-up was planned because of considerable variation in the all-cause mortality rate in different studies that had informed the sample size calculation. Interim analysis conducted in 1997 showed overall 1-year mortality rate was only 5.6% (well below the assumed 30%). As difference between the groups was only 2.6% randomisation was stopped (as per protocol) and scheduled follow-up of 2 years completed by randomised patients. Survival rates presented as Kaplan-Meier curves and compared with log-rank statistics. Cox proportional regression models calculated to estimate prognostic relevance of patient characteristics. Data described by mean (SD) if normally distributed or otherwise by median (25%-75% percentiles). Quantitative comparisons between groups performed by 2-sided analysis using Mann-Whitney exact test; qualitative characteristic compared by the exact Fisher chi-squared test.
- *Sample size/power calculation:* All-cause mortality rate assumed to be 30% in the first year with 40% of deaths being sudden. On this assumption 1348 patients had to be enrolled to show a 1-year survival benefit of 6% for ICD treatment, with power 80% and probability value of 0.05.
- *Attrition/drop-out:* No details reported.

General comments

- *Generalisability:* As the trial was stopped due to futility after one year due to the low event rate results are not likely to be generalisable.
- *Outcome measures:* Appear appropriate although the secondary outcome of heart transplantation was not commented on.
- *Inter-centre variability:* Not commented on.
- *Conflict of interests:* No statement other than support was by a grant from Guidant.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement^d	Support for Judgement
Selection bias		
Random sequence generation	Unclear	States 'were randomly assigned' but no further description.
Allocation concealment	Unclear	Envelopes used but does not state whether these were opaque and sequentially numbered.
Performance bias		
Blinding of participants and	High risk	Blinding unlikely.

personnel		
Detection bias		
Blinding of outcome assessment	Low risk	Blinding unlikely but the outcome of all-cause mortality is unlikely to be affected.
Attrition bias		
Incomplete outcome data addressed	Unclear	No details reported regarding attrition.
Reporting bias		
Selective reporting	High risk	Incidence of heart transplantation specified as a secondary outcome but no reporting on this.
Other bias		
Other sources of bias	Low risk	

^d 'Low risk', 'high risk' or 'unclear risk' of bias

CIDS

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Connolly <i>et al.</i>, 2000³⁸ Connolly <i>et al.</i>, 1993³⁹ Irvine <i>et al.</i>, 2002⁴⁰ Sheldon <i>et al.</i>, 2000⁴¹ (no additional data extracted) Bokhari <i>et al.</i>, 2004⁴²</p> <p>CIDS (Canadian Implantable Defibrillator Study)</p> <p><i>Study design:</i> RCT</p> <p>Canada Australia US</p> <p><i>Number of centres:</i> Canada: 19 Australia: 3 US: 2</p> <p><i>Funding:</i> Medical Research Council of Canada</p>	<p><i>Intervention:</i> ICD Implant criteria met with 3 consecutive successful defibrillations at ≥ 10 J below maximum device output. Either thoracotomy or nonthoracotomy lead systems used.</p> <p><i>Comparator:</i> Amiodarone ≥ 1200 mg/day for ≥ 1 week in hospital, ≥ 400 mg/day for ≥ 10 weeks, then ≥ 300 mg/day.</p> <p>Dose could be lowered to a minimum of 200 mg/day for intolerable side-effects.</p> <p><i>Other interventions used:</i> Antiarrhythmic drugs could be used in both groups to control supra-ventricular or nonsustained ventricular tachycardias that were symptomatic or</p>	<p><i>Indication for treatment:</i> Previous sustained ventricular arrhythmia</p> <p><i>Number of randomised participants:</i> ICD randomised: 328 ICD received implant: n=310 Amiodarone, n=331</p> <p>For QOL: 317 randomised and eligible 287 survived to 12 months 178 had data at 6 and 12 months</p> <p><i>Inclusion criteria:</i> Any of following in absence of either recent acute myocardial infarction (≤ 72 hrs) or electrolyte imbalance: documented VF; out-of-hospital cardiac arrest requiring defibrillation or cardioversion; documented, sustained VT causing syncope; other documented, sustained VT at a rate ≥ 150bpm causing presyncope or angina in a patient with a LVEF $\leq 35\%$; or unmonitored syncope with subsequent</p>	<p><i>Primary outcomes:</i> Death from any cause.</p> <p><i>Secondary outcomes:</i> Arrhythmic death (based on clinical classification of cardiac deaths, Hinkle and Thaler (ref provided), QoL⁴⁰, side effects, arrhythmia recurrence.</p> <p><i>Method of assessing outcomes:</i> 2 and 6 months after randomisation then every 6 months. All deaths adjudicated by an External Validation Committee not blinded to treatment.</p> <p>QoL:⁴⁰ Emotional functioning: Rand Corporations 38-item Mental Health Inventory HRQoL: Nottingham Health Profile</p> <p>Assessed in hospital</p>

	might cause discharge of the ICD.	documentation of either spontaneous VT \geq 10 s or sustained (\geq 30 s) monomorphic VT induced by programmed ventricular stimulation. Ventricular tachyarrhythmias induced in laboratory met criteria if had prior, spontaneous, documented sustained VT and the induced arrhythmia was monomorphic, sustained VT. <i>Exclusion criteria:</i> Amiodarone or ICD not considered appropriate, excessive perioperative risk for ICD implantation, previous amiodarone therapy for \geq 6 weeks, nonarrhythmic medical condition making 1-year survival unlikely, long QT syndrome.	before or just after randomisation (people after randomisation may have started therapy), then by mailed questionnaire at 2, 6 and 12 months. <i>Length of follow-up:</i> ICDs: mean 3.0 years Amiodarone: mean 2.9 years; <i>Recruitment:</i> October 1990- January 1997 For long-term follow-up of subset of patients from one centre ⁴² Follow-up until April 2002, mean 5.6 (SD 2.6 years), median 5.92 years, range 0.08 to 11.08).
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Participant characteristics	ICDs, n=328	Amiodarone, n=331	p value
Age years, mean (SD)	63.3. (9.2)	63.8 (9.9)	
Gender, male sex, %	85.4	83.7	
Ethnicity	Not reported	Not reported	
Index arrhythmia, %			
- VF or cardiac arrest	45.1	50.1	
- VT with syncope	15.9	10.6	
- Other VT	23.8	26.9	
- Unmonitored syncope	15.2	12.4	
Primary cardiac diagnosis, %			
- Ischaemic heart disease with myocardial infarction	75.6	73.1	
- Ischaemic heart disease without myocardial infarction	7.3	9.1	
- Dilated cardiomyopathy	8.5	10.6	
- Valvular heart disease	1.2	3.0	
- Other heart disease	3.7	2.4	
- No heart disease	3.7	1.8	
Congestive heart failure, %			
- NYHA Class 1 or 2	51.2	49.5	
- NYHA Class 3 or 4	37.8	39.9	
- None	11.0	10.6	
LVEF, mean (SD)	34.3 (14.5)	33.3 (14.1)	
LVEF <20, %	11.3	13.3	
Heart rate	Not reported	Not reported	
Baseline electrophysiological study, %			

Participant characteristics	ICDs, n=328	Amiodarone, n=331	p value
- Ever done	62.2	62.8	
- Inducible VT or VF	154/204 (75.7%)	147/208 (70.7%)	
Coronary angiography, %			
- Ever done	75.6	78.2	
- 3-Vessel disease	19.0	18.9	
Chest x-ray, %			
- Interstitial abnormality (document on previous standard chest x-ray report)	15.5	17.6	
- Other abnormality	31.4	34.6	
Current pharmacological therapy			
Cardiac history, %			
- Angina pectoris	51.2	57.1	
- Myocardial infarction	77.1	75.8	
- Coronary artery bypass grafting surgery	31.4	28.1	
Previous treatment			
Medical conditions, %			
- Liver disorder	1.5	2.7	
- Respiratory disease	17.5	17.8	
- Thyroid disease	5.8	3.9	
Comments:	<ul style="list-style-type: none"> Baseline characteristics are also presented for 317 English speaking participants undertaking QoL assessment.⁴⁰ QoL results reported for 178 of these. 		

RESULTS

Outcomes	ICDs, n=328	Amiodarone n=331	p value
30 day mortality in implanted patients (n=310)			
- in patients with thoracotomy (n=33)	1/33 (3.3%)		
- in patients with nonthoracotomy lead system (n=277)	1/277 (0.36%)		
Outcome event rate summary, No. of events (rate/year)			RRR ^a (95% CI), p value
- All-cause mortality	83 (8.3%)	98 (10.2%)	19.7% (-7.7 to 40.0), 0.142
- Arrhythmic death	30 (3.0%)	43 (4.5%)	32.8% (-7.2 to 57.8), 0.094
- Other cardiac death	37 (3.7%)	40 (4.2%)	13.5%, (-35.4 to 44.7), 0.526
- Noncardiac vascular death	3 (0.3%)	2 (0.2%)	-36.6% (-719.8 to 77.2), 0.732
- Nonvascular death	13 (1.3%)	13 (1.4%)	4.5%, (-106.1 to 55.7), 0.908
- Total cardiac death	6.7%	8.6%	23.4%, (-5.7 to 44.5), 1.04
Cumulative risks over time, %			ARR ^b , RRR
Total mortality			
- 1 year	9.46%	11.18%	1.72%, 15.4%
- 2 years	14.75%	20.97%	6.22%, 29.7%
- 3 years	23.32%	27.03%	3.71%, 13.7%
Arrhythmic mortality			
- 1 year	4.37%	6.23%	1.86%, 29.9%
- 2 years	6.68%	9.74%	3.06%, 31.4%
- 3 years	9.77%	11.88%	2.11%, 17.8%
Symptoms and complications related to	Not reported	Not reported	

tachyarrhythmias and/or heart failure			
Heart failure hospitalisations	Not reported	Not reported	
Change in NYHA class	Not reported	Not reported	
Change in LVEF	Not reported	Not reported	
Exercise capacity outcomes	Not reported	Not reported	
Concomitant antiarrhythmic medications, % patients			
- B-Blocker (other than sotalol)			
Hospital discharge	33.5	21.4	
1 year	37.0	21.2	
3 years	33.3	19.0	
5 years	29.6	22.4	
- Sotalol			
Hospital discharge	19.8	1.5	
1 year	21.5	2.5	
3 years	23.3	4.9	
5 years	24.1	4.1	
- Digoxin			
Hospital discharge	29.6	22.7	
1 year	34.5	21.9	
3 years	34.7	22.5	
5 years	33.3.	24.5	
- Class I (any Vaughan Williams Class I)			
Hospital discharge	5.5	2.4	
1 year	8.4	2.8	
3 years	10.0	2.1	
5 years	9.3	2.0	
<p>Comments: ^a Relative Risk Reduction. Treatment effect adjusted for left ventricular ejection fraction stratification. Total patient-years of follow-up were 957 for amiodarone and 995 for ICD groups. ^b Absolute Risk Reduction.</p> <ul style="list-style-type: none"> • Percentage of ICD patients who were receiving amiodarone at 1 year: 17.4 %; 3 years: 21.7%; 5 years: 28.1%. Mean dose of amiodarone in these patients at 3 years was 277 mg/day. • Proportion of amiodarone group receiving it at 2 months: 96.2%; 1 year: 88.7%, 3 years: 80.3%; 5 years: 85.4%. Mean doses 390, 306, 262, 255 mg/day, respectively. • 52/331 amiodarone group received ICD. • Cumulative proportion of amiodarone group receiving ICD at 1, 3 and 5 years was 9.0%, 18.6%, 21.4%. • States significantly more drugs were used in patients randomised to ICD treatment (statistical significance not reported) and the imbalance was most marked for sotalol. • Kaplan-Meier curve of cumulative risk of death from any cause over 4 years presented, not data extracted. • Figure of hazard ratios and 95% CIs for all-cause mortality for various subgroups of baseline characteristics presented (no data presented, figure only). Although the plot showed no statistically significant difference between ICDs and amiodarone, it was not stated whether subgroup analysis was pre-specified, and so it was not data extracted. 			
Health related quality of life ⁴⁰			
Domains of Mental Health Inventory, mean (SD):	ICDs, n=86	Amiodarone n=92	Time by group p value (ANOVA)
Total index ^c			
- baseline	173.2 (25.5)	180.4 (27.8)	
- 6 months	183.1 (30.2)	180.2 (31.1)	
- 12 months	184.3 (27.9)	178.3 (28.7)	0.001
Psychological distress ^d			

- baseline	51.3 (14.1)	47.8 (16.5)	
- 6 months	45.1 (17.6)	47.6 (18.3)	
- 12 months	43.4 (15.9)	48.8 (16.8)	0.001
Psychological well-being ^c			
- baseline	58.5 (12.7)	62.2 (12.3)	
- 6 months	62.2 (13.4)	61.8 (14.1)	
- 12 months	61.7 (13.2)	61.3 (13.3)	0.03
Domains of Nottingham Health Profile, mean (SD)			
Energy level ^d	n=83	n= 88	
- baseline	27.5 (32.2)	24.4 (32.4)	
- 6 months	18.6 (30.1)	27.8 (32.1)	
- 12 months	17.7 (26.1)	36.8 (37.3)	0.0001
Physical mobility	n=84	n=90	
- baseline	10.9 (12.0)	13.2 (20.5)	
- 6 months	10.5 (13.7)	15.1 (19.2)	
- 12 months	9.1 (13.6)	17.7 (19.2)	0.002
Social isolation ^d	n=81	n=88	
- baseline	8.5 (15.4)	9.9 (17.7)	
- 6 months	9.8 (18.6)	12.2 (22.4)	
- 12 months	8.5 (18.4)	11.1 (22.6)	0.9
Emotional reactions ^d	n=76	n=86	
- baseline	17.3 (18.1)	14.3 (20.1)	
- 6 months	11.1 (18.2)	15.3 (22.4)	
- 12 months	8.3 (16.6)	14.5 (19.6)	0.002
Pain ^d	n=83	n=90	
- baseline	4.4 (7.9)	7.5 (15.1)	
- 6 months	7.5 (17.1)	6.3 (13.6)	
- 12 months	4.5 (9.9)	8.2 (15.4)	0.52
Sleep disturbance ^d	n=78	n=88	
- baseline	31.4 (27.4)	29.6 (31.5)	
- 6 months	25.0 (29.7)	30.8 (31.0)	
- 12 months	23.9 (29.4)	30.2 (32.4)	0.02
Life impairment ^d	n=78	n=83	
- baseline	2.0 (1.9)	1.6 (1.7)	
- 6 months	1.6 (1.8)	1.9 (1.9)	
- 12 months	1.6 (1.3)	1.8 (1.9)	0.005
^c Higher values represents better functioning; ^d Higher values represents poorer functioning.			

Health related quality of life, ⁴⁰ Effect of ICD shocks on MHI scores					
Domains of Mental Health Inventory, mean (SD):	ICDs, no shocks, n=66	ICDs, 1-4 shocks, n=27	ICDs, ≥5 shocks, n=15	Amiodarone, without ICD, n=95	Between group p value
Total index ^c					
- baseline	175.9 (26.5)	171.7 (22.7)	171.2 (32.0)	177.9 (27.1)	
- 12 months follow-up	186.2 (26.9) ^{e, f}	186.6 (21.7) ^{e, f}	168.8 (41.2)	175.6 (29.2)	0.001
Within group P value	0.001	0.001	0.725		
Psychological distress ^d					
- baseline	50.2 (15.2)	50.8 (12.3)	51.9 (18.1)	49.8 (16.3)	
- 12 months follow-up	42.5 (15.3) ^{e, f}	41.4 (11.7) ^{e, f}	52.7 (25.2)	50.9 (17.5)	0.001
Within group P value	0.001	0.001	0.833		
Psychological well-being ^c					
- baseline	60.1 (12.5)	56.6 (11.6)	57.1 (15.0)	61.7 (12.0)	

- 12 months follow-up	62.8 (13.1)	62.1 (10.9) ^f	55.6 (16.8)	60.6 (13.3)	0.02
Within group P value	0.074	0.004	0.642		
Effect of ICD shocks on NHP scores ⁴⁰					
Domains of Nottingham Health Profile, mean (SD)	ICDs, no shocks	ICDs, 1-4 shocks	ICDs, ≥5 shocks	Amiodarone, without ICD	
Energy level ^d	n=64	n=27	n=15	n= 90	
- baseline	28.6 (32.5)	28.5 (30.5)	22.6 (34.2)	24.3 (30.8)	
- 12 months follow-up	19.5 (27.1) ^e	24.8 (33.4) ^e	23.5 (29.5)	37.0 (37.6)	0.003
Within group P value	0.02	0.115	0.859		
Physical mobility ^d	n=65	N=27	N=15	n=93	
- baseline	13.1 (15.0)	12.4 (10.2)	7.1 (9.8)	13.18 (20.1)	
- 12 months follow-up	9.3 (12.4) ^e	15.5 (17.3)	8.0 (13.3)	17.2 (19.1)	0.02
Within group P value	0.05	0.638	0.747		
Social isolation ^d	n=66	N=27	N=15	n=92	
- baseline	10.6 (16.7)	4.3 (9.2)	8.9 (16.1)	11.8 (18.5)	
- 12 months follow-up	8.8 (19.5)	6.4 (15.5)	12.8 (23.9)	12.5 (23.0)	0.57
Within group P value	0.03	0.991	0.817		
Emotional reactions ^d	n=61	N=27	N=14	n=90	
- baseline	16.2 (17.4)	16.3 (17.1)	21.6 (21.1)	16.3 (19.8)	
- 12 months follow-up	7.1 (14.6) ^{e, f}	6.8 (10.2) ^e	22.0 (31.0)	15.9 (20.3)	0.001
Within group P value	0.001	0.02	0.886		
Pain ^d	n=66	N=27	N=15	n=92	
- baseline	6.8 (11.8)	4.0 (8.5)	5.3 (8.3)	8.5 (15.6)	
- 12 months follow-up	6.4 (14.7)	5.4 (11.7)	5.5 (7.1)	7.7 (14.5)	0.71
Within group P value	0.086	0.710	0.721		
Sleep disturbance ^d	n=62	N=27	N=14	n=89	
- baseline	30.0 (26.9)	36.3 (31.4)	27.3 (27.1)	30.4 (30.5)	
- 12 months follow-up	22.1 (28.1)	29.1 (33.9)	34.6 (35.4)	30.1 (33.6)	0.3
Within group P value	0.002	0.042	0.680		
Lifestyle impairment ^d	n=65	N=26	N=14	n=82	
- baseline	2.0 (2.0)	2.4 (1.9)	2.2 (1.9)	1.7 (1.6)	
- 12 months follow-up	1.3 (1.5) ^e	1.4 (1.5) ^e	1.4 (1.6)	1.9 (1.9)	0.03
Within group P value	0.061	0.033	0.334		

^c Higher values represents better functioning

^d Higher values represents poorer functioning

^e Groups that differed significantly from amiodarone without ICD group (P<0.05)

^f Groups that differed from the ICD ≥5 shocks group (p<0.05)

Adverse effects of treatment	ICDs, n=328	Amiodarone, n=331	p value
ICD permanently or temporarily explanted due to infection, heart transplantation or patient preference	16/310		
Adverse experiences ever reported, n (%):			
Pulmonary infiltrate		18/331 (5.7%) (1.9% per year)	
Visual symptoms (blurred, halo or decreased)		48/331 (14.5%)	
Bradycardia		10/331 (3.0%)	
Skin discolouration		21/331 (6.3%)	
Photosensitivity		34/331 (10.3%)	
Ataxia		97/331 (17.2%)	

Tremor		91/331 (15.4%)	
Insomnia		64/331 (19.3%)	
Peripheral neuropathy		1/331 (0.3%)	
ICD product discomfort	25/328 (7.6%)		
ICD malfunction	2/328 (0.6%)		
ICD pocket infection	15/328 (4.6%) (1.4% per year)		
ICD dislodgement/fracture	8/328 (2.4%)		

Long term follow-up of subset of patients from one centre⁴²

Participant characteristics ⁴²	ICDs, n=60	Amiodarone, n=60	p value
Age years, mean (SD)	64 (9.2)	64 (8.7)	p=ns
Gender, male sex, %	50 (83)	50 (83)	p=ns
Index arrhythmia, %			
- VF	18	27	p=ns
- VT	35	23	p=0.044
Syncope/inducible VT, %	7	10	p=ns
History of myocardial infarction, n (%)	36 (60)	31 (52)	p=ns
CAD, n (%)	48 (80)	48 (80)	p=ns
- NYHA Class 1 or 2, n (%)	57 (95)	57 (95)	p=ns
- NYHA Class 3 or 4, n (%)	3 (5)	3 (5)	p=ns
LVEF, mean (SD)	33.9 (12.5)	32.1 (11.1)	p=ns
Coronary artery bypass grafting surgery	19 (32)	22 (37)	p=ns
Percutaneous coronary intervention, n (%)	4 (7)	2 (3)	p=ns
B-Blocker, n (%)	23 (38)	21 (35)	p=ns
Diabetes mellitus, n (%)	7 (12)	11 (18)	p=ns
Hypertension, n (%)	13 (22)	14 (23)	p=ns

Long term follow-up of subset of patients from one centre⁴²

RESULTS⁴²			
Outcomes	ICDs, n=60	Amiodarone, n=60	p value
Total deaths, n %	16 (27)	28 (47)	p=0.0231
Total mortality per year, %	2.8%	5.5%	HR 2.011 (1.087 to 3.721, p=0.0261) [§]
Presumed arrhythmic death, %	2	12	p=0.049
Cardiac death, %	8	11	
Vascular death, %	1	1	
Non-cardiac death, %	5	4	
Symptomatic non-fatal arrhythmia recurrence, n		12	
Adverse effects of treatment ⁴²	ICDs, n=60	Amiodarone, n=60	p value
Side effects related to amiodarone, n of patients (%)		49 (82)	
Side effects requiring dose reduction or discontinuation, n of patients (%)		30 (50)	
- serious adverse effects requiring discontinuation, n of patients		13	
Severe side effects requiring permanent removal of the ICD and crossover to amiodarone	0		
Procedures performed in addition to initial implants, n of procedures	68		
- defibrillators replaced	50		
- battery end of life	41		

- pocket infections	3		
- other reasons	6		
- leads replaced	18		
-lead fracture	16		
-lead failure/dislodgement	2		
Patients undergoing 2 or more procedures to replace device or change a lead (up to 7 procedures, details reported), n	41		
Perioperative death	0		
Pneumothorax	1		
Deep vein thrombosis	1		
Pocket hematoma postoperatively	1		
ICD turned off at patients request due to terminal cancer	2		
Inappropriate therapy, n (%)	30 (50)		
<ul style="list-style-type: none"> • 19/60 amiodarone group crossed over to ICD due to adverse events (12) or arrhythmia (7). • 26/60 ICD group were receiving or had received amiodarone by end of follow-up. • ^g states p=0.0261 in text but p=0.0231 in legend of figure 1. 			

Methodological comments

- *Allocation to treatment groups*: Central randomisation was stratified by clinical centre and LVEF ($\leq 35\%$ and $> 35\%$).
- *Blinding*: ‘All deaths adjudicated by an External Validation Committee whose members had no other affiliation to study. Despite best efforts, it was not always possible to blind Committee to treatment allocation’.
- *Comparability of treatment groups*: Described as well-balanced.
- *Method of data analysis*: States analysis based on intention-to-treat-principle. Study planned as one-sided comparison with hypothesis that ICD would be superior to amiodarone. Two-sided statistics presented in response to review process. Cumulative mortality summarised as Kaplan-Meier survival curve. Curves compared using Mantel Haenszel test incorporating stratification for LVEF. Cox’s proportional hazards method used to adjust for imbalances in baseline prognostic risk and to investigate potential subgroup effects. External Safety and Efficacy Monitoring Committee reviewed the unblinded study data every 6 months for safety and did 3 formal interim analyses of efficacy with intention to stop study early in favour of ICD if 1-sided $p \leq 0.001$. For QoL,⁴⁰ analysis of variance with repeated measures used. Significant time changes and group effects followed up by means of post-hoc tests (Tukey Honestly Significant Difference test). Scores on the NHP were normalised by use of a log-plus-1 transformation. Effects of the number of ICD shocks on QOL was assessed using analysis of covariance. Intention to treat basis by which participants retained in treatment group to which then had been randomised regardless of crossover.⁴⁰
- *Sample size/power calculation*: Study originally designed with a primary outcome of arrhythmic death, this was changed in 1993 to all-cause mortality because of concerns that the ICD might prevent some arrhythmic deaths but, due to competing risks, have little effect on overall survival. This change led to an increase in patient enrolment target from 400 to 650 patients, which provided 90% power to detect a relative reduction in all-cause mortality of 33% by the ICD from an anticipated 3 year mortality rate of 30% on amiodarone. Crossover rates of 5% per year for both treatment groups were anticipated. QoL only conducted with the original 400 patients due to cost. Of these, 317 spoke English, 79% participation rate.⁴⁰ In QoL study, 9/92 receiving amiodarone had ICD and 14/86 with ICD received amiodarone by 12 months. The long term follow-up of a subset of patients from one centre would not be adequately powered.⁴²
- *Attrition/drop-out*: For entire trial population, 328 randomised to ICD, 310 (94.5%) received one. Of 18 who did not receive ICD, 7 died in hospital awaiting ICD surgery, 10 decided against ICD (patient or physician) after randomisation, 1 technical problem. 16 patients had ICD explanted permanently or temporarily due to infection, heart transplantation or patient preference. 52/331

(15.7%) patients randomised to amiodarone received an ICD. For QoL: of original 400 participants, 317 spoke English, 79% participation rate.⁴⁰ Of 317 recruited, 287 alive at 12-month assessment (90.5%). 22/287 (7.7%) were missing baseline QoL assessment (11 from each group) and 127/287 (44%) missing data at one of the follow-up assessments (63 amiodarone, 64 ICD). Missing baseline data were replaced by the mean for the variable across both treatment groups, and 2 month data were excluded, resulting in a sample of 178/287 (62.0%) participants with 6 and 12 month data.⁴⁰ 9/92 amiodarone group received an ICD within first 12 months, and 14/86 ICD group were taking amiodarone at 12 months. For subset of patients from single centre,⁴² states follow-up was complete in the ICD group, 3/60 patients were lost to follow-up in amiodarone group. In amiodarone group 19/60 crossed over to ICDs due to adverse events (n=12) or arrhythmia recurrence (n=7). For these with an ICD 26/60 were receiving amiodarone during follow-up.⁴²

General comments

- *Generalisability:* People with VF, sustained VT, or unmonitored syncope likely due to VT. Most participants from centres in Canada.
- *Outcome measures:* Mortality, quality of life and adverse events only.
- *Inter-centre variability:* Not reported.
- *Conflict of interests:* Not stated. Amiodarone supplied by Wyeth-Ayerst Pharmaceuticals, Ltd.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	‘Central randomisation was stratified by clinical centre and LVEF ($\leq 35\%$ and $> 35\%$). Method not stated.
Allocation concealment	Low	‘Central randomisation’. No further details given, but assume allocation concealed by central allocation.
Performance bias		
Blinding of participants and personnel	High	No details reported, assume participants and personnel not blinded.
Detection bias		
Blinding of outcome assessment	Low High	‘All deaths adjudicated by an External Validation Committee whose members had no other affiliation to study. Despite best efforts, it was not always possible to blind Committee to treatment allocation’. Mortality unlikely to be influenced by lack of blinding. QoL
Attrition bias		
Incomplete outcome data addressed	Unclear	Changes to intervention reported, but missing data not reported. Crossover rates higher than anticipated in planned analysis. For QoL subgroup, missing data did not differ between treatment groups.
Reporting bias		
Selective reporting	High	Study design paper published, ³⁹ which specifies secondary outcome events ‘nonfatal recurrence of ventricular fibrillation or sustained ventricular tachycardia causing syncope or cardiac arrest requiring cardioversion or defibrillator, other than by an ICD’. Publication of these outcomes for the whole group not identified by the

		systematic review.
Other bias		
Other sources of bias	Low risk	

^a 'Low risk', 'high risk' or 'unclear risk' of bias

DEBUT

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Nademanee <i>et al.</i>, 2003⁴³</p> <p>DEBUT (Defibrillator versus B-Blockers for Unexplained Death in Thailand)</p> <p><i>Study design:</i> RCT - pilot study - main study</p> <p>Country Thailand</p> <p><i>Number of centres:</i> Not reported.</p> <p><i>Funding:</i> Grant-in Aid from Cardiac Rhythm Management and Guidant Corporation, St Paul, Minn.</p>	<p><i>Intervention:</i> ICD (Guidant Corporation, St Paul, Minn)</p> <p><i>Comparator:</i> B-blockade (long-acting propranolol 40 mg/day up to 160 mg/day)</p> <p><i>Other interventions used:</i> Other B-blocking agents or amiodarone permitted if intolerable side-effects developed from propranolol or if frequent shocks from recurrent VF developed.</p>	<p><i>Indication for treatment:</i> Sudden Unexplained Death Syndrome (SUDS) survivors or probable survivors.</p> <p><i>Number of randomised participants:</i> Pilot study n=20 ICD, n=10 B-Blocker n=10</p> <p>Main study n = 66 ICD, n=37 B-Blocker, n=29</p> <p>(155 screened, 88 not randomised, 1 randomised but refused ICD)</p> <p><i>Inclusion criteria:</i> SUDS survivor defined as a healthy subject without structural heart disease who had survived unexpected VF or cardiac arrest after successful resuscitation.</p> <p>Probable SUDS survivor defined as a subject without structural heart disease who experienced symptoms indicative of the clinical presentation of SUDs, especially during sleep, including agonal respiration, transient episodes of stress, abnormal respiration associated with grasping and groaning, syncope, or seizure-like symptoms. ECG abnormalities showing RBBB-like pattern with ST elevation in right precordial leads and inducible VT/VF in electrophysiology testing.</p>	<p><i>Primary outcomes:</i> Death from all causes</p> <p><i>Secondary outcomes:</i> Recurrent VT/VF or cardiac arrest.</p> <p><i>Method of assessing outcomes:</i> First month, 3-month intervals.</p> <p><i>Length of follow-up:</i> Maximum 3 years after randomisation. Median follow-up not reported.</p> <p><i>Recruitment:</i> Pilot study January 1995 to April 1997 Main study May 1997 to December 2000 (trial terminated by Data Safety Monitoring Board).</p>

		<i>Exclusion criteria:</i> No further detail.	
Participant characteristics (pilot study)	ICD, n=10	B-Blocker, n=10	p value
Age years, mean (SEM)	44 (11)	48 (15)	0.63
Male Gender, n (%)	10 (100)	10 (100)	
Ethnicity			
SUDS survivors, n	8	6	
Probable SUDS survivors, n	2	4	
NYHA class I	10 (100)	10 (100)	
LVEF, %, mean (SEM)	67 (12)	69 (6)	0.66
RVEF, %, mean (SEM)	60 (8)	58 (8)	0.76
Received CPR, n	9	6	0.30
Received defibrillation, n	8	5	0.35
Symptoms during index event, n			
- loss of consciousness, intervention	8	6	0.63
- loss of consciousness, spontaneous recovery	2	3	0.99
- near syncope	0	1	0.99
- agonal respiration during sleep	0	0	
- seizure	0	0	
- difficult to arouse with signs of distress	0	0	
Rhythm at time of recording, n			0.10
- VF	7	6	
- VT	0	0	
-unknown or not documented	0	4	
ECG abnormalities manifesting as RBBB and ST elevation at the precordial lead (V ₁ to V ₃), n (%)	NR	NR	
Heart rate, bpm, mean (SEM)	67 (12)	64 (7)	
PR interval, ms, mean (SEM)	166 (26)	169 (30)	
QRS interval, ms, mean (SEM)	98 (29)	92 (12)	
QT interval, ms, mean (SEM)	396 (51)	387 (31)	
Induced VF (≥ 300 bpm), n (%)	1 (13)	1 (10)	
Induced polymorphic VT (≤ 300 bpm), n (%)	4 (50)	8 (80)	
Non-inducible VF/VT, n (%)	3 (37)	1 (10)	
EPS not done	2	0	
Atrio-HIS conduction time, ms, mean (SEM)	94 (10)	94 (12)	
HIS-Purkinje conduction time, ms, mean (SEM)	58 (18)	54 (3)	
Signal-averaging electrocardiogram performed, n (%)	5	8	
- positive	4 (80)	4 (50)	
- negative	1 (20)	4 (50)	
Participant characteristics (main study)	ICD, n=37	B-Blocker, n=29	p value
Age years, mean (SEM)	40 (11)	40 (14)	0.95
Male Gender, n (%)	35 (95%)	29 (100%)	0.5
Ethnicity			
SUDS survivors, n	22	20	
Probable SUDS survivors, n	15	9	
NYHA class I	37 (100%)	28 (100%) ^a	
LVEF, %, mean (SEM)	66 (10)	67 (7)	0.55
RVEF, %, mean (SEM)	62 (13)	60 (8)	0.6
Received CPR, n	26	20	0.92

Received defibrillation, n	17	18	0.17
Symptoms during index event, n			
- loss of consciousness, intervention	26	21	0.85
- loss of consciousness, spontaneous recovery	5	4	0.99
- near syncope	2	1	0.99
- agonal respiration during sleep	3	3	0.99
- seizure	0	5	0.01
- difficult to arouse with signs of distress	2	4	0.67
Rhythm at time of recording, n			0.74
- VF	9	11	
- VT	2	2	
-unknown or not documented	26	16	
ECG abnormalities manifesting as RBBB and ST elevation at the precordial lead (V ₁ to V ₃), n (%)	23 (62%)	16 (55%)	
Heart rate, bpm, mean (SEM)	64 (11)	66 (12)	0.48
PR interval, ms, mean (SEM)	180 (98)	163 (27)	0.48
QRS interval, ms, mean (SEM)	99 (30)	95 (16)	0.43
QT interval, ms, mean (SEM)	404 (43)	394 (31)	0.33
Induced VF (≥ 300 bpm), n (%)	8 (22)	8 (30)	0.70
Induced polymorphic VT (≤ 300 bpm), n (%)	15 (40)	11 (41)	
Non-inducible VF/VT, n (%)	14 (38)	8 (30)	
EPS not done	0	2	
Atrio-HIS conduction time, ms, mean (SEM)	100 (22)	96 (22)	0.58
HIS-Purkinje conduction time, ms, mean (SEM)	51 (8)	49 (11)	0.47
Signal-averaging electrocardiogram performed, n (%)	29	21	0.74
- positive	11 (38)	7 (33)	
- negative	18 (62)	14 (67)	

^a Reported in paper as 28 (100%), however 28/29 would be (96.5%), not clear which is correct.
Comments: No differences in baseline characteristics or index arrhythmic events.

RESULTS (pilot study)

Outcomes	ICD, n=10	B-Blocker, n=10	p value
Died before main trial		1	
Deaths during follow-up	0	3 (2 SUDS survivors, 1 probable SUDS survivor) at 5.4, 11.8 at 24.6 months	p=0.07
Multiple VF episodes successfully treated by ICD	5		
Adverse effects of treatment	ICD, n=10	B-Blocker, n=10	p value
Operative mortality	0		
Adverse effects, n (%)	2/10 (20%)		
- defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia	1		
- T-wave oversensing	0		
ICD replaced because of insulation break	1		

RESULTS (main study)

Outcomes	ICD, n=37	B-Blocker, n=29	p value
Mortality during 3 year follow-up, 4 (%)	0	4 (14%)	0.02

Annual death rate	0	about 10%	
Mean survival, months, mean (SEM)		26.2 (1.4)	
Recurrent VF (effectively treated by ICD), n	7 (19%)		
• Kaplan-Meier survival curve presented.			
Adverse effects of treatment	ICD, n=37	B-Blocker, n=29	p value
Operative mortality	0		
Adverse effects, n (%)	11/37 (30%)	4 (14%)	
Minor complications, corrected by reprogramming devices without major intervention, n			
- defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia	7		
- T-wave oversensing	3		
Pocket erosion requiring removal of ICD	1		
Side-effects in B-Blocker group			
- Impotence / decrease in libido		1	
- Fatigue		1	
- Profound bradycardia		1	
- Hypotension plus central nervous system side effect		1	
Comments: Medication compliance in B-blocker group 98%.			

RESULTS (pilot and main study combined)

Outcomes	ICD, n=47	B-Blocker, n=39	p value
Sudden death	0	7	
Multiple VF episodes and defibrillation shocks	12		
Annual rate of VF episodes or sudden death	20%	10%	
• Kaplan-Meier survival curve of composite of primary and secondary endpoints (sudden death or VF episodes) for pilot and main trial data presented.			

Methodological comments

- *Allocation to treatment groups:* Randomisation stratified by SUDS survivor vs probable SUDS survivor.
- *Blinding:* Not reported.
- *Comparability of treatment groups:* Groups similar.
- *Method of data analysis:* Interim analyses planned after half of patients and three quarters of patients had been randomised. Trial planned to be stopped after first interim analysis if survival analysis was $p < 0.005$ and after second analysis if $p < 0.006$. Final statistical analysis at the 0.048 significance level. Trial stopped at first interim analysis by Data Safety Monitoring Board even though analysis did not reach level of significance, based on cumulative weight of all evidence gained from data (including pilot study) that ICDs were superior. Baseline characteristics compared and any significantly different factors were used as covariates in subsequent analysis. States intention to treat analysis contrasted mortality rates and used Kaplan-Meier methods for calculating survival curves, log-rank method for comparing survival curves and Cox regression methods for comparing survival curves adjusting for covariates found to be different between treatment arms.
- *Sample size/power calculation:* From pilot study, it was estimated that 114 patients needed to be randomised, based on an expected annual mortality rate of 20% for the SUDS population. Assuming the annual mortality rate would be reduced 10-fold (ie up to 2%) in the ICD arm, 57 patients per treatment arm were required to produce the expected difference at 80% power and 0.05 2-sided significance level. Note only 66 patients were randomised. The annual death rate in the B-blocker arm was about 10%, half that used for the sample size calculations.

- *Attrition/drop-out*: 155 screened, 64 probable SUDS either non inducible or unclear marker, 10 refused enrolment, 1 randomised to ICD but refused, 2 preferred ICD treatment, 5 brain anoxic encephalopathy, 6 presence of heart disease, 1 entered after trial stopped. Attrition/drop-out after randomisation not reported. Not clear if all 66 participants were followed for 3 years.

General comments

- *Generalisability*: Small trial stopped early. Population differs significantly from other trials, as participants are survivors of sudden unexplained death in otherwise normal hearts with no heart failure. All participants were of Thai origin, mostly men. Participants similar to Brugada syndrome (a genetic disorder characterised by abnormal ECG findings and increased risk of sudden cardiac death) - study findings should also apply to this group of people.
- *OPT used*: The use of beta-blockers is low in the ICD group (exact numbers in main trial not clear, but 8/47 in main trial and pilot study combined). The study used an active comparator.
- *Outcome measures*: Limited to death from all causes, VT/VF episodes and adverse events.
- *Inter-centre variability*: Not reported.
- *Conflict of interests*: Not stated. Supported by Grant-in Aid from Cardiac Rhythm Management and Guidant Corporation, St Paul, Minn.
- *Other*: Paper reports the results of a pilot study and main study.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Details not reported
Allocation concealment	Unclear	Details not reported
Performance bias		
Blinding of participants and personnel	High	Not reported but unlikely to be blinding due to surgical intervention in one arm.
Detection bias		
Blinding of outcome assessment	Low	Not reported, but assessment of mortality unlikely to be influenced by lack of blinding
Attrition bias		
Incomplete outcome data addressed	Unclear	States ITT analysis but loss to follow-up not reported. Follow-up for maximum 3 years, not clear how many participants followed for this length of time.
Reporting bias		
Selective reporting	Low	
Other bias		
Other sources of bias	Low risk	

^a 'Low risk', 'high risk' or 'unclear risk' of bias

DEFINITE

Reference and design	Intervention and Comparator	Participants	Outcome measures
Kadish <i>et al.</i> , 2004 ⁴⁴ Ellenbogen <i>et al.</i> 2006 ⁴⁵ Passman <i>et al.</i> 2007 ⁴⁶ Kadish <i>et al.</i> 2000 ⁴⁷ Schaechter <i>et al.</i>	<i>Intervention</i> : ICD + standard oral medical therapy for heart failure (OPT) Single chamber device. Programmed to back up VVI pacing at rate of 40bpm and to detect VF	<i>Indication for treatment</i> : nonischaemic cardiomyopathy & moderate-to-severe left ventricular dysfunction. <i>Number of randomised participants</i> : n = 458 ICD + OPT, n= 229	<i>Primary outcomes</i> : death from any cause <i>Secondary outcomes</i> : sudden death from arrhythmia Quality of life ⁴⁶

<p>2003⁴⁸</p> <p>DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation)</p> <p><i>Study design:</i> RCT</p> <p>USA & Israel</p> <p><i>Number of centres:</i> 48 (44 USA, 4 Israel)</p> <p><i>Funding:</i> St Jude Medical</p>	<p>at rate of 180bpm</p> <p><i>Comparator:</i> OPT</p> <p>Medical therapy in both groups for heart failure included: ACE inhibitors unless contraindicated (then hydralazine, nitrates or angiotensin II-receptor blockers). Beta-blocker therapy (unless not tolerated) with carvedilol. Doses of ACE inhibitors & beta-blockers adjusted to recommended levels for heart failure patients or to highest tolerated doses. Digoxin and diuretics used when necessary to manage clinical symptoms. Use of antiarrhythmic drugs (e.g. amiodarone) discouraged but allowed for some patients with symptomatic atrial fibrillation or supraventricular arrhythmias. No other antiarrhythmic drugs used.</p> <p><i>Other interventions used:</i> none reported.</p>	<p>OPT, n= 229</p> <p><i>Inclusion criteria:</i> NYHA class no reported LVEF < 36% LVEDD not reported QRS interval not reported Presence of ambient arrhythmias (episode of nonsustained VT 3 to 15 beats at a rate of >120 bpm or an average of at least 10 premature ventricular complexes per hour on 24-hour Holter monitoring), history of symptomatic heart failure, presence of nonischaemic dilated cardiomyopathy. Absence of clinically significant coronary artery disease. Age 21-80⁴⁵</p> <p><i>Exclusion criteria:</i> NYHA class IV, no candidates for ICD, electrophysiological testing within the prior 3 months, permanent pacemakers, cardiac transplantation appeared imminent, familial cardiomyopathy associated with sudden death, acute myocarditis, congenital heart disease.</p>	<p>(QoL)</p> <p><i>Method of assessing outcomes:</i> 3 month intervals</p> <p>Cause of death used Epstein classification. Therefore patients with progressive symptomatic deterioration of pump failure who died to terminal VF were not considered to have had sudden death from arrhythmia.</p> <p>ICD shocks assessed at each follow-up or when indicated by symptoms⁴⁶</p> <p>QoL assessed with self-administered 12-item Medical Outcomes Short-Form Health Survey (SF-12) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) at baseline, 1 month after randomisation & every 3 months thereafter (to 63 months).⁴⁶</p> <p><i>Length of follow-up:</i> duration computed from randomisation to death or to the date of the 68th death for those who did not die. Mean (SD) 29.0 (14.4) months.</p> <p><i>Recruitment:</i> July 1998 to June 2002</p>
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Participant characteristics^a	ICD + OPT, n= 229	OPT, n= 229	p value
Age years, mean (range)	58.4 (20.3-83.9)	58.1 (21.8-78.7)	
Gender male, n (%)	166 (72.5)	160 (69.9)	
Self-reported ethnicity, n(%)			
- White	154 (67.2)	154 (67.2)	
- Black	59 (25.8)	59 (25.8)	
- Hispanic	13 (5.7)	13 (5.7)	
- Pacific Islander	1 (0.4)	0	
- Asian	0	1 (0.4)	
- Other	2 (0.9)	2 (0.9)	
Qualifying arrhythmia, n (%)			
- Nonsustained ventricular tachycardia (NSVT) only	51 (22.3)	52 (22.7)	
- Premature ventricular complexes (PVCs) only	21 (9.2)	22 (9.6)	
- NSVT and PVCs	157 (68.6)	155(67.7)	
Severity of disease e.g. NYHA classification			
NYHA class I, n (%)	58 (25.3)	41 (17.9)	
NYHA class II, n (%)	124 (54.2)	139 (60.7)	
NYHA class III, n (%)	47 (20.5)	49 (21.4)	
LVEF %, mean (range)	20.9 (7-35)	21.8 (10-35)	
Heart rate	not reported	not reported	
QRS interval msec, mean (range)	114.7 (78-196)	115.5 (79-192)	
Left bundle-branch block, n (%)	45 (19.7)	45 (19.7)	
Right bundle-branch block, n (%)	8 (3.5)	7 (3.1)	
Pharmacological therapy, n (%)			
ACE inhibitor	192 (83.8)	200 (87.3)	
Beta-blocker	196 (85.6)	193 (84.3)	
Carvedilol	129 (56.3)	134 (58.5)	
Metoprolol	59 (25.8)	43 (18.8)	
Other	8 (3.5)	16 (7.0)	
Diuretic	200 (87.3)	197 (86.0)	
Angiotensin II-receptor blocker	31 (13.5)	20 (8.7)	
Amiodarone	9 (3.9)	15 (6.6)	
Digoxin	95 (41.5)	97 (42.4)	
Nitrate	21 (9.2)	30 (13.1)	
Duration of heart failure years, mean (range)	2.39 (0.0-21.33)	3.27 (0.0-38.5)	0.04
History of diabetes, n (%)	52 (22.7)	53 (23.1)	
History of atrial fibrillation, n (%)	52 (22.7)	60 (26.2)	
Distance walked in 6 minutes m, mean (range)	311.2 (29-1143)	328.3 (18-1317)	
HRQoL ⁴⁶	ICD + OPT, n= 227	OPT, n= 226	
Physical score (MLHFQ), mean (SD)	20 (12)	20 (12)	0.98
Emotional score (MLHFQ), mean (SD)	11 (8)	10 (8)	0.59
Physical component summary (PCS) (SF-12), mean (SD)	37 (11)	38 (10)	0.47
Mental component summary (MCS) (SF-12), mean (SD)	45 (11)	47 (11)	0.14
Comments: ^a separate participant characteristics are reported for the QoL study which excluded 5 patients with no data (ICD n=227, OPT n=226), but only those for baseline SF-12 and MLHFQ scores have been extracted, the remainder have not been extracted. In common with the data above, the only significant difference between the groups was for duration of heart failure > 1 year (p=0.01).			

RESULTS

Outcomes	ICD + OPT, n= 229	OPT, n= 229	p value
All-cause mortality, n	28	40	HR 0.65 (95% CI 0.40 to 1.06), ^b 0.08
All-cause mortality rate at 1 year	2.6%	6.2%	
All-cause mortality rate at 2 years	7.9%	14.1%	
Sudden death from arrhythmia, n	3	14	HR 0.20 (95% CI 0.06 to 0.71), 0.006
Deaths from heart failure, n	9	11	
Receipt of appropriate ICD shocks ^c	41 patients, 91 shocks		
Receipt of inappropriate ICD shocks ^c	49 patients		
Symptoms and complications related to tachyarrhythmias and/or heart failure	not reported	not reported	
Heart failure hospitalisations	not reported	not reported	
Change in NYHA class	not reported	not reported	
Change in LVEF	not reported	not reported	
Exercise capacity outcomes (e.g. 6 minute walk distance, total exercise time, peak oxygen uptake)	not reported	not reported	
Health related quality of life ⁴⁶	ICD + OPT, n= 227	OPT, n= 226	
- Long-term MCS scores			0.89
- Long-term PCS scores			ns, p-value not reported
- long-term MLHFQ subscale scores			ns, p-value not reported.
<p>Comments: ^b Hazard ratio for death among ICD patients compared to OPT. The hazard ratio was unchanged after adjustment for duration of heart failure. ^c unclear whether these data are for ICD group only or whether participants from the OPT group who had received an ICD are also included. Inappropriate shocks were primarily for atrial fibrillation or sinus tachycardia. More detailed reporting on shocks received is presented by Ellenbogen et al.⁴⁵ but these data, which differ from those reported in the main study paper (Kadish et al.⁴⁴), have not been extracted. The reason(s) for the difference between the two papers is not discussed in either paper.</p> <ul style="list-style-type: none"> • Mortality presented for treatment actually received not data extracted • Kaplan-Meier plots for death from any cause and sudden death from arrhythmia presented but not extracted. • One death in the OPT group was thought to be from cardiac causes but an arrhythmic and nonarrhythmic cause could not be distinguished from the available information. • 26 deaths classified as non-cardiac were not reported by treatment group (10 due to cancer, 7 to pneumonia, 5 to stroke, 1 each to drug overdose, suicide, liver failure, and renal failure). • Four 4 deaths (2 in each group) could not be classified (insufficient information). • Pairwise comparisons of unadjusted MLHFQ and SF-12 scores by treatment group we evaluated but none reached statistical significance. This indicated no detectable difference in QoL between the groups for this period. Results are presented in a figure and have not been extracted. • SF-12 scores adjusted by time in trial are presented in a figure but have not been data extracted. Higher scores represent better QoL. Numerical data for short term (approx. 3 months) changes within group showed statistically significant improvement from baseline for the ICD group and non-statistically significant trend toward improvement in the OPT group. After this short-term improvement scores in both groups declined slowly (statistically significant) toward baseline values. 			

<ul style="list-style-type: none"> • MLHFQ scores adjusted by time in trial are also presented in a figure but have not been data extracted. Significant improvements in the emotional and physical scale scores occurred from enrolment to the 2nd follow-up visit. After initial improvement scores remained stable for the emotional scale in both groups, and scores for the physical scale decreased equally toward baseline values. These numerical data reported but not extracted. • Potential interaction of QoL and patient variables were assessed but the results implied that clinical variables cannot be used to identify patients who are likely to show a decline in QoL after ICD implantation. 			
Adverse effects of treatment	ICD + OPT, n= 229	OPT, n= 229	p value
Complications during implantation of ICD ^d	3 (1.3%)		
- hemothorax	1		
- pneumothorax	1		
- cardiac tamponade	1		
Procedure related deaths	0		
Complications during follow-up	10 (4.4%)		
- lead dislodgement or fracture	6		
- venous thrombosis	3		
- infection	1		
Receipt of ICD upgrade during follow-up	13		
- dual chamber ICD due to development of sinus-node dysfunction	2		
- biventricular devices for NYHA class III or IV heart failure and prolonged QRS interval	11		
Comments: ^d - all resolved with medical therapy or drainage			
Prespecified subgroup analyses		RR (95% CI)	p value
Relative risk of death from any cause after receipt of ICD in comparison to OPT			
- for men		0.49 (0.27 to 0.90)	p= 0.018
-for NYHA class III heart failure patients		0.37 (0.15 to 0.90)	p= 0.02
Comments:			
<ul style="list-style-type: none"> • Six pre-specified subgroup analyses (age, sex, LVEF, QRS interval, NYHA class and history of atrial fibrillation) are presented in a figure, with data only reported for men and NYHA class III. For most of the subgroups the 95% CIs crossed 1.0, apart from men, NYHA class III and LVEF $\geq 20\%$ (favours ICD, data in figure only). • None of the differences between subgroups were significant. • The study was not powered to detect differences within subgroups. • Kaplan-Meier survival curves for NYHA class III patients in ICD and OPT groups are provided but have not been data extracted. • The quality of life paper reports an analysis of the impact of shocks on QoL (comparing those receiving shock with those not receiving shocks) however this analysis is not mentioned in either of the two available papers on study design and organisation.^{47;48} Therefore it is assumed that these are post-hoc analyses and they have therefore not been extracted. 			
Methodological comments			
<ul style="list-style-type: none"> • <i>Allocation to treatment groups</i>: Randomisation stratified by centre and to the use or non-use of amiodarone for supraventricular arrhythmias. • <i>Blinding</i>: Cause of death determined by an events committee unaware of patient' treatment assignments. Blinding process included editing information from progress notes or laboratory reports that could have identified the presence of an ICD. 			

- *Comparability of treatment groups:* Similar apart from duration of heart failure (ICD + OPT mean 2.39 years (range 0.0-21.33), OPT mean 3.27 years (range 0.0-38.5), $p=0.04$).
- *Method of data analysis:* All analyses ITT. Data collection and analysis independently performed at Northwestern University. Interim analyses performed after 22, 34, 45, 50 and 56 deaths. Critical values for interim and final analyses assumed an O'Brien-Fleming type of spending function. For patient safety stopping boundaries were defined in favour of the null hypothesis of no effect of the ICD on the risk of death at each interim analysis. No boundaries were crossed at any of the five interim analyses so the report presents the final analysis results at the time of the 68th death. P-value for significance in the final analysis was 0.041 on the basis of a two-sided test. Baseline characteristics compared using two-sample t-tests for continuous variables and chi-square test for categorical variables. Log-rank test used to compare Kaplan-Meier survival curves. Cox proportional-hazards model used to adjust for covariates and to estimate the hazard ratio for death and corresponding 95% confidence interval in the ICD group vs OPT group. Data for patients receiving heart transplant censored at time of transplantation. All reported p-values are two tailed. QoL outcomes compared using hierarchical linear regression. QoL analyses controlled for baseline differences and predetermined characteristics (sex, age, NYHA class, ethnicity, ejection fraction, duration of heart failure, history of atrial fibrillation). Covariates were entered into and removed from the model stepwise at the group level with $\alpha=0.05$ and $\alpha=0.10$ as criteria for entry and removal respectively.⁴⁶
- *Sample size/power calculation:* Designed to have statistical power of 85% based on a one-sided test. Two-year mortality rates of 15% assumed in the comparator group and 7.5% in the ICD group with enrolment of 458 patients and 56 deaths. To report results with the use of two-sided tests and 85% statistical power follow-up was extended to include 68 deaths.
- *Attrition/drop-out:* Pre-specified criteria meant that OPT group patients received an ICD if they had a cardiac arrest or an episode of unexplained syncope consistent with the occurrence of an arrhythmic event. Overall 23 (10%) of the OPT group received ICDs during follow-up, primarily for this reason (no further details provided). Two ICD group participants declined implantation of the device after randomisation. Additionally one patient had the ICD explanted, and 1 had the device inactivated. All four were included in the ICD group (ITT analysis). In the QoL analysis missing months of data were treated following a full information restricted maximum likelihood estimation approach.⁴⁶ The QoL analysis excluded 5 patients who did not provide any data (2 from ICD group, 3 from OPT group). QoL data were missing from 1 or 2 visits for 130 patients and 178 patients had missing QoL data from more than 2 visits. States no relationship between QoL and varying length of follow up or dropping out of study. No significant differences between complete and incomplete QoL data by patient age, sex or NYHA class but patients without missing data more likely to be white, have better ejection fractions, and less likely to have diabetes than those with missing data (all $p<0.05$). Those with complete data were more likely to report a better baseline QoL. No interactions between data completeness and treatment group ($p=0.2$).

General comments

- *Generalisability:* Focus was on primary prevention of sudden death in patients with nonischaemic cardiomyopathy & moderate-to-severe left ventricular dysfunction. Results unlikely to be generalisable to higher risk groups e.g. secondary prevention of sudden death.
- *Outcome measures:* Appear appropriate.
- *Inter-centre variability:* Randomisation stratified by centre but no comments regarding inter-centre variability.
- *Conflict of interests:* States study sponsor did not have access to the data. Three of the authors had received fees from one or more of Medtronic, Guidant and St. Jude Medical.
- *Other:* Included after receiving advice from experts who indicated that was similar to AMIOVERT investigating whether the ICD reduces mortality in a high risk population with cardiomyopathy and no coronary disease. Note that mean QRS interval is <120 in each group, so on average no cardiac dyssynchrony.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^c	Support for Judgement
Selection bias		
Random sequence generation	Unclear	No details about sequence generation
Allocation concealment	Unclear	No details reported
Performance bias		
Blinding of participants and personnel	High	Not reported
Detection bias		
Blinding of outcome assessment	Low High	Events committee determining cause of death blinded. QoL
Attrition bias		
Incomplete outcome data addressed	Low	ITT analysis and attrition for each group reported with reasons.
Reporting bias		
Selective reporting	High	A cost analysis is listed in both papers reporting on study design and organisation ^{47;48} but no cost outcomes are reported in the identified papers.
Other bias		
Other sources of bias	Low risk	

^c 'Low risk', 'high risk' or 'unclear risk' of bias

DINAMIT

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Hohnloser <i>et al.</i> 2004,⁴⁹ 2000⁵⁰</p> <p>DINAMIT (Defibrillator In Acute Myocardial Infarction Trial)</p> <p><i>Study design:</i> RCT</p> <p>12 countries worldwide</p> <p><i>Number of centres:</i> 73 (Canada 25, Germany 21, UK 4, Slovakia 2, Poland 4, France 8, Czech Republic 1, Austria 2, Switzerland 1, Sweden 2, Italy 1, USA 2)</p>	<p><i>Intervention:</i> ICD + OPT (supplied by St. Jude Medical, Sunnyvale, California). Single-chamber ICD implanted within 1 week after randomisation. Implanted leads were required to achieve an R wave of <4.9mV, a pacing threshold of >2.1V at 0.5msec, and a defibrillation threshold with a safety margin of at least 10J. Postoperatively, the ICD was set to detect ventricular tachycardia and fibrillation. The detection rate for tachycardia was set at ≥175 per min. for ≥16 beats. The device was programmed to deliver all discharges at maximal output in the ventricular-fibrillation zone (≥200 beats per min).</p>	<p><i>Indication for treatment:</i> recent MI (6-40 days), reduced LVEF and impaired cardiac autonomic function</p> <p><i>Number of randomised participants:</i> n = 674 ICD, n= 332 OPT, n=342</p> <p><i>Inclusion criteria:</i></p> <ul style="list-style-type: none"> • Age 18 - 80 • Recent MI (6 - 40 days previously) • LVEF ≤ 0.35 • Standard deviation of normal-to-normal RR intervals of ≤ 70 msec or a mean RR interval of ≤ 750 msec (HR ≥ 80 beats per min) over a 24-hour period as assessed by 24-hour Holter monitoring performed at least 3 days after the infarction. <p><i>Exclusion criteria:</i></p>	<p><i>Primary outcomes:</i> death from any cause.</p> <p><i>Secondary outcomes:</i> death due to cardiac arrhythmia</p> <p><i>Method of assessing outcomes:</i> cause of death ascertained by local investigators and documentation based on information obtained from witnesses, family members, death certificates, hospital records, and autopsy reports when available, not from ICD telemetry. All deaths were reviewed by a committee and classification of each death was agreed based on clinical</p>

<p><i>Funding:</i> Supported by a grant from St. Jude Medical, Sunnyvale, California.</p>	<p>Bradycardia pacing was programmed for activation at min. of 40 beats per min. Antitachycardia pacing within the ventricular-tachycardia zone (175 - 200 beats per min) could be activated to deliver four bursts of 6 - 10 beats beginning at 81% of the tachycardia cycle length, with 10-msec decrements between bursts.</p> <p><i>Comparator:</i> OPT (best conventional medical therapy).</p> <p><i>Other interventions used:</i> Best conventional medical therapy. Investigators were encouraged to treat all study patients with angiotensin-converting-enzyme inhibitors, beta-blockers, aspirin, and lipid-lowering drugs, as appropriate (reasons for not giving these medications were documented).</p>	<ul style="list-style-type: none"> • Congestive heart failure or NYHA class IV at time of randomisation • Non-cardiac disease that limited life expectancy • Coronary artery bypass grafting performed since the qualifying infarction or planned to be performed within 4 weeks after randomisation • Three-vessel percutaneous coronary intervention performed since the qualifying infarction • Name on a waiting list for a heart transplant • Current, on-going ICD therapy • Prior implantation of a permanent pacemaker • Requirement for an ICD (i.e., sustained ventricular tachycardia or fibrillation more than 48 hours after the qualifying infarction) • Low probability that the study ICD could be implanted within 7 days after randomisation • Expected poor compliance with the protocol 	<p>circumstances of death and not ICD information. Deaths were classified as either arrhythmic or non-arrhythmic in nature (based on criteria by Hinkle and Thaler, ref provided).</p> <p>Follow-up visits scheduled at 3 and 6 months after randomisation and six-monthly intervals thereafter. Follow-up ended in Sept 2003, about 15 months after last patient recruited.</p> <p><i>Length of follow-up:</i> mean follow-up 30 months (SD 13), maximum 4 years from randomisation.</p> <p><i>Recruitment:</i> April 1998 – June 2002</p>
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Participant characteristics	ICD, n=332	OPT, n=342	p value
Age years, mean (SD)	61.5 (10.9)	62.1 (10.6)	nr
Gender M, n %	252 (75.9)	262 (76.6)	nr
Ethnicity	Not reported	Not reported	
Diagnosis			
Congestive heart failure with index MI, n (%)	156 (47.0)	167 (48.8)	nr
NYHA class I, n (%)	21 (13.5)	20 (12.0)	nr
NYHA class II, n (%)	95 (60.9)	98 (58.7)	nr
NYHA class III, n (%)	40 (25.6)	49 (29.3)	nr
LVEF, mean (SD)	0.28 (0.05)	0.28 (0.05)	nr
Heart rate	Not reported	Not reported	
Electrophysiology			
QRS duration (msec), mean (SD)	107 (24)	105 (23)	nr
Peak creatine kinase (U/litre), mean (SD)	2329 (3837)	2138 (2349)	nr
New Q-wave infarction, n (%)	240 (72.3)	256 (74.9)	nr
SD of normal-to-normal RR intervals (msec), mean (SD)	61 (21)	61 (22)	nr
24-hr RR interval (msec), mean (SD)	745 (106)	747 (105)	nr

Participant characteristics	ICD, n=332	OPT, n=342	p value
Beta-blockers, n (%)	289 (87.0)	296 (86.5)	nr
ACE inhibitors, n (%)	315 (94.9)	323 (94.4)	nr
Antiplatelet agents, n (%)	306 (92.2)	315 (92.1)	nr
Lipid-lowering agents, n (%)	255 (76.8)	272 (79.5)	nr
Cardiac history			
Prior MI, n (%)	123 (37.0)	111 (32.5)	nr
Prior CABG, n (%)	25 (7.5)	24 (7.0)	nr
Prior PTCA, n (%)	49 (14.8)	38 (11.1)	nr
Location of index MI, n (%)			
Anterior	239 (72.0)	247 (72.2)	nr
Other	93 (28.0)	95 (27.8)	nr
In-hospital therapy for MI, n (%)			
Any	208 (62.7)	212 (62.0)	nr
PTCA only,	87 (26.2)	92 (26.9)	nr
Thrombolysis only	88 (26.5)	76 (22.2)	nr
Both PTCA and thrombolysis	33 (9.9)	44 (12.9)	nr
None	115 (34.6)	111 (32.5)	nr
Unknown	9 (2.7)	19 (5.6)	nr
Comorbidities			
Diabetes mellitus, n (%)	102 (30.7)	98 (28.7)	nr
Hypertension, n (%)	155 (46.7)	154 (45.0)	nr
Comments: authors state that there were no significant differences between treatment groups in baseline characteristics; not all percentages total 100 due to rounding.			
<ul style="list-style-type: none"> • Average time from MI to randomisation was 18 days and similar in both groups • The average time between randomisation to ICD implant was 6.3 (SD 7.3) days • Average time between implantation and hospital discharge: 4.7 (SD 6.4) days 			
RESULTS			
Outcomes: Mortality rate,^a average follow-up 30 (SD 13) months	ICD, n=332	OPT, n=342	Hazard ratio (95% CI),^b p value^c
Primary outcome: death from any cause, n (rate: %/yr)	62 (7.5)	58 (6.9)	1.08 0.76-1.55, 0.66
Secondary outcome: death from arrhythmia, n (rate: %/yr)	12 (1.5)	29 (3.5)	0.42 (0.22-0.83), 0.009
Non-arrhythmic causes, n (rate: %/yr)	50 (6.1)	29 (3.5)	1.75 (1.11-2.76), 0.02
Cardiac, non-arrhythmic, n (rate: %/yr)	34 (4.1)	20 (2.4)	1.72 (0.99-2.99), 0.05
Vascular, non-cardiac, n (rate: %/yr)	5 (0.6)	3 (0.4)	1.69 (0.40-7.06), 0.47
Non-vascular, n (rate: %/yr)	11 (1.3)	6 (0.7)	1.85 (0.68-5.01), 0.22
Comments: ^a The data were analysed with use of the Cox model; ^b Hazard ratios are for the ICD group vs OPT; ^c p values are two-sided.			
<ul style="list-style-type: none"> • KM curves also reported for cumulative risk of death from any cause, cumulative risk of death from arrhythmia and cumulative risk of death from non-arrhythmic causes were presented, • Hazard ratios for death from any cause also reported according to selected clinical characteristics (age, gender, diabetes, NYHA class, LVEF, Rhythm, QRS duration, non-sustained ventricular tachycardia, HR, SD of normal RR intervals and early reperfusion), • States that for each feature, the ICD effect remained consistent and did not differ significantly between or among subgroups, 			
Percutaneous or surgical coronary revascularisation, n (%)	33 (9.9)	50 (14.6)	p=0.08
Prescribed Amiodarone, n (%)	27 (8.1)	46 (13.5)	p=0.04
Comments:			
Adverse effects of treatment		ICD, n=332	

Number of death related to device implantation	0
In-hospital device-related complications, n	25/310
Comments:	
<ul style="list-style-type: none"> • Most common complications were lead dislodgement, pneumothorax and inappropriate shocks 	

Methodological comments

- *Allocation to treatment groups*: Central randomisation was performed at the study coordinating and methods centre. Patients were randomly assigned in a 1:1 ratio. The randomisation sequence was stratified according to centre and balanced within randomly varying blocks of two, four, or six patients.
- *Blinding*: un-blinded study, blinding reported for independent review committee.
- *Comparability of treatment groups*: described as well balanced in baseline clinical characteristics and early use of reperfusion therapy (states no significant differences). ICD group had slightly higher percentages for prior MI and PTCA, and in hospital therapy for ‘thrombolysis only’. The OPT group had slightly higher percentages for NYHA class III, as well as in hospital therapy for ‘both PTCA and thrombolysis’ and ‘unknown’. Average time from MI to randomisation: 18 days - similar between groups (no p value reported) Amiodarone use was higher in the OPT group.
- *Method of data analysis*: The primary study outcome was evaluated according to the ITT principle. The cumulative risks of death from any cause and from specific causes over time were estimated separately for each treatment group with use of the Kaplan–Meier procedure and were compared between groups with use of the Mantel–Haenszel test. A single interim analysis of efficacy was performed by an external safety and efficacy monitoring committee after 66 deaths (about half the anticipated number) had occurred. A one-sided p-value of less than 0.001 would have resulted in early termination of the study. Before un-blinding, a decision was made to use two-sided statistical testing.
- *Sample size/power calculation*: On the basis of mortality data from similar populations of patients, it was anticipated that the OPT group would have a three-year mortality rate of 30.0% and that 40.0% of these deaths would be accounted for by deaths due to arrhythmia. The net effect of preventing 80.0 % of these deaths due to arrhythmia with use of an ICD would reduce the total mortality rate to 20.4%. Based on a one-sided test at an alpha level of 0.05, 525 patients would be required in order for the study to have 80% power to identify a difference between the groups. Because mortality rates were lower than expected during the study, the target enrolment was increased to 674 patients. States that it is unlikely that the similarity between the 2 groups in the rate of death from all causes represents a false negative result due to inadequate sample size.
- *Attrition/drop-out*: 4 patients in OPT had only partial follow up available; ICD received: 310/332 , 20/332 patients refused ICD implantation, 2/332 died before receiving ICD.

General comments

- *Generalisability*: limited to high-risk patients with recent MI, reduced LVEF and impaired cardiac autonomic function.
- *Outcome measures*: limited to mortality. NO AE data for OPT, limited AE data for ICD group.
- *Inter-centre variability*: not reported
- *Conflict of interests*: Drs. Hohnloser, Kuck, Dorian, and Connolly are consultants to and have received lecture fees from St. Jude Medical. Dr. Fain is an employee of St. Jude Medical. Data analysis was performed at Hamilton Civic Hospitals Research Centre by two of the authors (Mr. Roberts and Dr. Gent). All investigators had full access to the data.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear risk	The randomisation sequence was stratified according to centre and balanced within randomly varying blocks of two, four, or six patients. No details of sequence generation.
Allocation concealment	Low risk	Central randomisation.

Performance bias		
Blinding of participants and personnel	High risk	Described as un-blinded study
Detection bias		
Blinding of outcome assessment	Low risk	Assessment of causes of death by un-blinded local investigators, but all causes of deaths were reviewed by an independent blinded central validation committee.
Attrition bias		
Incomplete outcome data addressed	Low risk	Primary outcome was evaluated according to the ITT principle, unclear how partially missing follow up data for 4 OPT patients was accounted for in relation to secondary outcomes.
Reporting bias		
Selective reporting	High risk	QoL in protocol, but not reported.
Other bias		
Other sources of bias	High risk	Block randomisation in un-blinded trial can lead to prediction of allocation.

^a 'Low risk', 'high risk' or 'unclear risk' of bias

IRIS

Reference and design	Intervention and Comparator	Participants	Outcome measures
Steinbeck <i>et al.</i> , 2009 ⁵¹ , Steinbeck 2004 ⁵² IRIS (Immediate Risk Stratification Improves Survival) <i>Study design:</i> RCT Austria, Czech Republic, Germany, Hungary, Poland, Russia, Slovak Republic <i>Number of centres:</i> 92 <i>Funding:</i> grants from Medtronic Bakken Research Center, AstraZeneca,	<i>Intervention:</i> ICD + OPT 78% received Medtronic models of the GEM family, 11% Micro Jewel II, 8% Maximo & 3% Marquis. 81% were single chamber ICDs. A Fidelis lead was used in 21% of patients. Protocol required 2 consecutive terminations of VF at 10J below maximum ICD output, VVI pacing at 40 bpm,, with maximal shock energy turned on for treatment of VF (threshold ≥ 200 bpm) and treatment for VT turned off initially. <i>Comparator:</i> OPT (not further described) <i>Other interventions used:</i> not stated	<i>Indication for treatment:</i> Recent MI (≤ 31 days) and predefined markers of elevated risk. <i>Number of randomised participants:</i> n = 898 ICD, n= 445 OPT, n= 453 <i>Inclusion criteria:</i> Predefined markers of elevated risk, at least one of: - heart rate ≥ 90 bpm on first available ECG (within 48 hrs of MI) and LVEF $\leq 40\%$ (on one of days 5-31 after MI) - nonsustained ventricular tachycardia of ≥ 3 consecutive ventricular premature beats during Holter ECG monitoring, with a 150 bpm or more (on days 5 to 31). <i>Exclusion criteria:</i> ventricular arrhythmia before the index MI or more than 48 hours after the event and required treatment. NYHA class IV,	<i>Primary outcomes:</i> overall mortality <i>Secondary outcomes:</i> sudden cardiac death [death occurred within minutes after onset of acute symptoms, resulted from a documented cardiac arrhythmia, or was not witnessed and occurred unexpectedly and without recognisable causes (e.g. during sleep)], nonsudden cardiac death, noncardiac death <i>Method of assessing outcomes:</i> 3 and 6 months after randomisation & then 6-months intervals. <i>Length of follow-up:</i> average 37 months (range 0-106) <i>Recruitment:</i> June 1999

and R. Becker.		interval > 31 days between MI and presentation, no ECG within 48 hours of chest pain onset, indication for coronary artery bypass surgery, psychiatric disorder, severe concomitant disease, history of poor compliance with treatment, current participation in another trial, unstable clinical condition.	to October 2007
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Participant characteristics	ICD, n= 445	OPT, n= 453	p value
Age years, mean (SD)	62.8 (10.5)	62.4 (10.6)	
Gender male, n (%)	345 (77.5)	344 (75.9)	
Ethnicity	not reported	not reported	
Criteria for inclusion n (%)			
- criterion 1 only (HR & LVEF)	299 (67.2)	303 (66.9)	
- criterion 2 only (NSVT)	99 (22.2)	109 (24.1)	
- criteria 1 and 2	47 (10.6)	41 (9.1)	
LVEF %, mean (SD)	34.6 (9.3)	34.5 (9.4)	
- criterion 1 only	32.2 (6.3)	31.9 (6.7)	
- criterion 2 only	45.9 (10.8)	44.8 (11.0)	
- criteria 1 and 2	29.6 (7.0)	31.4 (6.7)	
Heart rate	not reported	not reported	
Electrophysiology findings	not reported	not reported	
Medical therapy on admission n/N (%)			
- antiplatelet agents	438/443 (98.9)	442/452 (97.8)	
- beta-blockers	394/442 (89.1)	388/453 (85.7)	
- ACE inhibitors	361/443 (81.5)	373/453 (82.3)	
ST-elevation myocardial infarction (STEMI), n (%)	341 (76.6)	348 (76.8)	
Reperfusion in STEMI, n/N (%)			
- none	43/340 (12.6)	48/348 (13.8)	
- percutaneous transluminal coronary angiography (PTCA)	243/340 (71.5)	253/348 (72.7)	
- thrombolytic therapy, with or without PTCA	54/340 (15.9)	47/348 (13.5)	
Anterior wall MI n/N (%)	282/439 (64.2)	300/449 (66.8)	
Heart failure on admission n/N (%)	197/444 (44.4)	209/453 (46.1)	
Previous MI n/N (%)	77/444 (17.3)	89/453 (19.6)	
Atrial fibrillation n/N (%)	60/445 (13.5)	61/453 (13.5)	
Left-bundle-branch block n/N (%)	45/445 (10.1)	29/453 (6.4)	0.05
Hypertension n/N (%)	296/444 (66.7)	300/453 (66.2)	
Diabetes mellitus n/N (%)	165/444 (37.2)	137/453 (30.2)	0.03
NYHA class at discharge (in 885 surviving patients) n (%)			
- class I		247 (28)	
- class II		531 (60)	
- class III		106 (12)	
- class IV		1 (0.1)	
Discharge medications, % of patients			
- antiplatelet agents	96.1%	95.8%	
- beta-blockers	97.1%	95.3%	
- ACE inhibitors	90.9%	91.1%	

Participant characteristics	ICD, n= 445	OPT, n= 453	p value
- statins	91.6%	91.5%	
- antiarrhythmic drugs (mainly amiodarone)	13.4%	17.4%	=0.11
Comments:			
<ul style="list-style-type: none"> • Characteristics described as well balanced although diabetes and left bundle branch block more frequent in the ICD group. • Randomised to study treatment a mean (SD) 13 (7) days after infarction. Implantation performed 'as soon as possible' after randomisation.⁵² • Implantation performed during hospitalisation for index infarction in 378 (91.1%) of ICD group. 			

RESULTS

Outcomes	ICD, n= 445	OPT, n= 453	Hazard ratio (95% CI) unadjusted p value
Cause of death during average follow-up 37 months (range 0-106), n/N (%)			
- any cause	116/445 (26.1)	117/453 (25.8)	1.04 (95% CI 0.81 to 1.35) p= 0.15
- sudden cardiac death	27/445 (6.1)	60/453 (13.2)	0.55 (0.31 to 1.00) p= 0.049
- nonsudden cardiac death	68/445 (15.3)	39/453 (8.6)	1.92 (1.29 to 2.84) p= 0.001
- non cardiac death	21/445 (4.7)	18/453 (4.0)	1.23 p= 0.51
Cumulative 1 year death rate ^a	10.6%	12.5%	
Cumulative 2 year death rate ^a	15.4%	18.2%	
Cumulative 3 year death rate ^a	22.4%	22.9%	
Health related quality of life	Not reported	Not reported	
Symptoms and complications related to tachyarrhythmias and/or heart failure	Not reported	Not reported	
Heart failure hospitalisations	Not reported	Not reported	
Change in NYHA class	Not reported	Not reported	
Change in LVEF	Not reported	Not reported	
Exercise capacity outcomes (e.g. 6 minute walk distance, total exercise time, peak oxygen uptake)	Not reported	Not reported	

Comments: ^a States that no significant difference in survival was detected between the groups, p-value of 0.76 given which may relate to these data but reporting is unclear.

- 13 pre-specified subgroups and 1 post-hoc subgroup. Hazard ratios and p-values for deaths from any cause in 9 (age, gender, congestive heart failure on admission, criterion of inclusion, ST-elevation MI, early reperfusion for ST-elevation MI only, number of vessels, smoking and NYHA class at discharge) of 13 subgroups presented in figure only but not data extracted. Four other pre-specified subgroups (diabetes, hypertension, lipid abnormalities, number of risk factors) not shown in figure. P-values ranged from 0.01 (smoking) to 0.92 (Amiodarone at discharge – post hoc subgroup). The p-value for smoking was the only one < 0.05. States that a neutral effect of the ICD on overall mortality was seen in all 3 prespecified subgroups (patients meeting criterion 1, 2 or both).
- Kaplan Meier plots for all-cause mortality, risk of sudden cardiac death, and risk of nonsudden cardiac death are presented by have not been data extracted.
- Cause of death also reported separately for participants meeting inclusion criterion 1 only, 2 only, or meeting criteria 1 and 2 but these data have not been extracted. States the effects were almost identical in these 3 predefined subgroups (interaction p=0.99 or p=0.71 for sudden or nonsudden

cardiac death respectively).

Adverse effects of treatment	ICD, n= 445	OPT, n= 453	p value
Number of ICDs actually implanted	415	39 (median 7.6 months after randomisation)	
Inserted lead entangled in tricuspid valve, removed surgically	1/415 patient		
ICD explanted or permanently deactivated during follow-up (median 6.8 months after implantation)	14/415 patients		
Clinically significant complications requiring hospitalisation, surgical correction, or intravenous drug administration	65/415 (15.7%) patients 76 complications		
- up to 30 days after implantation	19 (4.6%) patients		
- during follow up	48 (11.6%) patients		
Lead related problems requiring surgical revision (included in the above complications)	10 patients (4 had lead replacements)		
Died within 30 days after implantation	7 (n=4 MI, n=3 heart failure)		
Died within 30 days of randomisation	9	11	

Comments:

Methodological comments

- *Allocation to treatment groups:* randomisation by the data coordinating centre with risk stratification to ensure a balanced number of patients with ST elevation and non-ST elevation infarction between ICD and control group within these strata.⁵² No further details on allocation.
- *Blinding:* An adverse-event committee unaware of treatment assignments classified deaths. An independent data-coordinating centre undertook unblinding, data collection and statistical analysis.
- *Comparability of treatment groups:* Comparable for most characteristics.
- *Method of data analysis:* Primary analysis was ITT including all randomised patients with written informed consent obtained. Conducted by independent data-coordinating centre and independently repeated by one of the authors. Subdistribution hazard analyses performed using R software. Baseline comparisons by Fisher's exact tests, chi-square tests of Wilcoxon tests as appropriate. Cumulative risks of death estimated by Kaplan-Meier method, compared between groups with log-rank test. Cumulative mortality by year & annual rates calculated using an inverse Kaplan-Meier analysis. Calculation of hazard ratios and subgroup analysis performed on the basis of Cox proportional hazards models. Proportional-hazards assumption tested on basis of Schoenfeld residuals. Subgroup analyses (13 pre-specified, and one post-hoc added for effect of amiodarone) performed on by one, with use of a corresponding interaction test for comparison of the treatment effect between subgroups. Causes of death were analysed on the basis of proportional-subdistribution-hazard models (as causes of death represent competing risks).
- *Sample size/power calculation:* 2-year survival rates assumed to be 70.6% for medical therapy group, and 79.4% for ICD group (relative risk reduction approximately 30% in ICD group). Assumed two-sided alpha error of 5%, beta error of 20%, 30-month recruitment period, and 2-year minimum follow-up. With a loss to follow-up of 1%/year and accounting for group-sequential design the number of patients required in each group was 350. Recruitment time was more than doubled because percentage of screened patients excluded was unexpectedly high. In December 2005 the data & safety monitoring board, because of lower than anticipated mortality, recommended increasing to 900 patients and extending follow up until the last patient had been in the study a year.
- *Attrition/drop-out:* 415/445 ICD group patients actually received an ICD - 30 did not: 14 withdrew consent; 11 refused ICD implantation; 5 died before implantation could take place.

<p>ICDs removed in 15, and 39 in OPT group were given ICDs.</p> <ul style="list-style-type: none"> • <i>Other</i>: To increase recruitment 2 modifications to the protocol were made: i) non-ST elevation MI included from June 2002; ii) qualifying heart rate on 1st ECG reduced from 100 bpm to 90 bpm from Oct 2004.
<p>General comments</p> <ul style="list-style-type: none"> • <i>Generalisability</i>: people within 31 days of an MI • <i>Outcome measures</i>: appear appropriate • <i>Inter-centre variability</i>: not reported on • <i>Conflict of interests</i>: Sponsors were informed of trial outcome after the evaluation had been completed. Sponsors had an opportunity to review and provide comments on the predefined final-analysis plan and the manuscript, but did not have a role in study design, data analysis or interpretation of results.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^b	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Details not reported
Allocation concealment	Low risk	Randomisation by data coordinating centre
Performance bias		
Blinding of participants and personnel	High risk	No blinding
Detection bias		
Blinding of outcome assessment	Low risk	No blinding but outcomes not likely to be influenced (deaths classified by blinded committee)
Attrition bias		
Incomplete outcome data addressed	Low risk	Primary analysis by ITT
Reporting bias		
Selective reporting	High risk	Protocol paper ⁵² indicates SF-36 will be used to determine QoL but this outcome not reported.
Other bias		
Other sources of bias	Low risk	

^b 'Low risk', 'high risk' or 'unclear risk' of bias

MADIT

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Moss <i>et al.</i>, 1996;⁵³ MADIT executive Committee 1991;⁵⁴</p> <p>MADIT (Multicenter Automatic Defibrillator Implantation Trial)</p> <p><i>Study design</i>:</p>	<p><i>Intervention</i>: ICD + medical therapy</p> <p>Pulse generators (monophasic n=79; biphasic n=11) and lead systems supplied by CPI/ Guidant (St. Paul, Minn). Non-thoracotomy transvenous leads included in 1993.</p> <p>Late in the trial, a</p>	<p><i>Indication for treatment</i>: Previous myocardial infarction and left ventricular dysfunction.</p> <p>.</p> <p><i>Number of randomised participants</i>: n = 196</p> <p>ICD, n=95 (transthoracic stratum n=45; transvenous stratum n=50)</p> <p>OPT, n=101(transthoracic stratum n=53; transvenous stratum n=48)</p> <ul style="list-style-type: none"> • Total transthoracic stratum: n=98 • Total transvenous stratum: n=98 	<p><i>Primary outcomes</i>: death from all causes</p> <p><i>Secondary outcomes</i>: none specified.</p> <p>Other outcomes reported: prevalence of medications; adverse events; impact of 11 pre-selected baseline characteristics and medication type on</p>

<p>RCT</p> <p>USA and Europe</p> <p><i>Number of centres:</i> 32 (USA: 30, Europe: 2)</p> <p><i>Funding:</i> research grant from CPI/Guidant Corporation, St. Paul, Minn (also donated ICDs)⁵⁴.</p>	<p>small number of patients had pulse generators with electrogram storage implanted (number not reported). Defibrillators were implanted using standard techniques and testing was carried out during the implantation procedure (endeavoured to achieve defibrillation within a 10-J safety margin).</p> <p><i>Comparator:</i> conventional medical therapy</p> <p>Attending physician elected medical therapy and use of FDA approved antiarrhythmic medications in both groups.</p> <p><i>Other interventions used:</i> none reported</p>	<p>Crossover: n=16</p> <ul style="list-style-type: none"> • ICD, n=5 (no ICD fitted) • Deactivated ICD, n=2 • OPT, n=11 (ICD fitted) <p>Loss to follow up: ICD, n=1; OPT, n= 2</p> <p><i>Inclusion criteria:</i> Age, years: 25-80; NYHA class: I, II or III; LVEF: ≤ 0.35; Q-wave or enzyme-positive myocardial infarction >3 weeks prior entry; A documented episode of asymptomatic, unsustained ventricular tachycardia (run of 3-30 ventricular ectopic beats at a rate >120bpm) unrelated to an acute myocardial infarction; No indications for coronary artery bypass grafting or coronary angioplasty within past 3 months; Sustained ventricular tachycardia or fibrillation reproducibly induced and not suppressed after the intravenous administration of procainamide (or equivalent).</p> <p><i>Exclusion criteria:</i> Previous cardiac arrest or ventricular tachycardia causing syncope not associated with an acute myocardial infarction; Symptomatic hypotension while in a stable rhythm; Myocardial infarction within past 3weeks; Coronary artery bypass grafting within past 2 months or coronary angioplasty within past 3 months; Non-contraceptives taking women of childbearing age; Advanced cerebrovascular disease; Any condition other than cardiac disease associated with a reduced likelihood of survival for the duration of the trial; Patients participating in other clinical trials.</p>	<p>observed hazard ratio for overall mortality.</p> <p><i>Method of assessing outcomes:</i> Causes of death: categorised as either cardiac or non-cardiac (Hinkle and Thaler classification, reference provided) by 2 people reviewing information on deaths on or prior to 24/3/1996. Cardiac causes further categorised into arrhythmic, nonarrhythmic or uncertain.</p> <p>Follow up visits: clinical evaluation; recorded use of medication; test of defibrillator. Final evaluation 1 month after end of trial. One month after randomisation, thereafter 3 monthly until trial was stopped.</p> <p><i>Length of follow-up:</i> < 1 month to 61 months (average 27 months). Average 37 months for earlier transthoracic stratum (n=98), 16 months for later transvenous stratum (n=98).</p> <p><i>Recruitment:</i> 27/12/1990</p>
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Participant characteristics	ICD, n=95	OPT, n=101	p value
Age years, mean (SD) ^a	62 (9)	64 (9)	nr
Gender M/F, % ^a	92/8	92/8	nr

Participant characteristics	ICD, n=95	OPT, n=101	p value
Ethnicity	Not reported	Not reported	
NYHA class II or III, % ^a	63	67	nr
Cardiac findings at enrolment, %			
Pulmonary congestion (defined radiographically as mild, moderate, or severe)	18	20	nr
Blood urea nitrogen >25mg/dl (8.92mmol/litre) ^a	22	21	nr
Cholesterol >200mg/d (5.17mmol/litre)	41	49	nr
Left bundle-branch block, ^a %	7	8	nr
LVEF, mean, (SD) ^a	0.27 (0.07)	0.25 (0.07)	nr
Qualifying unsustained ventricular tachycardia, number of consecutive beats, mean (SD)	10 (9)	9 (10)	nr
Electrophysiology – initial induction			
Monomorphic ventricular tachycardia	87	91	nr
Polymorphic ventricular tachycardia	7	7	nr
Ventricular fibrillation	6	2	nr
Induction after antiarrhythmic challenge			
Monomorphic ventricular tachycardia	92	94	nr
Polymorphic ventricular tachycardia	7	5	nr
Ventricular fibrillation	1	1	nr
Cardiac history, %			
≥2 prior myocardial infarction ^a	34	29	nr
Treatment for ventricular arrhythmias	42	35	nr
Treatment for congestive heart failure ^a	52	51	nr
Treatment for hypertension ^a	48	35	nr
Coronary bypass surgery ^a	46	44	nr
Coronary angioplasty	17	27	nr
Implanted pacemaker	2	7	nr
Interval of ≥6months between most recent myocardial infarction and enrolment ^a	75	76	nr
Insulin-dependent diabetic	7	5	nr
Cigarette smoking (any time)	79	73	nr
Comments: ^a denotes 11 pre-selected variables for inclusion in a Cox regression analyses.			
• States baseline characteristics of the 2 treatment groups were similar, no p value reported.			
• States distribution of the qualifying Q-wave myocardial infarctions in terms of anterior, inferior and posterior locations was similar in the 2 treatment groups, no p value reported.			
RESULTS			
Outcomes	ICD, n=95	OPT, n=101	Hazard ratio (95% CI); p value
Mortality: cause of death, n			
Cardiac cause	11	27	nr
Primary arrhythmia	3	13	nr
Non-arrhythmia	7	13	nr
Uncertain	1	1	nr
Non-cardiac cause	4	6	nr
Unknown cause	0	6	nr
Total	15	39	0.46 (0.26-0.82); 0.009
Comments:			
• Hazard ratio (HR) = ratio of the risk of death per unit of time among patients randomly assigned to ICD to that among patients randomly assigned to OPT. HR takes into account stopping rule, not adjusted for covariates.			
• Kaplan-Meier cumulative survival curves presented.			

- Authors note that there were more deaths from non-arrhythmic causes in the OPT group compared to the ICD group and suggest this could be due to an inaccuracy in classification of cause of death or the higher rate of use of Amiodarone in the this group.

Cardiac medication	1 month ^b		Last contact ^c		p value
	ICD, n=93	OPT, n=93	ICD, n=86	OPT, n=82	
Antiarrhythmic medication, %					
Amiodarone	2	74	7	45	nr
Beta-blockers	26	8	27	5	nr
Class I antiarrhythmic agents	12	10	11	11	nr
Sotalol	1	7	4	9	nr
Beta-blockers or sotalol	27	15	31	14	nr
No antiarrhythmic medication	56	8	44	23	nr
Other cardiac medication, %					
Angiotensin-converting-enzyme inhibitors	60	55	57	51	nr
Digitalis	58	38	57	30	nr
Diuretics	53	52	52	47	nr

Comments: ^b data missing for 2 patients in ICD group and 8 patients in OPT group; ^c last contact defined as the last recorded contact with the patient at the end of the trial, on the last clinic visit prior to death or on the last clinic visit before patient was lost to follow-up.

- Separate Cox regression analyses revealed that neither medication nor any of the 11 pre-selected baseline variables had any 'meaningful influence' on the hazard ratio ($p > 0.2$ for all interactions). However, authors acknowledge that the power of the analysis is limited due to small patient numbers for some of the variables.
- ICD effects did not differ between those with transthoracic and those with transvenous leads ($p = 0.78$).

Adverse effects of treatment	ICD, n=95	OPT, n=101	p value
Operative deaths in the first 30 days	0	0	
Hypotension	0	1	
Syncope	1	5	
Hypothyroidism	0	1	
Sinus bradycardia	3	3	
Pulmonary fibrosis	0	3	
Pulmonary embolism	1	1	
Atrial fibrillation	4	0	
Pneumothorax	2	0	
Bleeding	1	0	
Venous thrombosis	1	0	
Surgical infection	2	0	
Problems with defibrillator lead	7	0	
Malfunction of defibrillator generator	3	2	
Total number of patients with adverse events	19	12	

Comments: some patients had more than 1 adverse event;

Methodological comments

- *Allocation to treatment groups*: random assignment of eligible patients to either ICD or OPT group within 30 days after completing the qualifying electrophysiologic study. The randomisation scheme included stratification according to centre and the interval between the most recent myocardial infarction and enrolment (<6 months or ≥6 months). The random assignment was made by the co-ordinating centre and transmitted to the enrolling clinical centre by telephone (hard copy followed).⁵⁴ After March 1993 and once non-thoracotomy transvenous leads were approval at a centre, a new stratum consisting of patients assigned to transvenous ICD or OPT was initiated.
- *Blinding*: the executive committee was unaware of the results of the study throughout the trial and

revised the sequential design during the trial on 2 occasions.

- *Comparability of treatment groups*: baseline characteristics between the two treatment groups described as similar (no statistical testing reported).
- *Method of data analysis*: a triangular sequential design, modified for 2-sided alternatives, was used with pre-set boundaries to permit termination of the trial if the efficacy or inefficacy of ICDs was established, or if there was evidence that there was no difference in outcome between ICD and OPT. Weekly data analyses was used, starting at the point at which 10 deaths had been reported. The trial was designed to be terminated when the path of the log rank statistic, measuring imbalance between the survival curves for the two groups, crossed one of the pre-set termination boundaries (efficacy, inefficacy, or no difference in outcome) of the sequential design. Due to the slow rate of enrolment from 12/11/1995 (before first enrolled patient had reached the 5th year of the study), data on patients was censored for analytic purposes at 5 years, with subsequent follow-up information on such patients censored from the ongoing sequential analysis. Analyses were stratified according to the type of device (transthoracic or transvenous) and followed ITT principle. All analyses and potential covariates were pre-specified. After termination of the trial, sequential-analysis methods were used to calculate a p value and hazard ratio (median unbiased), along with a 95% CI based on the p-value function. Secondary analyses were performed with the Cox proportional-hazards regression model, adjusted for relevant covariates. Separate Cox regression analyses were carried out in the transthoracic and transvenous strata, to determine whether the efficacy of defibrillators was similar in these two groups. Pre-selected baseline covariates and prescribed cardiac medications recorded at the 1-month clinic visit were evaluated in the Cox model to determine their effect on the risk of death per unit of time in the ICD group as compared with that in the OPT group (the hazard ratio). Survival curves for patients assigned to ICD treatment and OPT treatment were determined according to the method of Kaplan and Meier (reference cited). However, a note in the text states that the hazard ratio, derived from the sequential design takes into account the sequential stopping rule, but was not adjusted for covariates.
- *Sample size/power calculation*: the trial was designed to have an 85% power to detect a 46% reduction in the mortality rate among ICD patients as compared with a postulated 2-year mortality rate of 30% among the patients randomly assigned to OPT, with a 2-sided significance level of 0.05. After the introduction of transvenous leads (1/9/1993), the power requirement of the trial was increased from 85 to 90% in order 'as not to compromise the credibility of the study'.
- *Attrition/drop-out*: numbers lost to follow up reported (ICD n=1; OPT n=2). Percentage of patients that completed the 1838 scheduled follow up clinic visits was 92% for the ICD and 86% for the OPT group. 16 crossovers: OPT group (n=11) - adverse drug reaction (n=2), unexplained syncope (n=2), investigator concern about episodes of ventricular tachyarrhythmia (n=6) and aborted cardiac arrest (ventricular fibrillation) (n=1); ICD group (n=5) - high defibrillation threshold (n=1) and patient's preference (n=4). Two patients had their defibrillators deactivated during the course of the trial.

General comments

- *Generalisability*: authors acknowledge that the change to transvenous leads altered the type of patient referred for entry into the trial. Generalisability is limited to high-risk patients with coronary heart disease and left ventricular dysfunction, spontaneous asymptomatic unsustained ventricular tachycardia, and inducible and non-suppressible ventricular tachyarrhythmia on electrophysiologic testing.
- *Outcome measures*: appear appropriate, although unclear if all ITT (cardiac medication).
- *Inter-centre variability*: not reported. However, an evaluation of the consistency of the beneficial effect of ICDs in each of the 2 centres with the highest enrolments (n=42 and n=21) and comparison of the results in the high-enrolment centres with the results in the 30 low-enrolment centres (total n=133) showed reductions in mortality with ICDs to be similar among these groups (no statistical testing reported).
- *Conflict of interests*: states that all investigators agreed in writing not to hold stock in CPI/Guidant or any other defibrillator-manufacturing company prior to study participation and to abide by the conflict-of-interest standards (reference cited).

- Study officially stopped when efficacy boundary of the sequential design was crossed (when 51 deaths were reported).

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	No details of randomisation procedure in either trial paper ⁵³ or protocol. ⁵⁴ Patients were 'randomly assigned' by clinical centre and chronology of the interval after a prior myocardial infarction. ⁵⁴
Allocation concealment	Low risk	Random assignment provided to centres over the phone prior to hard copy. ⁵⁴
Performance bias		
Blinding of participants and personnel	High risk	Unblinded trial
Detection bias		
Blinding of outcome assessment	Low risk	A two-member end-point subcommittee independently reviewed information on the causes and circumstances of deaths and categorised them, but does not state blinded to allocation. ^{53;54} Mortality unlikely to be influenced by lack of blinding.
Attrition bias		
Incomplete outcome data addressed	Low risk	Analyses 'followed the ITT principle'. For the purpose of analysis, patients were not withdrawn from the trial and every effort made to ascertain the occurrence or non-occurrence of the primary endpoint. ⁵⁴ While not a primary outcome, it is unclear how missing data for type of medication (n=10) were dealt with in analysis.
Reporting bias		
Selective reporting	Low risk	Described outcomes reported. Protocol published. ⁵⁴
Other bias		
Other sources of bias	Low risk	

^a 'Low risk', 'high risk' or 'unclear risk' of bias

MADIT II

Reference and design	Intervention and Comparator	Participants	Outcome measures
Moss <i>et al.</i> , 2002; ⁵⁵ 1999; ⁵⁶ Greenberg <i>et al.</i> , 2004; ⁵⁷ Noyles <i>et al.</i> , 2007 ⁵⁸ MADIT II (Multicenter Automatic Defibrillator Implantation Trial)	<i>Intervention:</i> ICD + Conventional Medical Therapy <i>Transvenous defibrillator systems (Guidant, St. Paul, Minn) and standard defibrillator implant techniques were used. ICD</i>	<i>Indication for treatment:</i> High risk cardiac patients with prior MI and advanced left ventricular dysfunction <i>Number of randomised participants:</i> n=1232 ICD, n=742 OPT, n=490 Crossovers: n=54 • ICD, n=32 (n=21 (2.8%))	<i>Primary outcomes:</i> All-cause mortality <i>Secondary outcomes:</i> adverse events; HRQoL, economic outcomes, incidence of SCD, incidence of cardiac death due to progressive LV failure. <i>Method of assessing outcomes:</i> patients followed

<p><i>Study design:</i> RCT</p> <p>USA and Europe</p> <p><i>Number of centres:</i> 76 (USA: 71, Europe: 5)</p> <p><i>Funding:</i> research grant from Guidant, St. Paul, Minn to the University of Rochester School of Medicine and Dentistry</p>	<p>programming and prescribing medications were at the discretion of the patients' physicians.</p> <p><i>Comparator:</i> Conventional Medical Therapy (OPT)</p> <p>The appropriate use of beta-blockers, angiotensin-converting-enzyme inhibitors and lipid-lowering drugs was strongly encouraged in both study groups.</p> <p><i>Other interventions used:</i> none reported</p>	<p>no ICD fitted; n=11 (1.5%) ICD removed (9 heart transplants)</p> <ul style="list-style-type: none"> • Deactivated ICD, n=12 (usually due to terminal illness) • OPT, n 22 (4.5%) ICD fitted <p>Loss to follow up: ICD, n=2; OPT, n= 1 had a status unknown</p> <p><i>Inclusion criteria:</i></p> <ul style="list-style-type: none"> • Age, years: >21 • LVEF: ≤ 0.30 last 3 months (assessed by angiography, radionuclide scanning, or echocardiography) • MI >1 month prior study entry (documented by an abnormal Q wave on electrocardiography, elevated cardiac-enzyme levels on laboratory testing during hospitalisation for suspected myocardial infarction, a fixed defect on thallium scanning or localised akinesis on ventriculography with evidence of obstructive coronary disease on angiography) • Frequent or repetitive ventricular ectopic beats during 24-hour Holter monitoring from July 1997 until 1/1/1998 (discontinued as majority of cases had such arrhythmias) <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"> • indication approved by the FDA for ICD (and patients who met the MADIT 1 criteria for ICD⁵⁶) • NYHA class IV at enrolment • undergone coronary 	<p>up 1 month post randomisation and 3 monthly intervals. Causes of death were assessed using a modified version of the Hinkle-Thaler system (see general comments below)</p> <p><i>Cause of death definitions⁵⁷: SCD (modified Hinkle-Thaler system):</i></p> <ol style="list-style-type: none"> 1) died suddenly and unexpectedly within 1hr of cardiac symptoms in the absence of progressive cardiac deterioration; 2) died unexpectedly in bed during sleep; 3) died unexpectedly within 24hr after last being seen alive. <p>SCD sub-classified into those with and without symptoms of severe LV dysfunction NYHA \geqIII HF.</p> <p><i>Non-SCD:</i> patients who died of progressive cardiac failure or patients who did not meet the time criteria for sudden death.</p> <p><i>Progressive cardiac failure:</i> unstable, clinical progression of deteriorating pump function in the setting of active therapy, most often in an intensive care setting (patients with advanced HF in whom death was not anticipated as imminent were categorised as sudden death if their terminal event met the time criteria).</p> <p><i>SCD (clinical classification):</i> death with 1 h of symptom onset - primary (without preceding symptoms or secondary (complaint of chest pain during the 1-h prior to death). Marked ECG changes indicative of active MI were absent in any of the reviewed records.</p> <p><i>Multiple cause category:</i> presence of several medical problems in which CHD</p>
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		revascularisation within last 3 months <ul style="list-style-type: none"> • MI within past month (evidenced by measurement of cardiac-enzyme levels) • advanced cerebrovascular disease • women of childbearing age not using medically prescribed contraception • any condition other than cardiac disease that was associated with a high likelihood of death during the trial • not willing to sign the consent form 	contributed to, but was not the dominant feature of, the mortality event. HRQoL ⁵⁸ : Health Utility Index3(HUI3) self-administered during face-to-face study visits at baseline, 3, 12, 24 and 36 months. Patients could complete HUI3 at home and mail it back. HUI3 has 8 attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain discomfort. -0.0371 = worse possible state, 0 = death, 1 being the best possible health state). <i>Length of follow-up:</i> average 20 months (range 6 days to 53 months; HUI3: up to 36 months ⁵⁸) <i>Recruitment:</i> 11-07-1997 to 20-11-2001.
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Participant characteristics	ICD, n=742	OPT, n=490	p value
Age years, mean (SD)	64 (10)	65 (10)	nr
Gender M/F, %	84/16	85/15	nr
Ethnicity	Not reported	Not reported	
Diagnosis	Not reported	Not reported	
NYHA functional class, % ^a			
I	35	39	nr
II	35	34	nr
III	25	23	nr
IV	5	4	nr
LVEF, mean (SD)	23 (5)	23 (6)	nr
Heart rate	Not reported	Not reported	
Blood urea nitrogen >25mg/dl (8.92 mmol/litre),%	29	32	nr
Atrial fibrillation	9	8	nr
QRS interval ≥12 sec	50	51	nr
Non-specific conduction defect	22	26	nr
Right bundle-branch block	9	7	nr
Left bundle-branch block	19	18	nr
Medication at last contact, % ^b			
Amiodarone	13	10	nr
Angiotensin-converting-enzyme inhibitors	68	72	nr
Beta-blockers	70	70	nr
Calcium-channel blockers	9	9	nr
Class I antiarrhythmic agents	3	2	nr
Digitalis	57	57	nr

Diuretics	72	81	nr		
Lipid-lowering statin drugs	67	64	nr		
Cardiac history					
Interval of >6 month between most recent myocardial infarction and enrolment, %	88	87	nr		
Previous treatment					
Hypertension, %	53	53	nr		
Coronary bypass surgery, %	58	56	nr		
Coronary angioplasty, %	45	42	nr		
Comorbidities Diabetes, %	33	38	nr		
Current or former cigarette smoker, %	80	82	nr		
Comments: ^a values reflect the highest NYHA functional class recorded in the 3 months prior enrolment, limited to NYHA class I, II or III at enrolment. ^b mean interval from enrolment to last follow-up visit when medication use was recorded was 18 months in the ICD and 17 months in the OPT group.					
Baseline characteristics by subgroup⁵⁷	ICD		OPT		p value
	Alive, n=637	Dead, n=105	Alive, n=393	Dead, n=97	
Age years, mean (SD)	64 (11)	69 (9) ^c	64 (10)	68 (10) ^c	
Gender M, %	84	82	86	84	
NYHA functional class, % ^a		^c		^c	
I	36	27	41	29	
II	37	27	36	27	
III	27	46	23	44	
LVEF, mean (SD)	23 (5)	22 (6) ^c	24 (5)	23 (6) ^c	
Blood urea nitrogen,%	25	51 ^c	28	49 ^c	
Atrial fibrillation	8	12	7	16 ^c	
QRS interval ≥12 sec	49	57	49	59	
Right bundle-branch block	9	7	7	8	
Left bundle-branch block	19	28	16	27	
Previous treatment					
Hypertension, %	53	54	53	55	
Coronary bypass graft surgery, %	58	59	56	56	
Coronary angioplasty, %	47	36	45	31	
Cardiac history					
Interval of >6 month between most recent myocardial infarction and enrolment, %	88	87	87	89	
Comorbidities: Diabetes, %	32	34	36	43	
Cardiac morbidity after enrolment					
Hospitalisation for heart failure	20	60 ^c	15	41 ^c	
MI	4	20 ^c	4	15 ^c	
Coronary revascularisation	5	6	4	6	
Comments: ^c p<0.01 for comparison between alive and dead within each treatment arm.					
Baseline HRQoL,⁵⁸ means					
	ICD, n=658		OPT, n=431		
HUI3 score	0.637		0.646		p>0.10
SF-12 physical component score	36.293		36.444		p>0.10
SF-12 mental component score	50.505		50.419		p>0.10
Hospitalised at baseline	14.7		10.9		p>0.10
Comments: all other baseline scores for these subgroups were similar to main-patient group above. HRQoL not used in European study centres (n=109).					

RESULTS

Outcomes	ICD, n=742	OPT, n=490	Hazard ratio (95% CI); p value
Primary outcome: mortality, number of deaths (%)	105 (14.2)	97 (19.8)	0.69 (0.51-0.93); 0.016 ^d 31% reduction of risk of death at any interval for ICD compared to OPT
<p>Comments: ^d adjusted for stopping rules;</p> <ul style="list-style-type: none"> • Kaplan-Meier estimates of survival were reported for year 1 to 4 and difference in survival between the groups was significant (nominal p=0.007). The 2 survival curves began to diverge at around 9 months. Survival curves showed reductions in rates of death after ICDs of 12% (95% CI -27%; 40%) at 1 year, 28% (95% CI 4%; 46%) at 2 years; 28% (95% CI 5%; 45%) at 3 years. • There were no significant differences in the effect of defibrillator therapy on survival in subgroup analyses stratified according to age, sex, ejection fraction, New York Heart Association class, or the QRS interval (presented in figure). • There were also no significant differences in the effect of ICD on survival in subgroup analyses classified according to the presence or absence of hypertension, diabetes, left bundle-branch block, or atrial fibrillation; the interval since the most recent myocardial infarction (≤6 months vs >6 months); the type of defibrillator implanted (single chamber vs. dual chamber); or the blood urea nitrogen level (≤25mg per decilitre vs > 25mg per decilitre) (not presented in figure). 			
Symptoms and complications related to tachyarrhythmias and/or heart failure	Not reported	Not reported	
Heart failure hospitalisations	Not reported	Not reported	
Change in NYHA class	Not reported	Not reported	
Change in LVEF	Not reported	Not reported	
Exercise capacity outcomes (e.g. 6 minute walk distance, total exercise time, peak oxygen uptake)	Not reported	Not reported	
Comments:			

Subgroup analyses: cause of death by treatment group (modified Hinkle-Thaler scheme)⁵⁷	ICD, n=105	OPT, n=97	p value
Cardiac death			
Sudden death	28 (27%)	49 (51%)	p<0.01
Without severe LV dysfunction	18	34	
With severe LV dysfunction	10	15	
Non-sudden death	43 (41%)	21 (22%)	p<0.01
Unclassified cardiac death	8 (8%)	10 (10%)	
Total cardiac death	79	80	
Non-cardiac death/non-coronary death	22 (21%)	12 (12%)	
Unknown/unclassified	4 (4%)	5 (5%)	
Nominal death rates:			
Cardiac death rate	10.6% (79/742)	16.3% (80/490)	p<0.01
Sudden cardiac death rate	3.8% (28/742)	10.0% (49/490)	
Non-sudden cardiac death rate	5.8% (43/742)	4.3% (21/490)	
Total all-cause mortality	14.2% (105/742)	19.8% (97/490)	
Clinical classification scheme, cause of death: cardiac death			
Sudden death	24 (23%)	48 (49%)	p<0.01

Primary arrhythmia (without preceding symptoms)	22	41						
Secondary arrhythmia (with chest pain symptoms)	2	7						
Primary mechanical	40 (38%)	19 (20%)						
Cardiac procedure	1	1						
Multiple causes	8 (8%)	3 (3%)						
Non-cardiac/non-coronary death	22 (21%)	12 (12%)						
Unknown/unclassified death	10 (10%)	14 (10%)						
Nominal death rate: cardiac rates								
Cardiac death	9.8% (73/742)	14.5% (71/490)	p<0.01					
Sudden cardiac death	3.2% (24/742)	9.8% (48/490)	p<0.01					
Primary mechanical cardiac death	5.4% (40/742)	3.9% (19/490)						
Total all-cause mortality	14.2% (105/742)	19.8% (97/490)	p<0.01					
Nominal death rates out-of-hospital ^e	3.8% (28/742)	9.6% (47/490)	p<0.01					
Nominal death rates in-hospital	5.7% (42/742)	4.5% (22/490)						
<p>Comments: data are presented as the percentage of sudden and non-sudden deaths calculated from the total number of deaths in each treatment group. The nominal cardiac, sudden and non-sudden cardiac death rates are calculated from the numbers of specified deaths per number of randomised patients in each treatment arm (ICD=742; OPT=490), expressed as a percent.</p> <p>^e ICD vs OPT, cardiac deaths include only SCD and non-SCD by the Hinkle-Thaler classification. Also reported are location and number of SCD and non-SCD, as well as chronology of cardiac death by treatment group (not extracted).</p> <ul style="list-style-type: none"> • Sudden death (of cardiac death): 35% (28/79) ICD vs 61% (49/80) OPT, p<0.001 (chi square). • Nominal (raw) death rate, SCD: 3.8% ICD vs 10.0% OPT, p<0.01; non-SCD higher for ICD than conventional, but not significant (p value not reported). • Kaplan-Meier: hazard ratio for SCD 0.33 (95% CI, 0.20 – 0.53), p <0.0001; non-SCD p=0.32 (cumulative KM of SCD rates reported year 0 to 4). 								
Health-related QoL	ICD, n=658				OPT, n=431			
HU13 scores while alive	0	Yr1	Yr2	Yr3	0	Yr1	Yr2	Yr3
Proportion alive		0.93	0.846	0.767		0.903	0.792	0.667
Mean	0.637	0.627	0.622	0.601	0.646	0.659	0.667	0.678
Mean annual change ^f		-0.019	-0.027 ^h	-0.019 ⁱ		-0.012	-0.011	-0.013
Overall mean score including death ^j	0.637	0.584	0.526	0.461	0.646	0.595	0.529	0.452
<p>Comments: ^f equals (difference from baseline)/y; ^h p<0.05; ⁱ p<0.10; ^j mean HRQoL score (among n patients) after setting score for death to 0)</p>								
Adverse effects of treatment	ICD, n=742			OPT, n=490			p value	
Death during implantation, n	0							
Lead problems, n (%)	13 (1.8)							
Non-fatal infections requiring surgical intervention, n (%)	5 (0.7)							
Hospitalisation due to heart failure, n (%)	148 (19.9%)			73 (14.9)				
Patients hospitalised per 1000 months of active follow up	11.3			9.4			p=0.09	
Adverse cardiac events in week prior to SCD⁵⁷	n=28 ICD			n=49 OPT				
Syncope	4%			4%				
Angina pectoris	4%			4%				

MI	4%	10%	
Ventricular arrhythmia	25%	10%	
Congestive HF	43%	16%	

Methodological comments

- *Allocation to treatment groups*: patients were randomly assigned by the Coordinating Centre in a 3:2 ratio to receive ICD (60.2%) or OPT (39.8%) stratified to clinical centre.
- *Blinding*: none reported. States that information will be reported periodically to the independent safety monitoring sub-committee but kept confidential from investigators, Executive Committee and sponsors.
- *Comparability of treatment groups*: authors state that base-line characteristics and prevalence of the use of various cardiac medications at the time of the last follow-up visit were similar between the 2 groups, but report no p values.
- *Method of data analysis*: analysis was performed according to ITT principle. A triangular sequential design modified for 2-sided alternatives and corrected for the lag in obtaining data accrued but not reported before the termination of the trial, for weekly monitoring, with pre-set boundaries to permit termination of the trial if ICD was found to be superior to, inferior to, or equal to OPT was used. Secondary analyses were performed with use of the Cox proportional-hazards regression model. Survival curves were determined according to the Kaplan and Meier method, with comparisons of cumulative mortality based on logarithmic transformation. P values were termed nominal when not adjusted for sequential monitoring. All p values were 2-tailed. Analyses used version 2.0 of the database, released 16-01-2002. The trial was stopped 20-11-2001 after analysis revealed difference in mortality between both groups had reached pre-specified efficacy boundary, $p=0.027$. Subgroups were pre-specified.
- Mortality events⁵⁷ were based on version 3.0 of the database (released 26/7/02), Chi-square statistics were used for categorical data, t-test for continuous variables (independent samples), Kaplan-Meier method for cumulative survival curves and log-rank method for statistical comparison of cumulative mortality. The Cox proportional hazards regression model was used to calculate the risk for SCD and non-SCD in the total population and in subgroups stratified by relevant baseline characteristics for patients randomized to ICD versus OPT.
- Missing HUI3 scores⁵⁸ were imputed using a multi-variate fixed-effects model, regressing the difference between baseline score and a score for each subsequent visit on time, treatment, gender, age, death during the trial, death within 6 months of HRQoL assessment, sudden death within 6 months of HRQoL assessment, presence of diabetes, use of diuretics, and having NYHA class II-IV.
- *Sample size/power calculation*: trial was designed to have 95% power to detect a 38% reduction in the 2-year mortality rate in the ICD group, given a postulated 2-year mortality rate of 19% among the OPT group with a 2-sided significance level of 0.05. For proportional-hazards modelling, power was maintained for a true hazard ratio of 0.63 after allowance for cross-over. Originally it was estimated that 1200 patients (720 ICDs and 480 OPT) were needed. On 4 May 2001, executive committee increased the enrolment goal to 1500 patients so that enrolment would be on-going while data on outcomes were still accruing.
- *Attrition/drop-out*: percentage of patients that completed the 8749 scheduled follow up clinic visits was 97% for the ICD and 94% for the OPT group (states that the status of 3 patients at termination of the trial unknown: 2 ICD, 1 OPT). Reasons for dropout not reported. HRQoL not used in European study centres (n=109). Patients with missing data at baseline (n=22) were excluded, as were patients with poor data quality (n=12). Questionnaires returned after trial termination were also excluded (n=8), but this number appears to have been accounted for as part of the number of patients with poor data quality. 8.5% of HRQoL data were missing and summary reasons were provided.

General comments

- *Generalisability*: limited to high risk cardiac patients with prior MI and advanced left ventricular dysfunction. *Outcome measures*: appear appropriate.
- *Inter-centre variability*: not reported.

- *Conflict of interests*: Supported by a research grant from Guidant, St Apul, Minn. Dr Cannom, Dr Daubert and Dr Higgins have given lectures sponsored by the grant provider (Guidant). States that all investigators agreed to abide by the conflict-of-interest guidelines. Authors state that investigators had full access to the data and performed the analysis with no limitation imposed by the sponsor.
- *Other*: ICD patients were not responsible for incurred costs of the ICD, implantation or hospitalisation for the procedure.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Patients randomly assigned, but no details of procedure.
Allocation concealment	Unclear	Not reported.
Performance bias		
Blinding of participants and personnel	High risk	No blinding reported.
Detection bias		
Blinding of outcome assessment	Low risk High	No blinding reported. Data was independently reviewed, but the committee was not blinded. ⁵⁷ Mortality unlikely to be influenced by lack of blinding. QoL
Attrition bias		
Incomplete outcome data addressed	Low risk	Analysis was performed according to ITT principle Missing and missing HUI3 scores were imputed using a multi-variate fixed-effects model (see methods).
Reporting bias		
Selective reporting	Unclear	Apart from the primary endpoint, the protocol paper only specifies 4 secondary objectives (1. association of induced ventricular tachycardia; on ICD discharge rate; 2. patients at risk of increased mortality according to pre-specified Holter-recorded electrocardiologic parameters at baseline; 3. cost-effectiveness of ICD; 4. QoL).
Other bias		
Other sources of bias	Low risk	No costs in relation to ICD were incurred by patients.

^a 'Low risk', 'high risk' or 'unclear risk' of bias

SCD-HeFT

Reference and design	Intervention and Comparator	Participants	Outcome measures
Bardy <i>et al.</i> , 2005 ⁵⁹ Packer <i>et al.</i> , 2009 ⁶⁰ Michell <i>et al.</i> 2008 ⁶¹ Mark <i>et al.</i> 2008 ⁶²	Group 1: ICD Single chamber ICD (Medtronic, model 7223) programmed to shock only mode (to treat only rapid,	Indication for treatment: broad population of patients with mild-to-moderate heart failure	Primary outcomes: death from any cause For QoL study: The Duke Activity Status Index (DASI) and Medical Outcomes Study

<p>SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)</p> <p><i>Study design:</i> RCT</p> <p>US (99%⁶²), Canada, & New Zealand⁶¹</p> <p><i>Number of centres:</i> 148⁶¹</p> <p><i>Funding:</i> Grants from NHLBI, NIH, and by Medtronic, Wyeth-Ayerst Laboratories, and Knoll Pharmaceuticals.</p>	<p>sustained VT or VF). Detection rate of ≥ 187 bpm. Antitachycardia pacing therapies not permitted.</p> <p><i>Group 2:</i> amiodarone Dose partly based on weight. Loading dose of 800mg daily for 1 week, 400mg daily for 3 weeks. Then patients >200lb (90.9kg) received 400mg daily, patients 150-200lb (68.2 to 90.9kg) 300mg daily, and patients less than 150lb (68.2kg) 200mg daily. If a patient had bradycardia the loading or maintenance dose could be lowered.</p> <p><i>Group 3:</i> placebo, administered in the same way as amiodarone.</p> <p><i>Other interventions used:</i> All participants received optimal HF medical therapy⁶⁰. If clinically reasonable all patients required to receive treatment with a beta-blocker and an ACE inhibitor. When appropriate to receive, aldosterone, aspirin and statins.⁵⁹</p>	<p><i>Number of randomised participants:</i> n = 2521 ICD, n= 829 Amiodarone, n= 845 Placebo, n= 847</p> <p><i>Inclusion criteria:</i> NYHA class II or III chronic, stable CHF due to ischaemic or non-ischaemic causes. LVEF $\leq 35\%$ ≥ 18 years Ischaemic CHF defined as LV systolic dysfunction associated with $\geq 75\%$ narrowing of at least 1 of 3 major coronary arteries (marked stenosis) or a documented history of MI. Nonischaemic CHF defined as LV systolic dysfunction without marked stenosis.</p> <p><i>Exclusion criteria:</i> None stated</p>	<p>36-item Short Form (SF-36) Mental Health Inventory 5 (MHI-5)</p> <p><i>Secondary outcomes:</i> Other scales from SF-36, number of 'bed days' and 'disability days', Minnesota Living with Heart Failure Questionnaire (MLHFQ), health status utility, global health status.</p> <p><i>Method of assessing outcomes:</i> Every 3 months with alternating clinic visits and telephone calls. Data downloaded from ICD memory regularly at visits.</p> <p>Deaths were classified by an events committee. Cardiac deaths were subclassified as sudden death (VT, bradyarrhythmic, HF related, other cardiac causes). Non cardiac deaths included stroke, peripheral arterial embolism, pulmonary embolism, aneurysm rupture, acute haemorrhage and nonvascular events (e.g. serious lung, liver, kidney or other organ failure, cancer and sepsis).⁶⁰</p> <p>QoL⁶² - measured by structured interviews at baseline (before randomisation), and months 3, 12 and 30 (or at end of study follow-up). Interviews at time of scheduled clinic visit or by phone if visit was missed. A short proxy form was used if patients were too ill, had language barrier, or were otherwise unable to participate in a full interview. The DASI reflects cardiac-specific physical functioning. Score 0-58, higher scores indicate better function, a difference ≥ 4 points is considered clinically significant. SF-36 MHI-5</p>
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			<p>reflects psychological well-being, score 0-100, higher scores indicate better function. A clinically significant difference was approximated as one quarter of 1 SD (5 points in this study). Other SF-36 scales scored the same way.</p> <p>‘Bed days’ defined as number of days in bed all or most of the day in the last 42 days.</p> <p>‘Disability days’ defined as number of days (excluding bed days) patient cut down usual activities for health reasons.</p> <p>MLHFQ scored 0-105, higher score indicates worse function, clinically significant difference approximately 5 points.</p> <p>Health status utility 0 (dead) to 1 (excellent) assessed with time trade off technique.</p> <p>Global health rated on a scale of 0 (dead) -100 (excellent health) and 5-point difference (one quarter of 1 SD) approximating clinical significance.</p> <p><i>Length of follow-up:</i> to October 31 2003. Median follow-up for surviving patients 45.5 months (range 24 - 72.6 months).</p> <p><i>Recruitment:</i> Sept 1997 to July 2001</p>
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Participant characteristics	ICD, n= 829	Amiodarone, n= 845	Placebo, n= 847	p value
Age years, median (IQR)	60.1 (51.9-69.2)	60.4 (51.7-68.3)	59.7 (51.2-67.8)	
Gender, male n (%) [calculated by reviewer]	639 (77)	639 (76)	655 (77)	
Non-white race n (%)	189 (23)	196 (23)	204 (24)	
LVEF, median (IQR)	24.0 (19.0-30.0)	25.0 (20.0-30.0)	25.0 (20.0-30.0)	
Heart rate beats/min median (IQR)	74 (65–84)	72 (64–82)	73 (64–84)	
Nonsustained ventricular tachycardia (NSVT) n (%) ^a	210 (25)	193 (23)	180 (21)	
Syncope n (%)	52 (6)	54 (6)	56 (7)	
Systolic blood pressure, mm Hg, median (IQR)	118 (104–131)	118 (106–130)	120 (108–132)	

Participant characteristics	ICD, n= 829	Amiodarone, n= 845	Placebo, n= 847	p value
Diastolic blood pressure, mm Hg, median (IQR)	70 (61–80)	70 (62–80)	70 (62–80)	
Medication use at enrolment, n (%)				
- ACE inhibitor	684 (83)	731 (87)	718 (85)	
- Angiotensin II receptor blocker (ARB)	114 (14)	118 (14)	132 (16)	
- ACE inhibitor or ARB	783 (94)	822 (97)	827 (98)	
- Beta-blocker	576 (69)	581 (69)	581 (69)	
- Diuretic				
Loop	676 (82)	696 (82)	692 (82)	
Potassium-sparing	168 (20)	174 (21)	165 (19)	
Thiazide	63 (8)	52 (6)	60 (7)	
- Digoxin	552 (67)	614 (73)	589 (70)	
- Aspirin	477 (58)	461 (55)	477 (56)	
- Warfarin	266 (32)	310 (37)	281 (33)	
- Statin	312 (38)	334 (40)	319 (38)	
Diabetes n (%)	253 (31)	243 (29)	271 (32)	
Pulmonary disease n (%)	175 (21)	147 (17)	158 (19)	
Hypercholesterolemia n (%) ^b	431 (52)	442 (52)	456 (54)	
Hypertension n (%)	453 (55)	469 (56)	478 (56)	
Atrial fibrillation or flutter n (%)	141 (17)	132 (16)	117 (14)	

Comments: ^a NSVT defined as ≥ 3 consecutive ventricular beats at a heart rate > 100 bpm.

^b Hypercholesterolaemia defined as low-density lipoprotein cholesterol at enrolment of > 130 mg/dl after an overnight fast.

- Baseline characteristics of electrophysiological study, weight, serum sodium, and serum creatinine reported but not extracted. Groups were well balanced.
- Overall 70% of the population had NYHA class II CHF and 30% had class III.
- Selected baseline characteristics are reported for the participants in the QoL study⁶² (ICD n=816; Amiodarone n=830; Placebo n=833) but have not been extracted.
- Baseline characteristics are reported by race⁶¹ but have not been extracted. Significant differences in demographic and clinical data were found between different racial groups.

RESULTS

Outcomes	ICD, n= 829	Amiodarone, n= 845	Placebo, n= 847	p value
Mortality from any cause n (%)	182 (22%)	240 (28%)	244 (29%)	HR amiodarone vs placebo 1.06 (97.5% CI 0.86 to 1.30), 0.53 HR ICD vs placebo 0.77 (97.5% CI 0.62 to 0.96), 0.007
Kaplan-Meier estimates death from any cause - 5 year event rate	0.289	0.340	0.361	
Cardiac deaths n/No. of deaths (%) ⁶⁰	122/182 (67)	162/240 (68)	167/244 (68)	HR amiodarone vs placebo 1.05 (95% CI 0.85 to 1.31), p= ns HR ICD vs placebo 0.76 (95% CI 0.60 to 0.95), 0.018
- tachyarrhythmic	37/182 (20)	75/240 (31)	95/244 (39)	HR amiodarone vs placebo 0.84 (95% CI 0.62 to 1.13), 0.25

				HR ICD vs placebo 0.40 (95% CI 0.27 to 0.59), p<0.001
- bradyarrhythmic	1/182 (<1)	5/240 (2)	3/244 (1)	
- HF	72/182 (40)	67/240 (28)	66/244 (27)	HR amiodarone vs placebo 1.14 (95% CI 0.81 to 1.60), p= ns HR ICD vs placebo 1.14 (95% CI 0.82 to 1.60), p=ns
- Nonarrhythmic, non-HF	9/182 (5)	10/240 (4)	2/244 (1)	
- Cardiac but unable to classify further	3/182 (2)	5/240 (2)	1/244 (<1)	
Noncardiac n/No. of deaths (%) ⁶⁰	48/182 (26)	54/240 (23)	53/244 (22)	HR amiodarone vs placebo 1.10 (95% CI 0.80 to 1.50) p= ns HR ICD vs placebo 0.80 (95% CI 0.57 to 1.12) p=ns
- vascular	11/182 (6)	10/240 (4)	12/244 (5)	
- nonvascular	37/182 (20)	44/240 (18)	41/244 (17)	
Unknown n/No. of deaths (%) ⁶⁰	12/182 (7)	24/240 (10)	24/244 (10)	p=ns
Medication use at last follow-up, n (%)	ICD, n= 822	Amiodarone, n= 840	Placebo, n= 838	
- ACE inhibitor	576 (70)	594 (71)	619 (74)	
- ARB	144 (18)	152 (18)	145 (17)	
- ACE inhibitor or ARB	706 (86)	718 (85)	740 (88)	
- Beta-blocker	672 (82)	605 (72)	662 (79)	<0.001
- Diuretic				
Loop	649 (79)	665 (79)	674 (80)	
Potassium-sparing	261 (32)	236 (28)	278 (33)	
Thiazide	80 (10)	95 (11)	88 (11)	
- Digoxin	512 (63)	496 (59)	524 (62)	
- Aspirin	449 (55)	474 (56)	451 (54)	
- Warfarin	279 (34)	272 (32)	300 (36)	
- Statin	395 (48)	405 (48)	387 (46)	
ICD shocks				
- received for any cause	259/829 (31%)			
- received for rapid VT or fibrillation	177/259 (68%)			
- annual rate of ICD shocks during 5 year follow up	7.5%			
- annual rate of appropriate shocks (sustained VT or VF) during 5 year follow-up	5.1%			
Comments:				
<ul style="list-style-type: none"> As indicated by the HR for mortality of ICD therapy compared to placebo the relative risk 				

reduction of ICD therapy was 23%. Absolute reduction at 5-years was 7.2 percentage points.				
<ul style="list-style-type: none"> Kaplan-Meier curves for mortality from any cause presented but not extracted.⁵⁹ Also presented for classifications of death but not extracted.⁶⁰ 				
Adverse effects of treatment	ICD, n= 829	Amiodarone, n= 845	Placebo, n= 847	p value
Implantation was unsuccessful	1 patient (<1%)			
ICD removed during follow-up.	32 patients (4%)			
Clinically significant ICD complications ^c				
- at time of implantation	5%			
- later in the course of follow-up	9%			
At time of last follow up				
- increased tremor		4% (amiodarone compared with placebo)		=0.02
- increased hypothyroidism		6% (amiodarone compared with placebo)		<0.001
Comments: ^c defined as clinical events requiring surgical correction, hospitalisation, or new and otherwise unanticipated drug therapy.				
Prespecified subgroup analyses⁵⁹⁻⁶¹				
Outcomes	ICD, n= 829	Amiodarone, n= 845	Placebo, n= 847	p value
Mortality from any cause - Ischaemic CHF ⁵⁹				HR amiodarone vs placebo 1.05 (97.5% CI 0.81-1.36), 0.66 HR ICD vs placebo 0.79 (97.5% CI 0.60-1.04), 0.05
Kaplan-Meier estimates of mortality from any cause - 5 year event rate Ischaemic CHF ⁵⁹	0.359 n=431	0.417 n=426	0.432 n=453	
Cause of death, participants with ischaemic CHF ⁶⁰				HR amiodarone vs placebo 0.96 (95% CI 0.73-1.26) HR ICD vs placebo 0.80 (95% CI 0.60-1.05)
- sudden tachyarrhythmic				HR amiodarone vs placebo 0.70 (95% CI 0.48-1.03) HR ICD vs placebo 0.43 (95% CI 0.27-0.67)
- heart failure				HR amiodarone vs placebo 1.17 (95% CI 0.78-1.77) HR ICD vs placebo 1.11 (95% CI 0.74-1.67)
- non-cardiac				HR amiodarone vs placebo 1.21 (95% CI 0.88 -1.94) HR ICD vs placebo 0.79 (95% CI 0.50-1.22)
Mortality from any cause - Nonishaemic CHF ⁵⁹				HR amiodarone vs placebo 1.07 (97.5% CI 0.76-1.51), 0.65 HR ICD vs placebo 0.73 (97.5% CI 0.50-1.07),

				0.06
Kaplan-Meier estimates of mortality from any cause - 5 year event rate Nonischaemic CHF ⁵⁹	0.214 n=398	0.258 n=419	0.279 n=394	
Cause of death, participants with Nonischaemic CHF ⁶⁰ - cardiac				HR amiodarone vs placebo 1.23 (95% CI 0.85-1.77) HR ICD vs placebo 0.68 (95% CI 0.44-1.03)
- sudden tachyarrhythmic				HR amiodarone vs placebo 1.13 (95% CI 0.68-1.85) HR ICD vs placebo 0.34 (95% CI 0.17-0.70)
- heart failure				HR amiodarone vs placebo 1.06 (95% CI 0.58-1.96) HR ICD vs placebo 1.21 (95% CI 0.67-2.18)
- non-cardiac				HR amiodarone vs placebo 0.81 (95% CI 0.48-1.36) HR ICD vs placebo 0.81 (95% CI 0.48-1.37)
Mortality from any cause - NYHA II ⁵⁹				HR amiodarone vs placebo 0.85 (97.5% CI 0.65-1.11), 0.17 HR ICD vs placebo 0.54 (97.5% CI 0.40-0.74), <0.001
Kaplan-Meier estimates of mortality from any cause - 5 year event rate NYHA II ⁵⁹	0.201 n=566	0.264 n=601	0.320 n=594	
Cause of death, participants with NYHA class II CHF ⁶⁰ - cardiac				HR amiodarone vs placebo 0.88 (95% CI 0.66-1.17) HR ICD vs placebo 0.50 (95% CI 0.36-0.70)
- sudden tachyarrhythmic				HR amiodarone vs placebo 0.68 (95% CI 0.47-0.99) HR ICD vs placebo 0.26 (95% CI 0.15-0.44)
- heart failure				HR amiodarone vs placebo 0.93 (95% CI 0.56-1.54) HR ICD vs placebo 0.93 (95% CI 0.56-1.54)
- non-cardiac				HR amiodarone vs placebo 0.79 (95% CI 0.52-1.20) HR ICD vs placebo 0.63 (95% CI 0.40-0.99)
Mortality from any cause - NYHA III ⁵⁹				HR amiodarone vs placebo 1.44 (97.5% CI 1.05-1.97), 0.010 HR ICD vs placebo 1.16 (97.5% CI 0.84-1.61), 0.30
Kaplan-Meier estimates of	0.484	0.528	0.456	

mortality from any cause - 5 year event rate NYHA III ⁵⁹	n=263	n=244	n=253	
Cause of death, participants with NYHA class III CHF ⁶⁰ - cardiac				HR amiodarone vs placebo 1.33 (95% CI 0.95-1.86) HR ICD vs placebo 1.17 (95% CI 0.84-1.64)
- sudden tachyarrhythmic				HR amiodarone vs placebo 1.22 (95% CI 0.73-2.03) HR ICD vs placebo 0.73 (95% CI 0.41-1.29)
- heart failure				HR amiodarone vs placebo 1.34 (95% CI 0.84-2.11) HR ICD vs placebo 1.34 (95% CI 0.86-2.09)
- non-cardiac				HR amiodarone vs placebo 1.68 (95% CI 1.03-2.73) HR ICD vs placebo 1.10 (95% CI 0.66-1.85)

Comments:

- There was no interaction of either amiodarone therapy (p=0.93) or ICD therapy (p=0.68) with the cause of CHF.
- The interaction between amiodarone and NYHA class was significant (p=0.004). Patients with NYHA class III CHF in the amiodarone group had a relative 44% increase in the risk of death compared with those in the placebo group (HR as above: 1.44). For patients with NYHA class II CHF no excess risk of death was associated with amiodarone therapy in comparison with placebo (HR as above 0.85).
- The interaction between ICD therapy and NYHA class was significant (p<0.001). Among patients with NYHA class II CHF there as a 46% relative reduction in the risk of death (HR as above 0.54). The absolute reduction in mortality among patients in NYHA class II was 11.9% at 5-years. Patients with NYHA class III CHF had no apparent reduction in risk of death with ICD therapy compared to placebo (HR as above 1.16).
- Kaplan-Meier plots presented but not extracted.
- Other subgroup analyses [sex, age, race (white vs non-white; see below for white vs African American), LVEF, QRS, 6 MWT, beta-blocker, diabetes] presented but not data extracted as not specified a priori.
- Packer et al.⁶⁰ reporting on impact of type of HF and HF class on mode of death state that the interaction between ICD therapy and NYHA class was significant for cardiac mortality (p=0.0004) and sudden death presumed to be ventricular tachyarrhythmic (p=0.0091) but not for HF (p=0.29) or non-cardiac (p=0.11) deaths. There was a significant interaction of amiodarone therapy on non-cardiac mortality between NYHA classes (p=0.020) but no significant interaction between NYHA classes for cardiac mortality (p=0.064), sudden death (p=0.073) or HF mortality (p=0.30).
- For type of HF (ischaemic/nonischaemic) Packer et al.⁶⁰ state that there was no significant interaction of ICD therapy with the type of HF for cardiac (p=0.53), sudden tachyarrhythmic (p=0.58), HF (p=0.82), or non-cardiac (p=0.92) modes of death. Similarly no interaction was seen with amiodarone therapy and type of HF in cardiac (p=0.29), sudden tachyarrhythmic (p=0.14), HF (p=0.79), and non-cardiac (p=0.15) mortality.

Prespecified analysis by race ^{61 d}	ICD		Amiodarone		Placebo	
	AA 36%	White 33%	AA 30%	White 34%	AA 34%	White 33%
Risk of death	HR ICD vs placebo 0.65 (95%	HR ICD vs placebo 0.73 (95%	HR amiodarone vs placebo 1.08 (95% CI 0.71-	HR amiodarone vs placebo 1.11 (95% CI 0.90-		

	CI 0.43-0.99), p= nr	CI 0.58-0.90), p= nr	1.64), p=nr	1.37), p= nr			
ICD discharges	No significant difference observed between whites and AAs HR 1.10 (95% CI 0.80-1.51) p=0.56						
Comments: ^d AA = African Americans. The remaining patients in each group were described as 'Latin American' or 'Other minority'. Separate data for these groups is not reported in the paper. <ul style="list-style-type: none"> There was no significant interaction between either randomised treatment and race (test for ICD vs placebo different across race groups (African American & White groups only) p=0.53, for amiodarone vs placebo across different race groups p=0.71).⁶¹ Data not reported. 							
Quality of life study⁶²	ICD, n=816	Amiodarone, n= 830	Placebo, n= 833	Difference (95% CI), p value			
DASI, mean score (SD)							
- baseline	24.6 (13.6) n=814	25.3 (14.1) n=825	24.9 (14.1) n=829	Amiodarone vs placebo 0.44 (-0.92 to 1.80) ICD vs placebo -0.34 (-1.68 to 1.00)			
- 3 months	26.9 (14.1) n=766	26.2 (14.7) n=756	26.2 (14.3) n=768	Amiodarone vs placebo -0.01 (-1.47 to 1.45) ICD vs placebo -0.69 (-0.73 to 2.11)			
- 12 months	26.8 (14.4) n=734	26.1 (14.5) n=676	26.6 (14.8) n=697	Amiodarone vs placebo -0.58 (-2.14 to 0.97) ICD vs placebo 0.16 (-1.35 to 1.68)			
- 30 months	26.8 (14.3) n=665	27.1 (15.3) n=575	25.9 (15.3) n=585	Amiodarone vs placebo 1.20 (-0.56 to 2.96) ICD vs placebo 0.89 (-0.75 to 2.53)			
MHI-5							
- baseline	71.7 (20.5) n=814	72.1 (20.1) n=827	70.0 (21.4) n=830	Amiodarone vs placebo 2.11 (0.11 to 4.11), ≤0.05 ICD vs placebo 1.64 (-0.39 to 3.67)			
- 3 months	74.4 (19.3) n=764	72.9 (20.6) n=759	71.3 (21.5) n=767	Amiodarone vs placebo 1.60 (-0.51 to 3.72) ICD vs placebo 3.15 (1.10 to 5.19), ≤0.05			
- 12 months	74.5 (18.9) n=734	72.9 (20.5) n=674	70.9 (21.5) n=693	Amiodarone vs placebo 1.99 (-0.24 to 4.22) ICD vs placebo 3.68 (1.58 to 5.78), ≤0.05			
- 30 months	72.2 (19.1) n=654	73.2 (20.3) n=560	71.0 (21.7) n=564	Amiodarone vs placebo 2.22 (-0.24 to 4.68) ICD vs placebo 1.24 (-1.06 to 3.53)			
MLHFQ, median							
- baseline	41	nr	43	0.77			
- 3 months	30	nr	36	0.006			
- 12 months	32	nr	36	0.07			
- 30 months	32	nr	36	0.05			
Global health status, median							

Quality of life study ⁶²	ICD, n=816	Amiodarone, n= 830	Placebo, n= 833	Difference (95% CI), p value
- 3 months	75		70	0.002
- 12 months	75		70	0.05
- 30 months	70		70	0.18

Comments:

- Median (interquartile range) for DASI reported but not extracted. This also showed no significant difference between ICD and placebo groups at baseline (p=0.76), and months 3,12, and 30 (p>0.10). There were also no significant differences at any point between the amiodarone and placebo groups.
- Median (interquartile range) for MHI-5 also reported but not extracted. This also showed no significant difference between ICD and placebo groups at baseline (p=0.17) but was better in the ICD group than placebo at 3 months (median scores 80 and 76 respectively, p=0.01) and at 12 months (median scores 80 and 76 respectively, p=0.003). There was no significant difference at 30 months (p=0.79). There were no significant differences at any point between the amiodarone and placebo groups.
- Data for each of the other SF-36 scales are presented in a supplementary appendix and have not been extracted. For each of these scales at least one interval comparison showed significantly better scores in the ICD group. However values were clinically similar and did not differ at baseline or at 30 months on any of these scales. Patients in the amiodarone group had significantly higher scores than placebo on the SF-36 pain index at all four time points.
- Baseline (for whole sample) but not follow-up data on number of bed days are reported. States an effect of ICD therapy compared to placebo could not be detected for number of bed days, or disability days, or on the proportion of patients who were able to drive a car, manage their finances, or maintain employment during the follow-up period.
- States there was a significant improvement in the ICD group over the placebo group at 3 months in the time-trade-off health status utility measure but not at any of the other time points. No numerical data presented (baseline utility measure averaged 0.80 at baseline in all 3 groups).
- Results are presented for an analysis accounting for the improved survival in participants in the ICD group but these have not been extracted. States that these results were not materially different from the unadjusted comparisons which have been extracted.

Subgroup analyses - QoL study⁶²

Outcomes	ICD, n= 816		p value
	Received shock ^c n=49	No Shock	
SF-36 score, mean change			
- general health perceptions	-6.3	3.4	0.002
- physical function	-8	10.9	<0.001
- emotional function	-11	4.5	0.02
- social function	-5.3	4.6	0.009
- self-related health	-3.2	6.6	0.009

Comments: ^c: 49 participants received a shock within 1 month before a scheduled QoL assessment

- Changes for patients who had received a shock calculated as the value after the shock was delivered minus the most recent value before the shock. Changes in scores for the non-shock groups were the QoL values at 3 months minus the values at baseline. States that results were similar when other follow-up time point were used to calculate the changes in scores. A positive change indicates better function.
- States that the pattern was the same for the 66 participants who had received a shock within 2 months before a scheduled QoL assessment, but with smaller differences.
- States that a comparison of 100 surviving patients who received an ICD shock at any time in the first year with 638 participants who had not received a shock showed no significant differences. Also, the number of ICD discharges (above a range of 2-5) did not have a significant effect on subsequent QoL. Further details not reported.

Methodological comments

- *Allocation to treatment groups:* Patients assigned to amiodarone or placebo began therapy as

outpatients immediately after randomisation. ICD group patients received device a median of 3 days after randomisation (IQR 2-5 days). Permuted-block randomisation, stratified by clinical site, cause of CHD (ischaemic vs nonischaemic) and NYHA class (II vs III). Block size randomly chosen as 3 or 6.

- *Blinding*: Placebo and amiodarone administered in double blind fashion. Wyeth-Ayerst Pharmaceuticals provided identical appearing tablets.⁵⁹ The events committee that adjudicated deaths was blinded to treatment assignment (a nurse removed all information identifying randomised therapy assignment from reports).⁶⁰
- *Comparability of treatment groups*: States there were no significant differences between the groups at baseline. By last follow-up visit there was a difference in use of beta-blockers ($p < 0.001$). Median dose of amiodarone and placebo was 300mg/day 3 months after randomisation and remained so throughout the study.
QoL study⁶²: Selected baseline characteristics are reported and described as well balanced between the groups.
- *Method of data analysis*: Pairwise comparisons (amiodarone vs placebo; ICD vs placebo) performed by ITT. All statistical tests 2 tailed. Cumulative mortality rates calculated by Kaplan-Meier method. Event (or censoring) times measured from time of randomisation (time zero). Differences in mortality rates assessed with log-rank test, with adjustment for NYHA class and cause of CHF. Relative risks expressed as hazard ratios with 97.5% CIs (consistent with α level of 0.025) derived from the Cox proportional-hazards model (however 95% CIs are reported by Parker et al.⁶⁰). Cox model also used to test significance of interactions between NYHA class and treatment, and between cause of CHF and treatment. Six interim analyses performed and reviewed by the independent data and safety monitoring board using two-sided, symmetric O'Brien-Fleming boundaries generated with the Lan-DeMets alpha-spending-function approach to group-sequential testing. Because of sequential testing the level of significance for each major treatment comparison at completion of the study was 0.023. Some patients may have had ICD discharges that were either not recorded or not reported to the ICD core laboratory which would limit the ability to know the true rate of ICD events.
For QoL study⁶²: continuous data described with means (SD) &/or medians (25-75 percentiles). Categorical variables described with percentages. Pearson's chi-square test used for categorical variable comparisons, Wilcoxon rank-sum test for continuous variables. Wilcoxon rank-sum test for changes in scores from most recent QoL scores used to compare patients who received a shock within the month preceding a QoL assessment with those who did not. Comparisons based on Wilcoxon Rank-sum test for changes in scores from most recent QoL measurements before shock occurred. Analysis repeated with 2 and 12 month time frames. To account for potential bias due to the significant difference in mortality between the groups an estimator for the survival average causal effect was applied as a sensitivity analysis. All reported p-values 2-sided and no adjustments made for multiple testing.
- *Sample size/power calculation*: based on assumption that placebo group would have an annual mortality rate of 10%. Powered at 90% to detect a 25% reduction in death from any cause by amiodarone or ICD therapy, as compared to placebo, on the basis of an α level for each comparison of 0.025.
- *Attrition/drop-out*: Vital status known for all 2521 patients at the time of the last scheduled follow-up visit. Noncompliance rate for study drug therapy (discontinuation of placebo or amiodarone for any period) was 27% (458 patients) - 22% of placebo group (189/847 patients) and 32% of amiodarone group (269/845 patients). Cross overs: 125 patients (7%) in the drug groups crossed over to open-label amiodarone, 44 in the amiodarone group and 81 in the placebo group. In the ICD group 113/829 (14%) received open-label amiodarone during some part of follow-up. 17/829 (2%) of patients assigned to ICD therapy declined to undergo implantation. Cross over to some form of ICD therapy occurred in 188 patients (11%) in the drug groups during follow-up. Median time from randomisation to crossover was 26.7 months. QoL study⁶²: 98% completed baseline QoL questionnaires. At each follow-up 93-95% of eligible patients were included, overall 95% of questionnaires were collected. 1.2% of patients declined to complete questionnaires, 1.4% of forms were judged incomplete and in 69/6268 (1.1%) of interviews proxy

forms were substituted for the full questionnaire.
<ul style="list-style-type: none"> • <i>Other</i>: None of the 716 patients for whom defibrillation-testing data were reported required more than a 30-J shock for defibrillation (the maximum device output).
General comments
<ul style="list-style-type: none"> • <i>Generalisability</i>: broad population of patients with mild-to-moderate heart failure and no exclusions stated. However majority of participants were American and the racial mix of participants differs to that likely in the UK. • <i>Outcome measures</i>: Appear appropriate. • <i>Inter-centre variability</i>: For QoL study specific training was provided at each site to ensure standardisation of data collection.⁶² No other details provided. • <i>Conflict of interests</i>: States companies provided study drugs and ICDs free of charge and provided additional clinical and research funding. However, neither company had any role in design, analysis or interpretation of the study.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^f	Support for Judgement
Selection bias		
Random sequence generation	Unclear	States permuted-block randomisation, stratified by clinical site, cause of CHD and NYHA class with block size randomly chosen as 3 or 6. However no details about generation of sequence.
Allocation concealment	Unclear	No details provided.
Performance bias		
Blinding of participants and personnel	High risk	No blinding of ICD arm. QoL - Risk of bias between ICD and non-ICD groups due to knowledge of intervention received.
Detection bias		
Blinding of outcome assessment - mortality outcomes	Low risk	Events committee that adjudicated deaths was blinded to treatment group.
Blinding of outcome assessment - QoL outcomes	High risk	QoL data obtained by structured interview, risk of bias between ICD and non-ICD groups due to knowledge of intervention received.
Attrition bias		
Incomplete outcome data addressed - mortality outcomes	Low risk	ITT analysis and vital status known for all patients at time of last visit.
Incomplete outcome data addressed - QoL outcomes	Unclear	Some explanation of missing data but not by treatment group.
Reporting bias		
Selective reporting	Low risk	Protocol not available but papers appear to report all the expected and stated outcomes.
Other bias		
Other sources of bias	Low risk	

^f 'Low risk', 'high risk' or 'unclear risk' of bias

Appendix 9: Data extraction: people with heart failure as a result of LVSD and cardiac dyssynchrony

CARE-HF

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Cleland <i>et al.</i>, 2005;⁹ 2001;⁶³ 2006;⁶⁴ 2007;⁶⁵ 2009;⁶⁶ Gras <i>et al.</i>, 2007;⁶⁷ Gervais <i>et al.</i>, 2009;⁶⁸ Ghio <i>et al.</i>, 2009⁶⁹</p> <p>CARE-HF (Cardiac Resynchronization - Heart Failure)</p> <p><i>Study design:</i> RCT</p> <p>Country or countries: European countries including UK, France, Germany, Switzerland, Italy⁹</p> <p><i>Number of centres:</i> 82⁹</p> <p><i>Funding:</i> Supported by a grant from Medtronic</p>	<p><i>Intervention:</i>⁹ CRT-P + Medical therapy. CRT (Medtronic InSync or InSync III device) providing atrial-based, biventricular stimulation + standard pharmacological therapy.</p> <p>Standard RV and Attain (Medtronic) LV leads.</p> <p>Backup atrial pacing set at 60 bpm, interventricular delay set at zero, atrioventricular delay echocardiographically optimised.</p> <p><i>Comparator:</i>⁹ Medical therapy (standard pharmacological therapy only)</p> <p><i>Other interventions used:</i> None reported. Standard medications adjusted if needed at follow up visits.</p>	<p><i>Indication for treatment:</i>⁹ NYHA III or IV due to LVSD and cardiac dyssynchrony receiving standard pharmacological therapy</p> <p><i>Number of randomised participants:</i>⁹ n = 813 CRT-P + medical therapy, n= 409 Medical therapy alone, n= 404</p> <p><i>Inclusion criteria:</i>⁹ NYHA class III or IV despite standard pharmacological therapy, LVEF \leq35%, LVEDD \geq30mm (indexed to height), QRS interval \geq120ms. Patients with QRS interval of 120 to 149 ms required to meet 2 of 3 additional criteria for dyssynchrony: aortic preejection delay $>$140ms; interventricular mechanical delay $>$40ms; delayed activation of posterolateral left ventricular wall.</p> <p>Age \geq18 years, heart failure for \geq 6 weeks</p> <p><i>Exclusion criteria:</i>⁹ Major cardiovascular event in previous six weeks, conventional indications for a</p>	<p><i>Primary outcomes:</i>⁹ Composite of death from any cause or an unplanned hospitalisation for major cardiovascular event (only first hospitalisation counted).</p> <p>For extension phase: death from any cause⁶⁴</p> <p><i>Secondary outcomes:</i>⁹ Death from any cause, composite of death from any cause and unplanned hospitalisation for HF 90 day NYHA class 90 day QoL</p> <p>For extension phase: mode of death.⁶⁴</p> <p><i>Method of assessing outcomes:</i>⁹ Assessment at baseline, 1, 3, 6, 9, 12 & 18 months. Then at 6 month intervals. For QoL⁶⁶ baseline, 3 months, then disease specific instrument only at 18 months & study end.</p> <p>QoL: patient assessed using disease specific Minnesota Living with Heart Failure questionnaire (MLWHFQ, score range 0-105, higher score indicates lower QoL) and generic European Quality of Life-5 Dimensions (EuroQoL EQ-5D, score range -0.594 to 1.0, lower score indicates lower QoL, negative scores QoL</p>

		pacemaker or an ICD, heart failure requiring continuous intravenous therapy, atrial arrhythmias.	considered worse than death) <i>Length of follow-up:</i> ⁹ mean 29.4 (range 18.0-44.7). For QoL ⁶⁶ median 29.6 (IQR 23.6-34.6) months. After 8 month extension phase mean 37.4 (range 26.1-52.6), median 37.6 (IQR 31.5-42.5). ⁶⁴ <i>Recruitment:</i> January 2001 to March 2003 ⁹
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Participant characteristics⁹	CRT-P + medical therapy, n= 409	Medical therapy, n= 404	p value
Age years, median (range)	67 (60-73)	66 (59-72)	
Gender, n (%) male	304 (74)	293 (73)	
Ethnicity	nr	nr	
Dilated cardiomyopathy, n (%)	177 (43)	193 (48)	
Ischaemic heart disease, n (%)	165 (40)	144 (36)	
Heart disease of other causes, n (%)	67 (16)	67 (17)	
NYHA class IV, n (%)	23 (6)	27(7)	
LVEF %, median (range)	25 (21-29)	25 (22-29)	
QRS interval msec, median (range)	160 (152-180)	160 (152-180)	
Heart rate bpm, median (range)	69 (60-78)	70 (61-78)	
Left ventricular end-systolic volume index ml/m ² , median (range)	121 (92-151)	117 (94-147)	
Interventricular mechanical delay, msec, median (range)	49 (32-67)	50 (30-66)	
Mitral-regurgitation area, median (range)	0.21 (0.12-0.33)	0.23 (0.11-0.34)	
Use of ACE inhibitor or angiotensin blocker, n (%)	387 (95)	383 (95)	
Use of beta-blocker, n (%)	288 (70)	298 (74)	
Use of spironolactone, n (%)	219 (54)	238 (59)	
Use of high-dose loop diuretic, n (%)	175 (43)	177 (44)	
Use of digoxin, n (%)	165 (40)	181 (45)	
Systolic blood pressure, mm Hg, median (range)	110 (100-125)	110 (100-125)	
Diastolic blood pressure, mm Hg, median (range)	70 (60-79)	70 (60-80)	
N-terminal pro-brain natriuretic peptide pg/ml, median (range)	1920 (744-4288)	1806 (719-3949)	
Glomerular filtration rate, ml/min/1.73m ² , median (range)	60 (46-73)	61 (46-73)	
Comments:			
<ul style="list-style-type: none"> • Beta-blockers were taken at some time during the study by 85% of the medical therapy group and by 84% of the CRT-P group. • Information on associations between baseline EQ-5D scores and baseline patient characteristics is reported but has not been data extracted.⁶⁶ • Baseline characteristics for the 735 participants who had an analysable echocardiographic 			

Participant characteristics ⁹	CRT-P + medical therapy, n= 409	Medical therapy, n= 404	p value
examination at baseline are presented in another paper ⁶⁹ on LV reverse modelling outcomes but have not been data extracted. The clinical characteristics of these participants are described as similar to the whole study population.			

RESULTS			
Outcomes ⁹	CRT-P + medical therapy, n= 409	Medical therapy, n= 404	HR or Difference in means (95% CI), p value
Death or unplanned hospitalisation for a cardiovascular event (primary outcome) n/N (%)	159/409 (39)	224/404 (55)	HR 0.63 (0.51 to 0.77), <0.001
Unplanned hospitalisation for a cardiovascular event (primary outcome), n/N (%) ^a	125/409 (31)	184/404 (46)	HR 0.61 (0.49 to 0.77), <0.001
Death from any cause n/N (%)	82/409 (20)	120/404 (30)	HR 0.64 (0.48 to 0.85), <0.002
Additional deaths during the extension phase ⁶⁴	19	34	
Deaths in main study + deaths in extension phase ⁶⁴	101/409 (24.7%, 7.9% per annum)	154/404 (38.1%, 12.2% per annum)	HR 0.60 (0.47 to 0.77), <0.0001
Principal cause of death, n/n deaths (%)			
- cardiovascular		167/202 (83)	
- non-cardiovascular		34/202 (17)	
- not classifiable		1/202 (0.5)	
Death attributed to worsening heart failure, n/n deaths (%)	33/82 (40)	56/120 (47)	
Death due to heart failure main study + extension phase ⁶⁴	38 deaths (3.0% per annum)	64 (5.1% per annum)	HR 0.55 (0.37 to 0.82), 0.003
Death classified as sudden	29/82 (35)	38/120 (32)	
Sudden deaths in the extension phase ⁶⁴	3/19	16/34	
Sudden deaths after main study + extension phase ⁶⁴	32 deaths (2.5% per annum)	54 (4.3% per annum)	HR 0.54 (0.35 to 0.84), 0.005
Mortality rate			
- 1 year	9.7%	12.6%	
- 2 years	18.0%	25.1%	
- 3 years ⁶⁴	23.6%	35.1%	
Death from any cause or unplanned hospitalisation with worsening heart failure, n/N (%)	118/409 (29)	191/404 (47)	HR 0.54 (0.43 to 0.68), <0.001
Unplanned hospitalisation with worsening heart failure, n/N (%) ^a	72/409 (18)	133/404 (33)	HR 0.48 (0.36 to 0.64), <0.001
Deaths in the first 90 days	12	15	
Heart transplantations ^b			
- emergency	1	3	
- elective	9	6	
Minnesota Living with Heart Failure score, mean value at 90 days (SD) ^c	31 (22)	40 (22)	Difference in means -10 (-8 to -12), <0.001

RESULTS					
Outcomes⁹	CRT-P + medical therapy, n= 409		Medical therapy, n= 404		HR or Difference in means (95% CI), p value
EuroQoL EQ-5D score, mean value at 90 days (SD) ^c	0.70 (0.28)		0.63 (0.29)		Difference in means 0.08 (0.04 to 0.12), <0.001
NYHA class, mean value at 90 days (SD) ^c	2.1 (1.0)		2.7 (0.9)		Difference in means 0.6 (0.4 to 0.7), <0.001
NYHA class at 18 months					
- class I	105		39		
- class II	150		112		
- class III or IV	80		152		
	Difference^d in means (95% CI)				p-value
LVEF %, at 3 months ^e	+3.7 (3.0 to 4.4)				<0.001
- at 18 months ^e	+6.9 (5.6 to 8.1)				<0.001
Heart rate, bpm, at 3 months	+1.1 (-1.2 to 3.4)				0.33
- at 18 months	+1.0 (-1.5 to 3.6)				0.43
Systolic blood pressure, mm Hg, at 3 months	+5.8 (3.5 to 8.2)				<0.001
- at 18 months	+6.3 (3.6 to 8.9)				<0.001
Diastolic blood pressure, mm Hg, at 3 months	+1.5 (0.1 to 2.9)				0.03
- at 18 months	+1.3 (-1.8 to 4.4)				0.42
Interventricular mechanical delay, msec, at 3 months ^e	-21 (-25 to -18)				<0.001
- at 18 months ^e	-21 (-25 to -17)				<0.001
Left ventricular end-systolic index, ml/m ² , at 3 months	-18.2 (-21.2 to -15.1)				<0.001
- at 18 months	-26.0 (-31.5 to -20.4)				<0.001
Mitral-regurgitation area, at 3 months	-0.051 (-0.073 to -0.028)				<0.001
- at 18 months	-0.042 (-0.070 to -0.014)				0.003
N-terminal pro-brain natriuretic peptide, pg/ml, at 3 months	-225 (-705 to -255)				0.36
- at 18 months	-1122 (-1815 to -429)				<0.002
LEVF %, median (IQR) ⁶⁹	IHD n=168	non-IHD n=197	IHD n=135	non-IHD n=235	
- baseline	25 (22-29)	24 (21-29)	26 (22-30)	24 (21-29)	0.1867 (IHD vs non-IHD)
- mean (SD) change at 18 months from baseline,% ^f	6.1 (1.2)	10.9 (1.5)	1.3 (0.7)	2.4 (1.7)	0.003 for interaction between CRT and aetiology

Comments: ^a these events contributed to the primary or secondary outcome, ^b all emergency heart transplantation patients died, the elective heart transplantation patients were all alive 7 days after transplantation at which point their data were censored from the analysis, ^c difference in means is for the CRT-P group as compared to the medical therapy group, ^d differences were not adjusted for the higher mortality rate in the medical therapy group. A plus sign indicates CRT-P value greater than medical therapy group value, a minus sign indicates CRT-P value smaller than medical therapy group value. ^e Similar but not identical data also presented by Ghio et al.⁶⁹ ^f values estimated using digitising software by reviewer from figure.⁶⁹ Not stated, but error bars presumed to show SD.

- States there were 384 unplanned hospitalisations for a major cardiovascular event in the medical

therapy group and 222 in the CRT-P group. Although not explicitly stated it is assumed that since these values differ from those in the above table that these include all events (not just the first event which contributed to the outcome above).

- Of the 383 events in the total trial population contributing to the primary outcome of death or unplanned hospitalisation death was the primary event in 74 patients and hospitalisation in 309.
- CRT-P = 12 and OPT = 10 had unplanned hospitalisations for a major cardiovascular event that occurred within 10 days after randomisation and these hospitalisations were therefore not counted as primary end points.
- Kaplan-Meier estimates of time to primary end point and the principal secondary outcome are presented but have not been data extracted. Kaplan Meier-estimates also presented including the extension phase for time to all-cause mortality, time to death from worsening heart failure, and time to death from sudden death but these have not been data extracted.
- The 72 CRT-P group participants with unplanned hospitalisation with worsening heart failure had 122 hospitalisations in total, whereas the 133 participants in the medical therapy group had 252 in total.
- Outcomes from a multivariable analysis⁶⁵ of 15 baseline variables and 8 markers of response which investigated whether these factors could predict all-cause mortality have not been extracted. Similarly outcomes from single and multiple variable analyses⁶⁸ of electrocardiographic measures which assessed whether surface electrocardiogram can predict outcome have not been data extracted

Ejection fraction outcomes for subgroups with or without ischaemic heart disease have been extracted from the LV reverse remodelling paper⁶⁹ but not for subgroups with restrictive/non-restrictive left ventricular filling or measures of right ventricular dysfunction. Other outcomes (end-diastolic and end-systolic volumes, severity of mitral regurgitation, predictors of long-term response) have not been extracted.

QOL RESULTS⁶⁶

Outcomes	CRT-P + medical therapy, n= 409	Medical therapy, n= 404	Mean difference (95% CI), p value
Mean QALY (95% CI)			
- 3 months	0.16 (0.15-0.16)	0.15 (0.14-0.15)	0.01 (0.001 to 0.018), 0.285
- 18 months	0.95 (0.91-0.99)	0.82 (0.78-0.86)	0.13 (0.07 to 0.018), <0.0001
- End of study	1.45 (1.38-1.53)	1.22 (1.15-1.29)	0.23 (0.13 to 0.33), <0.0001
Mean life-years (95% CI)			
- 3 months	0.241 (0.238-0.244)	0.241 (0.238-0.244)	0.0003 (-0.004 to 0.0045), 0.90
- 18 months	1.37 (1.34-1.40)	1.33 (1.29-1.37)	0.04 (-0.01 to 0.09), 0.13
- End of study	2.07 (1.99-2.15)	1.96 (1.88-2.05)	0.10 (-0.01 to 0.22), 0.07 ^g
EQ-5D (95% CI)			
- baseline	0.60 (0.58-0.63)	0.60 (0.57-0.63)	-
- 3 months	0.69 (0.66-0.72)	0.61 (0.59-0.64)	0.08 (0.04 to 0.11), <0.0001
- 18 months	0.61 (0.58-0.64)	0.51 (0.48-0.54)	0.10 (0.06 to 0.15), <0.0001
- End of study	0.56 (0.52-0.59)	0.43 (0.39-0.46)	0.13 (0.08 to 0.18), <0.0001 ^h
MLWHFQ (95% CI)			
-baseline	44.6 (42.5-46.7)	43.7 (41.5-45.8)	-
- 3 months	30.1 (27.9-32.3)	38.9 (36.6-41.2)	-10.6 (-8.1 to -13.1), <0.0001 ⁱ
- 18 months	28.4 (26.2-30.5)	36.0 (33.5-38.5)	-10.7 (-7.6 to -13.8), <0.0001 ⁱ
- End of study	27.2 (24.9-29.5)	35.1 (32.6-37.6)	-10.1 (-6.8 to -13.3), <0.0001 ⁱ
Mean days in hospital by 3 months	7.5 median 4 (IQR 2-8)	3.4 median 0 (IQR 0-1)	
Days in hospital after 3	222	384	

QOL RESULTS⁶⁶			
Outcomes	CRT-P + medical therapy, n= 409	Medical therapy, n= 404	Mean difference (95% CI), p value
months			
Mean days in hospital overall during entire study (median 29.6 months)	20.7 median 9 (IQR 4-26)	22.4 median 9 (IQR 0-31)	

Comments: ^g p-value based on restricted mean survival used to estimate QALYs. This is not the best estimator of survival differences between groups (statistically inefficient), see instead all-cause mortality above. ^h Decline in EQ-5D despite maintained effect with MLWHFQ scores is because death has a health use of zero in EQ-5D and is not included in the MLWHFQ. ⁱ MLWHFQ scores include last value carried forward for missing items. Patients who died not included. Difference between groups accounts for baseline NYHA class and MLWHFQ score.

- Baseline EQ-5D score [mean 0.60 (95% CI 0.58-0.62)] is lower than a representative age-matched general population (mean 0.78, 95% CI 0.76-0.80)
- In the CRT group at 3 months most QALYs gained in comparison to the control group came from improved QoL. With longer follow up deaths in the control group caused a larger proportion of lost QALYs and a larger proportion of the gain with CRT.
- Data presented for proportion of patients with improved, same, or worse EQ-5D scores but not data extracted (incomplete data, 320/409 in CRT group, 315/404 in medical therapy group). Data presented in a figure for proportion of patients with deterioration, improvement or same MLWHFQ score presented by not extracted.
- Figure showing that by 3 months CRT reduced proportion of patients reporting problems in all EQ-5D dimensions has not been data extracted.
- Data showing that subgroup analyses (predefined) showed there was little heterogeneity in the effect of CRT on QALYs are reported but not extracted.
- In first 3 months CRT group spent more days in hospital due to device implantation but overall spent fewer days due to small number of unplanned hospitalisation for major cardiovascular events.
- There are minor differences between the QoL results reported in the main trial publication⁹ and those reported in this paper.⁶⁶ The reasons for these minor differences are not clear.

Adverse effects of treatment⁹	CRT-P + medical therapy, n= 409	Medical therapy, n= 404	p value
Device related death	n=1, heart failure aggravated by lead displacement	n=1, septicaemia after receiving a device	
Most common adverse device- or procedure- related events, n patients			
- lead displacement	24		
- coronary-sinus dissection	10		
- pocket erosion	8		
- pneumothorax	6		
- device related infection	3		
Worsening heart failure, n patients	191	263	<0.001
Atrial arrhythmias or ectopy, n patients	64	41	0.02
Comments:			
<ul style="list-style-type: none"> • Frequency of respiratory tract infections, hypotension, falls or syncope, acute coronary syndromes, renal dysfunction, ventricular arrhythmias or ectopy, and neurologic events were similar in the two groups, numerical data not presented. 			

- More detailed reporting of adverse events in the paper by Gras *et al.*⁶⁷ suggests that some of the CRT-P group adverse events reported above may have occurred in participants who crossed over from medical therapy to CRT-P but some of these data don't appear to match up with those data above reported from the main paper⁹ and thus have not been extracted.

Subgroup analyses ⁹	Patients with event/ Total number of patients	Hazard ratio (95% CI)
Overall with primary end point	383/813	0.63 (0.51-0.77)
Age ^j < 66.4 year	163/406	0.55 (0.40-0.75)
≥ 66.4 year	220/407	0.68 (0.52-0.89)
Sex male	290/597	0.62 (0.49-0.79)
Sex female	93/215	0.64 (0.42-0.97)
NYHA class III	349/763	0.64 (0.52-0.80)
NYHA class IV	34/50	0.50 (0.25-1.01)
Dilated cardiomyopathy - No	238/443	0.68 (0.53-0.88)
Dilated cardiomyopathy - Yes	145/370	0.51 (0.36-0.73)
Systolic blood pressure ^j < 117 mmHg	208/401	0.60 (0.46-0.80)
Systolic blood pressure ≥ 117 mmHg	170/402	0.66 (0.48-0.89)
NT-BNP < 214.5 pg/ml	122/366	0.53 (0.36-0.76)
≥ 214.5 pg/ml	224/366	0.70 (0.54-0.91)
Ejection fraction ^j < 24.7%	205/372	0.65 (0.49-0.86)
≥ 24.7%	152/373	0.62 (0.44-0.85)
End-systolic volume index ^j < 119.2 ml/m ²	156/366	0.71 (0.52-0.98)
≥ 119.2 ml/m ²	193/366	0.54 (0.40-0.73)
QRS interval < 160 msec	152/290	0.74 (0.54-1.02)
≥ 160 msec	222/505	0.60 (0.46-0.79)
Interventricular mechanical delay ^j < 49.2 msec	199/367	0.77 (0.58-1.02)
≥ 49.2 msec	147/368	0.50 (0.36-0.70)
Mitral-regurgitation area ^j < 0.218	114/302	0.86 (0.60-1.25)
≥ 0.218	175/303	0.56 (0.41-0.75)
Glomerular filtration rate ^j < 60.3 ml/min/1.73m ²	196/369	0.67 (0.50-0.89)
≥ 60.3 ml/min/1.73m ²	142/370	0.57 (0.40-0.80)
Beta-blockers, No	131/227	0.72 (0.51-1.02)
Yes	252/586	0.59 (0.46-0.76)
Spirolactone, No	166/356	0.58 (0.43-0.79)
Yes	217/457	0.67 (0.51-0.88)
Loop diuretics < 80 mg of furosemide or equivalent	181/461	0.56 (0.42-0.76)
≥ 80 mg of furosemide or equivalent	202/352	0.69 (0.53-0.92)
Digoxin, No	218/467	0.66 (0.50-0.86)
Yes	165/346	0.59 (0.43-0.81)

Comments: ^j divided according to the median value in the study population

- All analyses were stratified according to NYHA class, except the subgroup analysis of NYHA class.
- For some data many patients had results at the median value and this led to some inequality in the sizes of subgroups (e.g. QRS interval).
- There were missing baseline data for sex, systolic blood pressure, NT-BNP, ejection fraction, end-systolic volume index, QRS interval, interventricular mechanical delay, mitral-regurgitation area and glomerular filtration rate. Consequently these subgroup numbers do not total 813.
- A similar subgroup analysis was conducted after the extension phase for deaths only (whereas data above are for the composite primary outcome of death from any cause or an unplanned hospitalisation for major cardiovascular event). As the extension phase subgroup analysis is not

for the primary outcome and because it showed no heterogeneity of effect these data have not been extracted.⁶⁴

Methodological comments

- *Allocation to treatment groups*: Randomisation stratified by NYHA class & carried out by an independent clinical-research organisation (Quintiles, Dublin) using a minimisation procedure.⁹
- *Blinding*: Not blinded.⁹ However members of end-points committee (who classified all hospitalisations and some adverse events) were not aware of patients' treatment assignments. Adverse events procedure- or device-related classified by an unblinded independent expert.⁹
- *Comparability of treatment groups*: Baseline characteristics similar.
- *Method of data analysis*: All prespecified analyses by ITT. Time to event calculated by Kaplan-Meier method and analysed with Cox proportional-hazard models (baseline NYHA as a covariate). Continuous data (including QoL⁶⁶, and echocardiographic outcomes⁶⁹) analysed by mixed models which included baseline variables as patient-level covariates and study centres as random effects. Dichotomous outcomes analysed by nonlinear mixed models with NYHA class a patient-level covariate and study centres as random effects. Adverse event rates compared by Fisher's exact test. Two planned interim analyses were conducted by the data and safety monitoring board with the use of non-symmetric stopping rules.⁹ Missing QoL scores imputed using EQ-5D and MLWHFQ scores, sex, NYHA class, interventricular mechanical delay and mitral regurgitation at baseline. Zero assigned at time of patient death or time of heart transplantation.⁶⁶ Quality of life years calculated for each patient as the area under the curve estimated through linear interpolation of individual patient-level estimates of health utility based on EQ-5D scores at baseline, 3 months 18 months and end of study.⁶⁶
- *Sample size/power calculation*: Statistical power of 80% to identify a 14% relative reduction or a 5.7% point reduction in the rate of events (α value 0.025, 300 events predicted).⁹
- *Attrition/drop-out*: Of the 409 patients assigned to CRT-P, an attempt at implantation was made in 404. One patient died before the procedure and in the other 4 cases the patient or the investigator decided not to proceed with implantation. A CRT-P device was implanted and activated in 390 (95%) of patients, 6 patients had an unplanned hospitalisation for cardiovascular reasons (reached primary end point) before the device was activated, and 8 patients received a CRT-D. In 43 patients from the medical therapy group implantation of a CRT-P device was attempted, and in 23 patients implantation of a CRT-D device was attempted (both attempted in one patient). The device was activated in 50 patients. In 10 cases the device was programmed to provide standard pacemaker or ICD only functions to avoid crossover. In the remaining 5 patients implantation was unsuccessful. In 19 patients (5%) the device was activated before the primary end point was reached, 8 subsequently reached the primary end point (6 died). Among the 31 patients who reached the primary end point before the device was activated, 7 subsequently died.⁹ At the end of the extension phase the survival of one participant in the medical therapy group was unknown.⁶⁴ During the extension phase 4 patients who had received a device in the main phase had it activated, and 41 additional patients had a CRT device implanted and activated. Therefore at the end of the extension phase a total of 95/404 participants in the medical therapy group had received a CRT device and had it activated, of whom 22 (23.2%) had died.⁶⁴ In the paper reporting LV reverse modelling outcomes⁶⁹ baseline echocardiograms were not analysable for 78 (10%) of participants. Reasons were baseline data not received by core echocardiographic laboratory n=36, damaged video tape n=4, poor quality examination n=38.
- *Other*: extension phase was declared before study closure and without knowledge of the results.⁶⁴

General comments

- *Generalisability*: Left ventricular systolic dysfunction and cardiac dyssynchrony who have moderate or severe heart failure and who are in sinus rhythm.
- *Outcome measures*: appear appropriate
- *Inter-centre variability*: Not commented on but data analysis included study centres as random effects as noted above in method of data analysis which presumably took this into account.⁹
- *Conflict of interests*: All the authors had conflicts of interest which are stated at the end of the report.⁹ The sponsor had no access to the database and did not participate in the analysis of the results or the writing of the article.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^k	Support for Judgement
Selection bias		
Random sequence generation	Low risk	Randomisation used a minimisation procedure
Allocation concealment	Low risk	Allocation by independent organisation
Performance bias		
Blinding of participants and personnel	High risk	Unblinded trial
Detection bias		
Blinding of outcome assessment - mortality and hospitalisation	Low risk	End-points committee not aware of patients' treatment assignments
- echocardiographic outcomes	High risk	Unblinded trial. No indication that core laboratory quantifying these data were unaware of treatment assignment.
- adverse events	Unclear risk	Some adverse events (not specified which) classified by end-points committee unaware of patients' treatment assignments but other procedure- or device-related adverse events classified by an unblinded independent expert.
Attrition bias		
Incomplete outcome data addressed - mortality, hospitalisation, echocardiographic outcomes	Low risk	Analyses by intention to treat. Cross overs reported.
- QoL	Unclear risk	Missing QoL scores imputed but amount of missing data not reported.
- LV reverse remodelling outcomes	Unclear risk	Not all participants included because not all had a readable baseline echocardiogram (10% missing). States clinical characteristics of groups similar to those of total trial population. Reasons for missing data not reported for each group, only overall so not clear if reasons for missing data similar between groups.
Reporting bias		
Selective reporting	Low risk	Rationale, design and end-points paper available. ⁶³ Primary and secondary outcomes appear to have been reported as planned. Separate papers report outcomes. ^{9;64;66;69}
Other bias		
Other sources of bias	Low risk	

^k 'Low risk', 'high risk' or 'unclear risk' of bias

COMPANION

Reference and design	Intervention and Comparator	Participants	Outcome measures
Bristow et al., 2004 ¹² Carson et al., 2005 ⁷⁰ FDA report ⁷¹ Anand et al., 2009 ¹⁰	<i>Intervention:</i> OPT and either CRT-P Guidant model 1241 Contak TR or CRT-D Guidant model 1823 Contak CD	<i>Indication for treatment:</i> Advanced chronic heart failure and intraventricular conduction delays <i>Number of randomised</i>	<i>Primary outcomes:</i> All-cause mortality and all cause hospitalisation (composite end point) <i>Secondary outcomes:</i> Cardiac morbidity

<p>Bristow et al., 2000⁷²</p> <p>COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure)</p> <p><i>Study design:</i> RCT</p> <p>USA</p> <p><i>Number of centres:</i> 128</p> <p><i>Funding:</i> Guidant corporation, St Paul, Minn.</p>	<p><i>Comparator:</i> OPT: loop diuretics, ACE inhibitors, spironolactone, beta-blockers (unless not tolerated). Also permitted: booster diuretics, angiotensin-receptor blockers/angiotensin II inhibitors, digoxin, alternate vasodilators, calcium channel blockers.</p> <p><i>Other interventions used:</i> None reported</p>	<p><i>participants:</i> n = 1520 CRT-P, n=617 CRT-D, n=595 OPT, n=308</p> <p><i>Inclusion criteria:</i> NYHA class III, IV; QRS ≥120 ms; PR interval > 150 ms; LVEF ≤35%; OPT; LVEDD ≥ 60 mm; ≥18 years; sinus rhythm.</p> <p><i>Exclusion criteria:</i>⁷² ICD indications; Life expectancy < 6 months; chronic atrial tachyarrhythmias; indications for antibradycardia pacing; unexplained syncope; MI within 60 days of randomisation; uncontrolled blood pressure; surgically uncorrected primary valvular HD; progressive or unstable angina; pregnancy; hypertrophic obstructive cardiomyopathy; amyloid disease; tricuspid prosthesis; hospitalisation for HF > 4 hours in previous month.</p>	<p>All-cause mortality</p> <p>Cardiac hospitalisation</p> <p>Six minute walk</p> <p>NYHA class before and after treatment</p> <p>Adverse events</p> <p>Health related QoL – Minnesota Living with Heart Failure questionnaire</p> <p><i>Method of assessing outcomes:</i> First events for hospitalisation related to cardiovascular causes or heart failure, use of outpatient iv medication and cause of death adjudicated by end-points committee.</p> <p>Clinical evaluations at baseline, 1 week, 1 month, then 3 monthly⁷²</p> <p><i>Length of follow-up, median:</i> Primary endpoint: CRT-P 16.2 months (vs OPT p<0.001) CRT-D 15.7 months (vs OPT p<0.001) OPT 11.9 months</p> <p>Mortality: CRT-P 16.5 months (vs OPT p<0.028) CRT-D 16.0 months (vs OPT p<0.129) OPT 14.8 months</p> <p><i>Recruitment:</i> Jan 2000-Dec 2002</p>
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Participant characteristics (Pre-randomisation/implant)	CRT-P, n=617	CRT-D, n=595	OPT, n=308	p value
Age years, median	67	66	68	
Male, %	67	67	69	
Ethnicity	not reported	not reported	not reported	
Severity of heart failure, %: - NYHA class III - NYHA class IV (calculated by reviewer)	87 13	86 14	82 18	
QRS interval, msec, median	160	160	158	
LVEF, median	0.20	0.22	0.22	
LVEDD, mm, median	68	67	67	

Participant characteristics (Pre-randomisation/implant)	CRT-P, n=617	CRT-D, n=595	OPT, n=308	p value
Heart rate, bpm, median	72	72	72	
Blood pressure, mm Hg, median				
- systolic	110	112	112	
- diastolic	68	68	64	
Ischemic cardiomyopathy, %	54	55	59	
Pharmacological therapy, %				
- Beta-blocker	68	68	66	
- Spironolactone	53	55	55	
- ACE inhibitor	70	69	69	
- ACE inhibitor or angiotensin blocker	89	90	89	
- Loop diuretic	94	97	94	
Left branch bundle block, %	69	73	70	
Right branch bundle block, %	12	10	9	
Duration of heart failure, yr, median	3.7	3.5	3.6	
6 min walk distance, m, median	274	258	244	
Diabetes, %	39	41	45	
Comments: states no clinically significant differences between groups				
RESULTS				
Outcomes	CRT-P, n=617	CRT-D, n=595	OPT, n=308	HR (95% CI), OPT vs CRT-P; OPT vs CRT-D
Composite endpoint (all-cause mortality or hospitalisation) (primary end point) ^a				
- number of events during study	414	390	216	
- 12 month rate	56%	56%	68%	0.81 (0.69, 0.96), 0.014; 0.80 (0.68,0.95), 0.010
All-cause mortality ^a				
- events during entire study	131/617 (21.2%)	105/595 (17.6%)	77/308 (25.0%)	
- 12month all-cause mortality rate	15%	12%	19%	0.76 (0.58,1.01), 0.059; 0.64 (0.48, 0.86), 0.003
Death or hospitalisation due to cardiovascular causes ^a				
- number of events	338	312	188	
- 12 month event rate	45%	44%	60%	0.75 (0.63, 0.90), 0.002; 0.72 (0.60, 0.86), <0.001
Death or hospitalisation due to heart failure ^a				
- number of events	237	212	145	
- 12 month event rate	31%	29%	45%	0.66 (0.53,0.87), 0.002; 0.60 (0.49, 0.75), <0.001
<ul style="list-style-type: none"> ^aKaplan-Meier curves presented. Subgroup analyses presented according to baseline characteristics – not data extracted 				

Cause of death, ⁷⁰ n (% of patients) [% of deaths]	CRT-P, n=617	CRT-D, n=595	OPT, n=308	HR (95% CI), OPT vs CRT-P; OPT vs CRT-D
- Cardiac ^b	109 (17.1) [83.2]	76 (12.8) [72.4]	54 (18.8) [75.3]	0.334; 0.006
- sudden cardiac death ^b	48 (7.8) [36.6]	17 (2.9) [16.2]	18 (5.8) [23.4]	1.21 (0.70, 2.07), 0.485; 0.44 (0.23, 0.86), 0.020
- pump failure ^b	53 (8.6) [40.5]	52 (8.7) [49.5]	34 (11.0) [44.2]	0.71 (0.46,1.09), 0.112; 0.73 (0.47, 1.11), 0.143
- ischemic	2 (0.3) [1.5]	4 (0.7) [3.8]	4 (1.3) [5.2]	
- cardiac procedure	6 (1.0) [4.6]	2 (0.3) [1.9]	2 (0.6) [2.6]	
- others	0	1 (0.2) [1.0]	0	
- Vascular	5 (0.8) [3.8]	3 (0.5) [2.8]	0	
- Non-cardiac ^b	14 (2.3) [10.7]	21 (3.5) [20.0]	11 (3.6) [14.3]	0.122, 0.717
- Unknown	3 (0.5) [2.3]	5 (0.8) [4.8]	8 (2.6) [10.4]	
• ^b Kaplan-Meier curves of time to first event presented but not extracted				
Hospital admissions: ¹⁰	CRT-P, n=617	CRT-D, n=595	OPT, n=308	P value OPT vs CRT-P; OPT vs CRT-D
Patients hospitalised at least once, n/N (%)				
- All hospital admissions	388/617 (63%)	372/595 (63%)	199/308 (65%)	0.02; ^c 0.03 ^c
- Cardiac	301/617 (49%)	284/595 (48%)	164/308 (53%)	<0.01; ^c <0.01 ^c
- Heart failure	179/617 (29%)	166/595 (28%)	112/308 (36%)	<0.01; ^c <0.01 ^c
- Non-cardiac	222/617 (36%)	207/595 (35%)	84/308 (27%)	
Number of admissions (% of total admissions), number of average admissions per patient year of follow-up				
- All hospital admissions	993 (n/a), 1.25	919 (n/a), 1.20	516 (n/a), 1.59	
- Cardiac	628 (63), 0.79	580 (63), 0.76	338 (75), 1.20	
- Heart failure	329 (33), 0.41	333 (36), 0.43	235 (46), 0.73	
- Noncardiac	365 (37), 0.46	339 (37), 0.44	126 (24), 0.39	
Hospitalisation time, days: average days per patient-year of follow-up (average length of stay per admission)				
- All hospital admissions	8.3 (6.7)	8.6 (7.2),	11.0 (6.9)	
- Cardiac	5.2 (6.5)	5.5 (7.2)	8.1 (6.8)	
- Heart failure	3.6 (8.6)	3.8 (8.8)	5.9 (8.2)	
- Non-cardiac	3.2 (6.9)	3.2 (7.2)	2.8 (7.1)	p=ns

Cardiac procedure, number of hospital admissions per patient year ^d	0.13	0.09	0.24	<0.01
- CRT implants, n (% of procedures)			33/78 (42%)	
- Electrophysiological studies			13/78 (17%)	
- pacemaker / ICD implants	13/101 (13%)		10/78 (13%)	
- heart transplants			5/78 (6%)	
- other			15/78 (19%)	
- lead revision	42/101 (42%)	36/69 (52%)		
<ul style="list-style-type: none"> • Total follow-up time for hospital admissions: OPT 324 years, CRT-P 793 years, CRT-D 768 years. • ^c Analysis adjusted for multiple hospital admissions, follow-up time and competing risk of death. Hospitalisation curves presented. States that no significant differences were found in any of the end-points for CRT-P vs CRT-D. • Predictors of hospitalisation reported but not data extracted. • ^dStates that after hospitalisations for heart failure, cardiac procedures were the next most common cause for hospitalisation. Selected procedures are reported in the paper. 				
	CRT-P, n=617	CRT-D, n=595	OPT, n=308	CRT-P vs OPT; CRT-D vs OPT
Increase in 6 min walk, m, mean change (SD)				
- 3 months	(n=422) 33 (99)	(n=420) 44 (109)	(n=170) 9 (84)	p<0.001; p<0.001
- 6 months	(n=373) 40 (96)	(n=378) 46 (98)	(n=142) 1 (93)	p<0.001; p<0.001
Increase in quality of life ^e , %, mean change (SD)				
- 3 months	(n=510) -24 (27)	(n=514) -24 (28)	(n=243) -9 (21)	p<0.001; p<0.001
- 6 months	(n=460) -25 (26)	(n=478) -26 (28)	(n=207) -12 (23)	p<0.001; p<0.001
Proportion of patients with improvement in NYHA class symptoms, %				
- 3 months	(n=551) 58	(n=543) 55	(n=242) 24	p<0.001; p<0.001
- 6 months	(n=489) 61	(n=497) 57	(n=199) 38	p<0.001; p<0.001
	CRT-P, n=617	CRT-D, n=595		
Duration of procedure, mins, median (patients randomised after 1/7/2001)	(n=nr) 164	(n=nr) 176		
Comments: <ul style="list-style-type: none"> • ^e21 questions rated on a 6-point scale, total score 105, higher scores indicate poorer quality of life. • Median changes in systolic blood pressure from baseline to 3, 6, 12 months in CRT-P and CRT-D were significantly better than the OPT group. No significant changes in diastolic blood pressure in any group (data presented in figure, not data extracted). 				
Adverse effects of treatment	CRT-P, n=617	CRT-D, n=595	OPT, n=308	p value: CRT-P vs OPT; CRT-D vs OPT

Unsuccessful implantation	78/617 (13%)	54/595 (9%)		
Deaths due to procedural complications	5/615 (0.8%)	3/595 (0.5%)		
Mortality rate 30 days after randomisation, %	1.0%	1.8%	1.2%	0.34; 0.97
Moderate or severe adverse event from any cause ^f	66%	69%	61%	0.15; 0.03
Moderate or severe adverse event related to implantation procedure	10%	8%		
- coronary venous dissection	0.3%	0.5%		
- coronary venous perforation	1.1%	0.8%		
- coronary venous tamponade	0.5%	0.3%		
Withdrawal rate				
- for all patients	6%	7%	26%	
- for patients who had not reached primary endpoint	2%	2%	13%	
Comments: [†] CRT-P vs CRT-D, p=0.042. More detailed adverse event reporting for CRT-D available in FDA report. ⁷¹				

Methodological comments

- *Allocation to treatment groups*: Randomisation ratio 1:2:2 (OPT: CRT-P: CRT-D). Randomisation stratified by centre and beta –blocker use.
- *Blinding*: Patients, physicians, statisticians, data management group and safety and monitoring board not blinded. Steering committee, end-points committee and sponsor were unaware of assignments.
- *Comparability of treatment groups*: Groups similar at baseline.
- *Method of data analysis*: All analyses ITT. Efficacy analyses based on time to first event (unless otherwise stated), differences determined by log-rank statistic, time to event used Kaplan-Meier method. Nominal p values and p values adjusted for sequential monitoring reported. Hazard ratios were unadjusted for covariates, Wald chi-square statistic used for subgroups. Baseline differences were evaluated with the Wilcoxon rank-sum test for continuous and ordered data and Pearson's chi-square test was used for categorical data.
- *Sample size/power calculation*: Trial designed with 2200 participants to detect a reduction of 25% in the primary end point and rate of death from any cause at an alpha value of 0.02 in CRT-P group and 0.03 in CRT-D group, each compared with OPT. With a target of 1000 primary events, trial had statistical power of > 90% for primary end point and 80% for secondary end point. Trial stopped early when pre-established boundaries had been crossed. 1520 participants had been randomised and 1000 primary end points already or almost met.
- *Attrition/drop-out*: Substantial withdrawals from OPT group (see table above) to receive commercially available implants, due to arrhythmia or heart failure. Patients contacted to consent to collection of data for duration of study, data censored if this information could not be obtained. Status for primary end point through end of study known for 91% OPT group and 99% in each of other groups, data on mortality complete for 96% OPT group and 99% of each of other groups.

General comments

- *Generalisability*: People with advanced heart failure and increased QRS interval.
- *Outcome measures*: States that the composite end point based on both mortality and hospitalisation was chosen to avoid the analytic difficulty encountered with competing risk: death precludes subsequent hospitalisation for chronic heart failure decompensation.⁷² Demonstration of a favourable hospitalisation outcome may be offset by the inability to survive, and benefit of survival may be offset by incremental chronic heart failure morbidity requiring recurrent hospitalisations.
- *Inter-centre variability*: Not reported.
- *Conflict of interests*: States sponsor had no role in data analysis.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Details not reported.
Allocation concealment	Unclear	Details not reported.
Performance bias		
Blinding of participants and personnel	High risk	No blinding.
Detection bias		
Blinding of outcome assessment	Low risk	Steering committee and end-points committee unaware of assignment. Outcomes objective and unlikely to be influenced.
Attrition bias		
Incomplete outcome data addressed	Low risk	ITT analysis. Data censored for people who withdrew and data could not be obtained.
Reporting bias		
Selective reporting	Low risk	protocol published, no evidence of missing outcomes
Other bias		
Other sources of bias	Low risk	

^a 'Low risk', 'high risk' or 'unclear risk' of bias

MIRACLE

Reference and design	Intervention and Comparator	Participants	Outcome measures
Abraham <i>et al.</i> , 2002 ¹¹ St John Sutton <i>et al.</i> , 2003 ⁷³ Abraham 2000 ⁷⁴ FDA report ⁷⁵ MIRACLE (Multicenter InSync Randomised Clinical Evaluation) <i>Study design:</i> RCT USA & Canada <i>Number of centres:</i> 45 <i>Funding:</i> Medtronic, Inc,	<i>Intervention:</i> Optimal medical therapy, CRT-P VDD 30. InSync model 8040, Medtronic Inc. 3 pacing leads. <i>Comparator:</i> Optimal medical therapy CRT-P OFF: VDI 30 (ventricular paced, A&V sensed, no response to sensing) InSync model 8040, Medtronic Inc. <i>Other interventions used:</i>	<i>Indication for treatment:</i> Moderate to severe heart failure and a prolonged QRS interval <i>Number of randomised participants:</i> n = 453 CRT-P, n= 228 OPT, n= 225 <i>Inclusion criteria:</i> ^{11;74} Heart failure due to ischemic or non-ischemic cardiomyopathy for > 1mth; NYHA III or IV; LVEF ≤ 35%; LVEDD ≥ 55 mm; QRS interval ≥ 130 msec ≥ 18 yrs; 6-min walk distance ≤450m; optimal medical therapy. <i>Exclusion criteria:</i> ^{11;74} Pacemaker or ICD; indication for or contra-indication to cardiac pacing; cardiac or cerebral ischemic	<i>Primary outcomes:</i> NYHA class QoL 6 minute walk distance <i>Secondary outcomes:</i> All-cause mortality Heart failure hospitalisations Exercise capacity – peak O ₂ consumption, time on treadmill LVEF Left ventricular end diastolic dimension QRS duration Severity of mitral regurgitation Clinical composite response (improved, worsened or unchanged) An analysis of death or worsening heart failure (as safety variables), Number of days spent in hospital <i>Method of assessing</i>

Minneapolis, Minn	Medication for heart failure for both groups kept constant	event \leq 3-months; AF \leq 1 month; severe primary pulmonary disease; systolic blood pressure >170 or <80 mmHg; heart rate >140 bpm, serum creatinine >3.0 mg/deciliter, serum aminotransferase >3 times upper limit of normal; unstable angina, acute MI or coronary surgery \leq 3 months; life expectancy $<$ 6 months.	<p><i>outcomes:</i> Questionnaires at baseline, 1, 3 & 6 months. Clinical Events Review committee adjudicated adverse events / endpoints.⁷⁴</p> <p><i>Length of follow-up:</i> 6 months</p> <p><i>Recruitment:</i> Nov 1998 - Dec 2000</p>
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Participant characteristics (pre-randomisation and \leq 7 days pre-implantation)	CRT-P, n=228	OPT, n=225	p value
Age years, mean (SD)	63.9 (10.7)	64.7 (11.2)	
Gender, male n (%)	68	68	
Ethnicity, white race %	90	91	
Ischemia, %	50	58	
NYHA class III %	90	91	
LVEF %, mean (SD)	21.8 (6.3)	21.6 (6.2)	
Duration of QRS interval, msec, mean (SD)	167 (21)	165 (20)	
Heart rate, bpm, mean (SD)	73 (13)	75 (13)	
Left ventricular end diastolic dimension, mm, mean (SD)	70 (10)	69 (10)	
Area of mitral regurgitant jet, cm ² , mean (SD)	7.6 (6.4)	7.2 (4.9)	
Distance walked in 6 minutes, m, mean (SD)	305 (85)	291 (101)	
Minnesota Living with Heart Failure score (0 to 105, higher scores = more severe impairment)	59 (20)	59 (21)	
Total exercise time, sec, mean (SD)	484 (209)	462 (217)	
Peak exercise consumption, ml/kg bodyweight/min, mean (SD)	14.0 (3.5)	13.7 (3.8)	
Systolic blood pressure, mm Hg, mean (SD)	114 (18)	115 (18)	
Diastolic blood pressure, mm Hg, mean (SD)	69 (10)	68 (10)	
Receiving digitalis, %	78	79	
Receiving diuretic agents, %	94	93	
Receiving ACE inhibitors or angiotensin-receptor antagonists, %	93	90	
Receiving beta-blockers, %	62	55	
Comments: groups similar at baseline			

RESULTS			
Outcomes (at 6 months)	CRT-P, n=228	OPT, n=225	HR (CI 95%) p value
All-cause mortality at 6 month	12/228	16/225	0.73 (0.34 to 1.54), 0.40
Hospitalisations for worsening heart failure			
- at 6 months (people)	18/228	34/225	0.50 (0.28 to 0.88), 0.02
- at 6 months (events)	25/228	50/225	
- total number of days	83	363	
Death or worsening heart failure requiring hospitalisation	28/228	44/225	0.60 (0.37 to 0.96), 0.03

Death or worsening heart failure requiring hospitalisation or intravenous treatment	36/228	55/225	0.61 (0.40 to 0.93), 0.02
Worsening heart failure leading to use of intravenous:			
- diuretic agents	13/228	24/225	0.51 (0.26-1.00), 0.05
- vasodilators or positive inotropic agents	6/228	14/225	0.41 (0.16 to 1.08), 0.06
- medication for heart failure	16/228	35/225	0.43 (0.24 to 0.77), 0.004
Change in NYHA class (primary outcome)			<0.001
- improved ≥ 2 classes, n (%)	34/211 (16)	12/196 (6)	
- improved 1 class	109/211 (52)	62/196 (32)	
- no change	64 /211 (30)	115/196 (59)	
- worsened	4/211 (2)	7/196 (4)	
Change in distance walked in 6 min, metres, median (95% CI) (primary outcome)	(n=214) +39 (26 to 54)	(n=198) +10 (0 to 25)	0.005
Change in Minnesota Living with Heart Failure score, median (95% CI) (primary outcome)	(n=213) -18 (-22 to -12)	(n=193) -9 (-12 to -5)	0.001
Change in peak oxygen consumption, ml/kg/min, median (95% CI)	(n=158) +1.1 (0.6 to 1.7)	(n=145) +0.2 (-0.2 to 0.8)	0.009
Change in total exercise time, sec, median (95% CI)	(n=159) +81 (62 to 119)	(n=146) +19 (-1 to 47)	0.001
Absolute change in LVEF, %, median (95% CI)	(n=155) +4.6 (3.2 to 6.4)	(n=146) -0.2 (-1.0 to 1.5)	<0.001
Change in LVEDD, mm, median (95% CI)	(n=90) -3.5 (-6 to -1)	(n=98) 0.0 (-1 to 2)	<0.001
Change in area of mitral regurgitation jet, cm ² , median (95% CI)	(n=116) -2.7 (-4.0 to -2.1)	(n=118) -0.5 (-1.1 to 0.0)	<0.001
Change in QRS duration, msec, median (95% CI)	(n=206) -20 (-20 to -12)	(n=192) 0 (-10 to 0)	<0.001
Clinical composite heart-failure score at 6 months			<0.001
- improved	67%	39%	
- worsened	16%	27%	
Comments: states that the magnitude of the effect on the 3 primary endpoints was not influenced by use of a beta-blocker, cause of heart failure, (ischemic or non-ischemic), configuration of QRS complex (left or right bundle branch block), or baseline duration of QRS interval (analysed as a continuous variable, p>0.10 for all interactions).			

Adverse effects of treatment	CRT-P, n=228	OPT, n=225	p value
Hospitalised for repositioning or replacement of left ventricular lead, n of patients	11	3	
Hospitalisations not related to heart failure or function of left ventricular lead, n	37	33	
• Median duration of procedure reported, not extracted.			
Adverse effects of treatment	All participants undergoing implantation (n=571)		
Complete heart block requiring permanent cardiac pacing	2/571		

Death due to progressive hypotension	1/571
Asystole, resuscitated but died 1 month later	1/571
Coronary-sinus dissection	23/571 (4%)
Cardiac vein or coronary-sinus perforation (3 of these recovered and continued in study)	12/571 (2%)
	Participants who had successful implantation (n=528)
Left ventricular lead repositioned	20/528
Left ventricular lead replaced	10/528
Pacemaker-related infection requiring explantation	7/528

Methodological comments

- *Allocation to treatment groups:* Randomisation in permuted blocks to ensure balance between groups within centres. Sealed envelopes used.
- *Blinding:* Patients and physicians treating them for heart failure and performing study evaluations were unaware of treatment assignment. An electrophysiologist who was uninvolved with clinical care, opened a sealed envelope at the time of randomisation, programmed the device and performed all tests that could reveal the identity of the pacing mode.
- *Comparability of treatment groups:* States similar with respect to all baseline characteristics
- *Method of data analysis:* States all end points analysed according to ITT principle, patients who crossed over analysed according to original assignment. For continuous variables, comparisons of changes from baseline to 6 months between groups evaluated with Wilcoxon rank-sum test. Chi square test used for categorical end points. Only patients with data at baseline and 6 months included in these analyses, but results similar if patients with incomplete data were included and using value carried forward. Cumulative survival curves for the risk of a major clinical event used Kaplan-Meier method and tested for significance by the log-rank statistic. Cox proportional-hazard regression models used to estimate hazard ratios.
- *Sample size/power calculation:* Sample size of 224 patients per group estimated on basis of assumption that the study would have 80% power (2 sided alpha 0.0167) to detect a difference in NYHA class of 0.75, quality of life of 13 points, or distance walked in 6 mins of 50m
- *Attrition/drop-out:* 571 agreed to participate, 43 device not successfully implanted. 528 successfully implanted: 2 required cardiac pacing, 2 became clinically unstable, 71 enrolled in initial pilot phase, 453 randomised to main study. Control group: 24/225 did not complete 6 months follow-up (16/225 died, 2/225 had heart transplant, 1/225 had complications related to device, 5/225 missed the 6-month visit). CRT-P group: 13/228 did not complete 6 months follow-up (12/228 died, 1/228 had complications related to device). No patient lost to follow-up for analysis of death or worsening heart failure. 10/225 in control group crossed over to CRT-P, 7 due to worsening heart failure, 3 due to bradycardia.

General comments

- *Generalisability:* Only those successfully implanted underwent randomisation. Generalisability limited to people with moderate to severe heart failure and prolonged QRS interval.
- *Outcome measures:* Clinical Events Review committee adjudicated adverse events/endpoints. QoL assessed using validated questionnaire.
- *Inter-centre variability:* not reported.
- *Conflict of interests:* Stated. Some of the authors are consultants or investigators for, or employees of, Medtronic, one author also on Advisory Board of St Jude Medical. States that investigators had full access to all data and performed analyses without restrictions or limitations from sponsor.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Randomised in permuted blocks Further details not reported

Allocation concealment	Unclear	Sealed envelopes used but unclear if they were opaque and sequentially numbered
Performance bias		
Blinding of participants and personnel	Low risk	Patients and physicians treating them for heart failure and performing study evaluations were unaware of treatment assignment.
Detection bias		
Blinding of outcome assessment	Low risk	Patients and physicians treating them for heart failure and performing study evaluations were unaware of treatment assignment.
Attrition bias		
Incomplete outcome data addressed		
- primary outcomes	Unclear	States ITT analysis used and attrition reported, also reports analysis included last value carried forward analysis. However, numbers are low for NYHA class (primary outcome) without reasons why.
- secondary outcomes	Unclear	Reasons for different sample sizes unclear
Reporting bias		
Selective reporting	High risk	SF-36 is stated in the protocol paper ⁷⁴ but results not reported.
Other bias		
Other sources of bias	Low risk	

^a 'Low risk', 'high risk' or 'unclear risk' of bias

MUSTIC

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Cazeau <i>et al.</i>, 2001⁷⁶</p> <p>MUSTIC (Multisite Stimulation in Cardiomyopathies)</p> <p><i>Study design:</i> Randomised cross-over study</p> <p>Europe (France, Germany, Italy, Sweden, Switzerland, UK)</p> <p><i>Number of centres:</i> 15</p> <p><i>Funding:</i> ELA Recherche, Medtronic and</p>	<p><i>Intervention:</i> CRT-P ON Atrioventricular (active) pacing Chorum 7336 MSP, ELA Medical, France; InSync 8040, Medtronic, USA</p> <p><i>Comparator:</i> CRT-P OFF Ventricular (inhibited) pacing at a basic rate of 40 bpm.</p> <p><i>Other interventions used:</i> No modification to medication other than adjustment of dose of diuretic permitted.</p>	<p><i>Indication for treatment:</i> Severe heart failure and major intraventricular delay but without standard indications for a pacemaker.</p> <p><i>Number of enrolled participants:</i> n=67 <i>Number of randomised participants:</i> n = 58 Group 1 (CRT-ON, CRT-P OFF), n= 29 Group 2 (CRT-P OFF, CRT-P ON), n=29</p> <p><i>Inclusion criteria:</i> Severe heart failure due to idiopathic or ischemic LVSD; NYHA class III for ≥ one month whilst on OPT; LVEF < 35%; LVEDD >60mm; QRS interval >150 ms; in sinus rhythm, without a standard indication for a pacemaker.</p>	<p><i>Primary outcomes:</i> Distance walked in 6 minutes</p> <p><i>Secondary outcomes:</i> QoL Peak oxygen uptake, Hospital admissions due to decompensated heart failure, Patient's preference Death</p> <p><i>Method of assessing outcomes:</i> Assessed at baseline (4 weeks before implantation), randomisation (2 weeks after implantation) and at end of each crossover phase. QoL used Minnesota Living with Heart Failure questionnaire, total score 0 to 105, higher the score the worse the QoL.</p>

Swedish Heart and Lung Association, and Swedish MRC.	OPT (n=67): ACE inhibitors or equivalent 96%, diuretics 94%, digoxin 48%, amiodarone 31%, beta-blockers 28%, spirololactone 22%.	<i>Exclusion criteria:</i> Hypertrophic or restrictive cardiomyopathy; suspected acute myocarditis; correctable valvulopathy; acute coronary syndrome lasting < 3 months; coronary revascularisation during last 3 months, or scheduled revascularisation; treatment-resistant hypertension; severe obstructive lung disease; inability to walk; life expectancy < 1 year not associated with cardiovascular disease; indication for ICD.	6 minute walk test according to Guyatt et al and Lipkin et al (references provided), 2 tests at each visit with an interval of at least 3 hours between them, the maximal difference between the 2 tests was 15% and the value recorded was the mean of the results of the two tests. Patient preference – at end of crossover phase, patients asked which three month period they preferred. <i>Length of follow-up:</i> Participants received intervention and comparator for 3 months each in random order. <i>Recruitment:</i> March 1998-March 1999
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Participant characteristics (at randomisation 2 weeks post implant)	Group 1 (CRT-ON, CRT-P OFF), n= 29	Group 2 (CRT-P OFF, CRT-P ON), n=29	p value
Age years, mean (SD)	64 (11)	64 (8)	0.91
Gender, male n/N	19/29	24/29	0.13
Ethnicity	not reported	not reported	
NYHA class III	100%	100%	
Weight, kg, mean (SD)	79 (19)	78 (16)	0.97
Distance walked in 6 minutes, m, mean (SD)	354 (110)	346 (111)	0.82
Peak oxygen uptake, ml/kg of body weight/min, mean (SD)	13.5 (8.4)	14.1 (4.6)	0.41
QoL score, mean (SD)	48 (19)	46 (25)	0.66
Heart rate, bpm, mean (SD)	75 (12)	75 (14)	0.89
QRS interval, msec, mean (SD)	172 (22)	175 (19)	0.48
<ul style="list-style-type: none"> Note baseline characteristics for n=67 at baseline (4 weeks before implantation) also presented but not extracted. 			

RESULTS			
Outcomes	CRT-P ON	CRT-P OFF	p value
Mortality over 6 month period			
- First crossover period: sudden death after 26 days of active pacing	1		
- Second crossover period: acute MI few hours after premature switch to active pacing due to severe decompensation	1		
- Second crossover period: sudden death 2 hours after switching from inactive to active pacing	1		
Distance walked in 6 minutes, m, mean (SD)			
- Group 1 (CRT-ON, CRT-P OFF), n=22	384.1 (78.9)	336.1 (128.3)	

- Group 2 (CRT-OFF, CRT-P ON), n=24 - Both Groups, n=46	412.9 (116.9) 399.2 (100.5)	316.2 (141.8) 325.7 (134.4)	p<0.001
Peak oxygen uptake, ml/kg of body weight/min, mean (SD) - Group 1 (CRT-ON, CRT-P OFF), n=18 - Group 2 (CRT-OFF, CRT-P ON), n=20 - Both Groups, n=38	15.9 (5.8) 16.4 (3.6) 16.2 (4.7)	15.3 (5.9) 14.8 (3.9) 15 (4.9)	p=0.029
QoL score, mean (SD) - Group 1 (CRT-ON, CRT-P OFF), n=23 - Group 2 (CRT-OFF, CRT-P ON), n=22 - Both Groups, n=45	33.3 (22) 25.7 (20.4) 29.6 (21.3)	42.6 (20.9) 44 (25) 43.2 (22.8)	p<0.001
Heart failure hospitalisations at 3 months (first crossover period only)	3/29	9/29	p<0.05
Patient preference after 6 months (n=48) ^a	41/48 (85%)	2/48 (4%)	p<0.001
Comments: ^a 48 patients completed both phases of study. Patient preference: 5/48 (10%) had no preference. P value reported in abstract of paper but not in results section.			
<ul style="list-style-type: none"> In the per-protocol analysis (n=23), mean distance walked (CRT-P ON vs CRT-P OFF) was 424 m (SD 83) vs 375 m (SD 83), p<0.04. 			
Adverse effects of treatment	CRT-P ON	CRT-P OFF	p value
Uncorrectable loss of left ventricular pacing efficacy	2		
Severe decompensating leading to a premature switch to active pacing		1	
Decompensation attributed to rapidly progressive aortic stenosis	1		
Decompensation due to persistent atrial fibrillation		1	
<ul style="list-style-type: none"> Implantation of a left ventricular lead was attempted in 64/67 patients, with a 92% (59/64) success rate. The 5 failures were not randomised. A lateral position was reached in 80% of patients with a mean pacing threshold of 1.4 V (SD 1.1). Early dislodgement occurred in 8 patients was successfully corrected in 5. Overall, 88% of patients had a functional left ventricular lead at the end of the cross over phase. 			

Methodological comments

- Allocation to treatment groups:** Randomisation of order of treatment followed a block design with stratification according to study centre. Also states patients were 'randomly assigned to and equally distributed between the two study groups'.
- Blinding:** Described as single-blind. States patients had no knowledge of the order of treatment, but no details provided.
- Comparability of treatment groups:** Similar.
- Method of data analysis:** States all analyses based on ITT principle, thus all enrolled patients were included in the analysis, but each efficacy end point could be assessed only in patient with no data missing after the completion of both crossover phases. Baseline characteristics assessed using chi-square for dichotomous variables and Student's t-test or Wilcoxon's nonparametric test for quantitative or categorical variables. Responses obtained for all criteria assessing clinical efficacy were compared with Wilcoxon test and according to a two-period and two-treatment (two by two) crossover design. Period and carryover effects were checked before the efficacy of treatment was evaluated. Morbidity and mortality were compared during the first crossover period and were described for all other phases of the study. Stability of the results was assessed by a per-protocol analysis, which included only patients without any deviations from the protocol. States that no significant carryover and period effects were noted. Threshold of significance 0.05.
- Sample size/power calculation:** On basis of previous reports of mortality rates in NYHA class III,

a 10% mortality rate at 6 months was estimated. 10% failure rate of the implantation of the LV lead and a 20% rate of premature termination because of loss of LV pacing efficacy of unstable heart failure was expected. A 10% increase in the distance walked in 6 minutes with active pacing was estimated. The total target sample needed as estimated to be 22 patients, for a study with 95% confidence level and 95% power. For the Minnesota QoL score, a predicted 10% reduction with active pacing necessitated a 30 patient sample. Considering mortality and drop-outs, 40 patients were needed.

- *Attrition/drop-out*: 3 withdrew before implantation: 2 unstable heart failure (1 subsequently died) and 1 pre-existing indication for pacing. Implantation of a left ventricular lead attempted in 64 patients. 6 patients removed before randomisation: 5 due to failed implantation of the left ventricular lead and one due to sudden death with device was inactive. 10 did not complete 2 crossover periods (including 5 who did not complete first period), first crossover period: 1 withdrew consent at randomisation, 2 had uncorrectable loss of ventricular pacing efficacy, 1 switched from inactive to active pacing due to severe decompensation, 1 died suddenly after 26 days of active pacing; second crossover period: 3 worsening heart failure (1 decompensation with active pacing, 1 decompensation during inactive pacing), 1 sudden death after switching to active pacing, 1 lung cancer.

General comments

- *Generalisability*: Patients randomised 2 weeks after implantation. Only patients who were successfully implanted were randomised.
- *Outcome measures*: Appropriate, but change in NYHA not reported.
- *Inter-centre variability*: Not reported.
- *Conflict of interests*: Part funded by ELA Recherche and Medtronic. Four authors paid consultants of Medtronic or ELA Recherche and one author employee of ELA Recherche.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	details not reported
Allocation concealment	Unclear	details not reported
Performance bias		
Blinding of participants and personnel	High risk	States that participants had no knowledge of order of treatments, but not clear how this was maintained. Personnel not blinded, 6 min walk test and QoL outcomes may be influenced by lack of blinding.
Detection bias		
Blinding of outcome assessment	High risk	States 'single blind' so assume only participants were blinded.
Attrition bias		
Incomplete outcome data addressed	Low risk	Numbers and reasons reported.
Reporting bias		
Selective reporting	High risk	Change in NYHA class assessed but data not reported.
Other bias		
Other sources of bias	High risk	Use of block randomisation without blinding means it may be possible to predict future assignments. Crossover design appears appropriate.

^a 'Low risk', 'high risk' or 'unclear risk' of bias

Appendix 10: Data extraction: people with both conditions

CONTAK-CD

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Higgins <i>et al.</i>, 2003⁷⁷, Lozano <i>et al.</i>, 2000⁷⁸, FDA report⁷⁹, Saxon <i>et al.</i>, 1999⁸⁰</p> <p>CONTAK-CD</p> <p><i>Study design:</i> Crossover RCT in phase I. Parallel RCT in phase II</p> <p>USA (see General Comments - Inter-centre variability)</p> <p><i>Number of centres:</i> 47</p> <p><i>Funding:</i> Guidant Corporation, St. Paul, Minnesota.</p>	<p><i>Intervention:</i> CRT-D + optimised pharmacological therapy (OPT)</p> <p><i>Comparator:</i> ICD +OPT</p> <p>Devices were either Model 1822 Ventak CHF Automatic Implantable Cardioverter Defibrillator or Model 1283 Contak CD device (Guidant Corporation, St. Paul, Minnesota).</p> <p>Initially the left ventricle (LV) was paced with a commercially available epicardial pace/sense lead. Later a lead that could be placed transvenously using over-the-wire techniques in the coronary venous vasculature was introduced. A cardioversion/defibrillation lead was implanted in the right ventricle, and a pace/sense lead was placed in the right atrium for this 3 lead CRT system.</p> <p>Details of lead positioning are reported but have not been data extracted.</p> <p>Randomised therapy programmed after a minimum 30 day period with no CRT. During this period investigators were permitted to optimise pharmacologic therapy. OPT not defined.</p> <p><i>Other interventions used:</i> none stated.</p>	<p><i>Indication for treatment:</i> Patients with symptomatic heart failure, intraventricular conduction delay, and malignant ventricular tachyarrhythmias (VT/VF) requiring therapy from an ICD.</p> <p><i>Number of randomised participants:</i> n=490. CRT-D, n=245 CRT, n=245</p> <p><i>Inclusion criteria:</i> NYHA class II to IV; LVEF ≤35%; QRS interval ≥120ms; conventional indications for an ICD (American College of Cardiology/American Heart Association guidelines);⁷⁷ Age ≥ 18 years; symptomatic heart failure despite OPT (must include ACE inhibitors if tolerated).⁸⁰</p> <p><i>Exclusion criteria:</i> Atrial tachyarrhythmias or conventional indications for a permanent pacemaker;⁷⁷ concomitant cardiac surgery; unable to undergo device implant; unable to comply with protocol and follow-up including exercise testing; life expectancy < 6 months due to other conditions; amyloid disease; hypertrophic obstructive cardiomyopathy; requires in-hospital continuous intravenous inotropes; use of pre-existing</p>	<p><i>Primary outcome:</i> Progression of heart failure composite end point of all-cause mortality, hospitalisation for worsening HF, ventricular tachyarrhythmias requiring device therapy. (initially the primary outcome was peak oxygen consumption (VO₂) but this was changed when the study design was changed)</p> <p><i>Secondary outcomes:</i> VO₂, QoL, six minute walk distance, biventricular antitachycardia pacing efficacy, defibrillation therapy safety.⁸⁰</p> <p><i>Method of assessing outcomes:</i> VO₂ assessed by cardiopulmonary exercise test⁸⁰</p> <p>QoL used the Minnesota Living with Heart Failure Questionnaire</p> <p>A Heart Failure Events Committee (HFEC) adjudicated all deaths and hospitalisations.</p> <p>Operative mortality defined as death from any cause within 30 days of the implant procedure</p>

		cardioversion/defibrillation leads other than those specified in the protocol; involved in other cardiovascular clinical investigations of active therapy or treatment. ⁸⁰	<p><i>Length of follow-up:</i> maximum of six months (but some patients, presumed to be all those in phase I, only 3 months).</p> <p><i>Recruitment:</i> February 1998 to December 2000</p>
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Participant characteristics	CRT-D, n=245	ICD, n=245	p value
Age years, mean (SD) ^a	66 (11)	66 (11)	
Gender, % male	85	83	
Ethnicity	not reported	not reported	
Aetiology ischaemic, %	67	71	
NYHA class II, n (%)	32	33	
class III, n (%)	60	57	
class IV, n (%)	8	10	
LVEF %, mean (SD) ^a	21 (7)	22 (7)	
QRS interval ms, mean (SD) ^a	160 (27)	156 (26)	
Intraventricular conduction delay, %			
- left bundle-branch block	54	55	
- non-specific	32	33	
- right bundle-branch block	14	12	
Diuretic, %	88	83	
ACE inhibitor/ARB, %	86	89	
Beta-blocker, %	48	46	
Digoxin, %	69	68	
Peak VO ² ml/kg/min, mean (SD) ^a	13.8 (4.6)	13.5 (3.8)	
QoL points, mean (SD) ^a	44 (25)	40 (23)	
6 minute walk distance m, mean (SD) ^a	316 (119)	320 (121)	
Left ventricular internal diameter (LVID) in diastole mm, mean (SD) ^a	71 (11)	70 (10)	
LVID in systole mm, mean (SD) ^a	59 (11)	58 (11)	
Heart rate	not reported	not reported	
Cardiac history	not reported	not reported	
Previous treatment	not reported	not reported	
Comorbidities	not reported	not reported	

Comments: ^a - Data are assumed to be mean (SD) although this is not specifically stated anywhere in the paper.

- Characteristics are reported for the 490 participants who entered randomisation at the time of the implant.
- During the 30-day post-implant recovery period, when investigators were permitted to adjust or initiate heart failure medications, many patients demonstrated significant improvement. This meant that of the 328 patients who presented in NYHA class III/IV, 131 (40%) improved to NYHA class I or II, whereas 30 of 162 (19%) NYHA class II patients worsened to NYHA class III/IV. After optimisation of medical therapy therefore 227 patients were in NYHA class III/IV and 263 were in NYHA class I/II before randomisation.
- Participant characteristics in an earlier paper reporting only on the 222 patients enrolled in phase 1 of the study⁷⁸ have not been extracted. It is not clear whether some or all of these participants are included in the data from Higgins et al.⁷⁷ reported above.

RESULTS

Outcomes	CRT-D, n=245	ICD, n=245	p value
Progression of heart failure, n/N - mortality, n/N - heart failure hospitalisations (at least 1), n/N - at least 1 ventricular tachycardia/ventricular fibrillation event	79/245 11/245 32/245 36/245	94/245 16/245 39/245 39/245	0.35
All cause mortality ^b - death during study treatment phase (detail by group below) - death during long-term follow-up phase		109 27 70	
Causes of death n/N (%) - pump failure - non-cardiac - arrhythmic - ischaemic - cardiac in nature but unknown aetiology - insufficient information for independent events committee to be able to adjudicate		47/109 (43%) 21/109 (19%) 9/109 (8%) 2/109 (2%) 2/109 (2%) 28/109 (26%)	
Deaths during study treatment phase ⁷⁹ n/N (%) - cardiac, pump failure - cardiac, arrhythmic - cardiac, other - non-cardiac - unknown	11/245 (4.5%) 4/245 (1.6%) 1/245 (0.4%) 2/245 (0.8%) 2/245 (0.8%) 2/245 (0.8%)	16/245 (6.5%) 9/245 (3.7%) 0/245 (0%) 1/245 (0.4%) 3/245 (1.2%) 3/245 (1.2%)	
Total survival at - 1-year - 2-years - 3-years		85% 74% 70%	
Received appropriate treatment of ventricular tachyarrhythmias, n/N (%) - VT alone - VF alone - VT and VF	36/245 (15%) 25/245 (10%) 7/245 (3%) 4/245 (2%)	39/245 (16%) 27/245 (11%) 6/245 (2%) 6/245 (2%)	
VT/VF episodes during therapy evaluation phase (excluding those with no episodes), median	2.5	2	
QoL points, mean change (SE) ^c	-7 (2) n=234	5 (2) n=225	0.39
NYHA Class - improved 2 classes, % - improved 1 class, % - no change, % - worsened, %	n=109 11 25 51 13	n=116 2 30 51 17	0.10 ^d
LVEF %, mean change (SE) ^c	5.1 (0.7) n=222	2.8 (0.7) n=216	0.020
LV internal diameter (ID) in diastole mm, mean change (SE) ^c	-3.4 (0.6) n=228	-0.3 (0.6) n=219	<0.001
LVID in systole mm, mean change (SE) ^c	-4.0 (0.7) n=228	-0.7 (0.7) n=219	<0.001
Peak VO ₂ ml/kg/min, mean change (SE) ^c	0.8 (0.3) n=216	0.0 (0.3) n=201	0.030
Six minute walk distance m, mean change (SE) ^c	35 (7) n=224	15 (7) n=220	0.043
Comments: ^b two of these deaths are not accounted for in the division between deaths occurring during treatment and those during long-term follow up. ^c - Data are assumed to be mean (SE)			

although this is not specifically stated anywhere in the paper.^d - not clear if the p-value relates to the specific comparison for improved 1 class or for NYHA class changes overall.

- Results are also presented separately for patients of NYHA class III/IV at randomisation and NYHA class I/II at randomisation (i.e. at the conclusion of the post-recovery period) but as this appears to be a post-hoc analysis these results have not been data extracted.
- Overall relative reduction in composite heart failure progression was 15% with CRT.
- Kaplan-Meier curves illustrating time to event for all-cause mortality, for all-cause mortality plus heart failure hospitalisation, and for mortality during the study treatment phase are presented but have not been data extracted.
- Spontaneous monomorphic VT was successfully treated with biventricular antitachycardia pacing in 927/1053 (88%) episodes.
- Results in an earlier paper reporting only on the 222 patients enrolled in phase 1 of the study⁷⁸ have not been data extracted. It is not clear whether some or all these participants are included in the data from Higgins et al.⁷⁷ reported above.

Adverse effects of treatment	CRT-D, n=245		ICD, n=245
Operative mortality ^{77;79}	12/567 2.1% (95% CI 0.9 to 3.3)		
Causes of death for operative mortality ⁷⁹	Implants n=501	Attempts n=66	Total n=567
Total	10	2	12
- Cardiac: Pump failure	5	1	6
- Cardiac: Arrhythmic	2	1	3
- Non-cardiac ^e	2	0	2
- Unknown	1	0	1
Overall lead-related adverse event rate	n=75 (unique patients), 14.5% (95% CI 11.5 to 17.5)		
- lead-related	53/448		
- procedure-related	27/517		
Severe device-related events, no. of patients/N	7/567 (1.2% with at least one event)		
- telemetry difficulty; device explanted	2 (0.4%, 95 CI 0.0 to 0.9)		
- ventricular tachycardia during cardiopulmonary exercise testing	1 (0.2%, 95 CI 0.0 to 0.5)		
- coronary sinus perforation	1 (0.2%, 95 CI 0.0 to 0.5)		
- inappropriate shock due to oversensing	1 (0.2%, 95 CI 0.0 to 0.5)		
- lead dislodgement	1 (0.2%, 95 CI 0.0 to 0.5)		
- anaphylaxis in association with use of pulmonary artery catheter	1 (0.2%, 95 CI 0.0 to 0.5)		
Device-related complications (only those occurring in >1% of patients) in all patients implanted (n=448)			
- loss of LV capture	31 (6.9%)		
- loss of right atrial capture	7 (1.6%)		
- ventricular oversensing	6 (1.3%)		
- Extracardiac stimulation	5 (1.1%)		
Device-related complications (only those occurring in >1% of patients) in all patients attempted or implanted (n=517)			
- infections	7 (1.4%)		
<p>Comments: ^e - In Higgins et al.⁷⁷ two of the 10 'Implants' deaths were described as perioperative (1 attributed to pulseless electrical activity resulting from defibrillation threshold testing and 1 to incessant ventricular tachycardia during the implant procedure). The causes of the remaining eight deaths were pump failure (n=5), cardiac causes unrelated to pump failure (n=2) and unknown (n=1). Higgins et al.⁷⁷ state that none of these eight deaths were attributed to the implant procedure.</p> <ul style="list-style-type: none"> • Adverse events reported in the Summary of Safety and effectiveness⁷⁹ focus on adverse events related to Easytrack leads or the implant procedure required to place an Easytrack lead. In defining adverse event rates the main dominators used are 517 for adverse events relating to the 			

procedure to implant Easytrack leads, and 448 for adverse events relating to events occurring in participants successfully implanted.

- Of the 53 lead-related adverse events the most common (>1% incidence) were loss of left ventricular capture (31 patients, 6.9%), ventricular oversensing (11 patients, 2.5%), and extra cardiac stimulation (9 patients, 2.0%). These were typically resolved with surgical intervention.
- Of the 27 procedure-related events the most common (>1% incidence) were coronary venous trauma (10 patients, 2.0%), transient atrioventricular block (6 patients 1.2%), and transient renal failure (5 patients, 1.0%). These events typically resolved without intervention and with no permanent long-term sequelae.
- The incidence of severe, device-related events (1.2%) was reported as significantly less than the hypothesized rate of 20% ($p<0.01$).
- The operative mortality (2.1%) was reported to be significantly less than the hypothesized rate of 9% ($p<0.01$).

Methodological comments

- *Allocation to treatment groups*: Not described
- *Blinding*: Double blind
- *Comparability of treatment groups*: Groups are described as balanced with no statistically significant differences with respect to baseline characteristics (no statistical testing reported).
- *Method of data analysis*: Patients from phase I contributed data from a three month treatment phase and patients from phase II contributed data from a six-month treatment phase for the analysis of the primary end-point. The three month treatment phase from the first phase of the study correlates to the first study period (i.e. before any cross over). Cox proportional hazard models were fit for the combination of events with the treatment effect adjusted for covariates chosen by the HFEC before primary end point analysis. The covariates included NYHA class, QRS interval, ischaemic aetiology, LVEF, and bundle-branch morphology. The Wei method (reference provided) was used to calculate a composite effect of the treatment and covariates. For continuous variables the longitudinal (repeated measures) analysis method (reference provided) was used to compare the difference in the sample means. This method accounted for the patterns of missing data, took full advantage of the correlation structure, and all the data were used to estimate the model parameters. Model parameters were estimated using maximum likelihood. Values of $p<0.05$ were considered to be significant for all tests. The events contributing to the composite primary end point appear to be analysed as ITT. It is clear from the numbers reported for the secondary outcomes that analyses for change in QoL, NYHA class, % LVEF, LVID in diastole and in systole, peak VO_2 , and 6 minute walk distance are not analysed as ITT. No reasons are given for the missing data. The study authors do not comment on whether the alteration of study design between phase I and phase II of the study was expected to have an impact on the methods of data analysis.
- *Sample size/power calculation*: Not described although Higgins et al.⁷⁷ state that it was postulated that the therapy would reduce the events contributing to the composite primary end point by 25%. However the actual event rate observed was approximately half that expected in the original study design and consequently the authors state that the study was not adequately powered to detect a statistically significant difference in HF events.
- *Attrition/drop-out*: Initially $n = 581$ were enrolled ($n=248$ in phase I and $n=333$ in phase II) but 14 either withdrew consent or were withdrawn by the investigator (found not to meet eligibility criteria) before an implant procedure and 66 patients did not receive the system being used in this trial because of the inability to place the coronary venous lead. These patients received a conventional ICD instead. Therefore 501 were implanted ($n=222$ in phase I and $n=279$ in phase II) with the intervention system. Of these 448/501 (89%) received a transvenous system and 53/501 (11%) a transthoracic system (phase I $n=51$, phase II $n=2$ transthoracic leads). Of the 501 patients implanted, 11 did not enter the randomised part of the study 30 days after the implant procedure - 10 patients died (adverse events section, Causes of death for operative mortality⁷⁹, Implanted column) and one withdrew in the 30-day post-implant recovery period before the randomised therapy was programmed. As noted above not all analyses were by ITT and where data are missing no reasons for this are provided.

- *Other:*
 - The study design was modified due to regulatory concerns about morbidity and mortality associated with CRT and the length of follow-up in the randomised mode of the initial design. This meant that the design changed from a crossover RCT design (cross over to occur after the first 3 months of randomised therapy) to a parallel RCT design with 6 months of follow up in phase II.
 - During the course of the trial positive clinical trial results led to the widespread adoption of HF medications such as beta-blockers and spironolactone. There was also an evolution in HF management focussing on increased outpatient surveillance. Both of these factors may have contributed to the reduction in the number of HF events expected. The improvement seen in many patients once medical management was optimised before randomisation also may have made it more difficult to show a benefit of treatment in healthier patients, and also contributed to the reduction in statistical power to show improvement in those patients who remained in NYHA class III/IV despite optimal HF medication.

General comments

- *Generalisability:* The study authors point out that the results may not be generalisable to patients with chronic atrial fibrillation, chronotropic incompetence and sinus bradycardia. The study also only studied CRT delivered in an atrial synchronous manner (i.e. the VDD mode). Therefore the effects of atrial pacing as well as adaptive-rate pacing delivered with the DDD(R) modes are not known.
- *Outcome measures:* Appear to be appropriate however the reason(s) the study sponsor decided to change the primary end point from peak VO₂ to a composite heart failure outcome are not provided.
- *Inter-centre variability:* The key paper for this study Higgins 2003⁷⁷ and the Summary of Safety and Effectiveness for the device used⁷⁹ state that the centres were based in the USA. However, an earlier paper reporting on phase 1 of the study⁷⁸ states that patients were enrolled from sites in the USA, Europe and Australia (number of centres not reported). Therefore it is not clear whether all or only some of the trial centres involved in phase I contributed data to the key paper for the study.
- *Conflict of interests:* not stated but note that the study sponsor (manufacturer of the device) chose to change the primary end point during the course of the study.
- *Other:* The chief sources of information for this data extraction were the peer-reviewed publications of Higgins et al.⁷⁷, Saxon et al.⁸⁰ and Lozano et al.⁷⁸. As operative mortality was the only adverse event reported by the key trial paper⁷⁷, the Summary of Safety and Effectiveness⁷⁹ submitted by the manufacturer Guident Corporation to the FDA as part of their approvals process was used as a source of adverse event data.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^f	Support for Judgement
Selection bias		
Random sequence generation	Unclear risk	Study described as randomised controlled study but no further details provided.
Allocation concealment	Unclear risk	No details provided.
Performance bias		
Blinding of participants and personnel	Low risk	Study described as double-blind. “Both the patient and the heart failure specialist treating the patient are blinded to the pacing mode” ⁸⁰
Detection bias		
Blinding of outcome assessment	Low risk	Study described as double-blind. “Both the patient and the heart failure specialist treating the patient are blinded to the pacing mode” ⁸⁰ “A Heart Failure Event Committee (HFEC)

		adjudicated all deaths and hospitalisations". It is not clear whether this committee were blind to the pacing mode. However these outcomes are unlikely to have been influenced by a lack of blinding.
Attrition bias		
Incomplete outcome data addressed - primary outcome progression of heart failure (composite including mortality, heart failure hospitalisations, ventricular tachycardia and ventricular fibrillation events)	Low risk	From the data provided these analyses appear to account for all participants.
Incomplete outcome data addressed - change in QoL, NYHA class, % LVEF, LVID in diastole and systole, peak VO ₂ , and 6 minute walk distance	High risk	It is clear from the numbers provided that there are missing data. No reasons for missing data are given.
Reporting bias		
Selective reporting	Low risk	A description of the study is available ⁸⁰ and the only outcome mentioned here that is missing from the published papers is blood laboratory tests. However these are not likely to be a key outcome for this intervention.
Other bias		
Other sources of bias	Unclear risk	The study design and primary outcome measure were changed during the course of the study. The length of follow up from phase I was 3 months whereas that from phase II was six months. The potential for these issues to introduce a bias into the results is unknown.

[†] 'Low risk', 'high risk' or 'unclear risk' of bias

MADIT-CRT

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Moss <i>et al.</i>, 2009[;]⁸¹ 2005[;]⁸² Solomon <i>et al.</i> 2010[;]⁸³ Goldenberg <i>et al.</i> 2011[;]^{84;85} Arshad <i>et al.</i> 2011⁸⁶</p> <p>MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy)</p> <p><i>Study design:</i> RCT</p> <p><i>Number of centres:</i> Text states 110, 88 in USA, 2 in Canada, 20 in Europe.</p>	<p><i>Intervention:</i> CRT-ICD Programmed mode was DDD with lower rate of 40 bpm and hysteresis off.</p> <p><i>Comparator:</i> ICD only Programmed pacing mode was VVI for single- chamber units and DDI for dual-chamber units with lower rates of 40 bpm and hysteresis off in both single- and dual- chamber units.</p> <p>Commercially available transvenous devices (Boston Scientific) were</p>	<p><i>Indication for treatment:</i> mild cardiac symptoms, reduced ejection fraction and wide QRS complex. All met the guideline indication for ICD therapy.</p> <p><i>Number of participants:</i> n = 1820 (1271 in US, 22 in Canada, 527 in Europe) CRT-ICD, n= 1089 ICD only, n= 731</p> <p><i>Inclusion criteria:</i> NYHA class: I or II; LVEF: ≤30%; QRS interval: ≥130 msec; people ≥ 21 years of age with ischaemic</p>	<p><i>Primary outcomes:</i> death or nonfatal heart-failure events (whichever came first)</p> <p><i>Secondary outcomes:</i></p> <p><i>Method of assessing outcomes:</i> Baseline 12- lead electrocardiogram and echocardiogram. Baseline physical examination and 6- minute walk test (6MWT).</p> <p>Two dimensional echocardiography assessed changes in left</p>

<p>(Czech Republic 1, Denmark 1, France 1, Germany 4, Hungary 1, Italy 2, Israel 3, Poland 1, Spain 2, Switzerland 1, The Netherlands 3, United Kingdom 1) Inconsistency between numbers reported in text and appendix.</p> <p><i>Funding:</i> Supported by a research grant from Boston Scientific to the University of Rochester with funds distributed to the coordination and data centre, enrolling centres, core laboratories, committees and boards under subcontracts from the University of Rochester.</p>	<p>used.</p> <p><i>Other interventions used:</i> Optimal pharmacologic therapy for heart failure.⁸²</p>	<p>cardiomyopathy (NYHA class I or II) or nonischaemic cardiomyopathy (NYHA class II only); sinus rhythm; ejection fraction $\leq 30\%$ and prolonged intraventricular conduction with QRS duration of ≥ 130 msec; met guideline indication for ICD therapy.</p> <p><i>Exclusion criteria:</i> existing indication for CRT; implanted pacemaker, ICD, or resynchronisation device; NYHA class III or IV symptoms, previous coronary-artery bypass grafting, percutaneous coronary intervention, or an enzyme-positive myocardial infarction within 3 months before enrolment, NYHA class 1 with non-ischaemic cardiomyopathy, angiographic evidence of coronary disease who are candidates for coronary revascularisation and likely to undergo a procedure in the foreseeable future, second or third degree heart block, irreversible brain damage from pre-existing cerebral disease, pregnant or planning to become pregnant women, reversible non-ischemic cardiomyopathy, chronic atrial fibrillation within one month prior to enrolment, presence of other life limiting disease e.g. cancer, participating in other trials, unwilling to cooperate, living too distant from clinic for ease of follow up visits, unlikely to be resident in the area for duration of the trial, unwilling to consent.</p>	<p>ventricular volumes and ejection fraction between baseline and 1-year follow up. Volumes were estimated by averaging those derived from the two-chamber and four-chamber views according to Simpson's method (no ref provided). States ejection fraction was calculated in the usual fashion (no further details or reference).</p> <p>Diagnosis of heart failure required signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy (outpatient basis) or an augmented decongestive regimen with oral or parenteral medication during inpatient hospital stay.</p> <p>Clinical follow-up 1 month after randomisation and then at 3-month intervals until termination of the trial. Clinical and device testing carried out at each visit.</p> <p><i>Length of follow-up:</i> to trial termination. The trial was stopped on June 22, 2009. Average follow up was 2.4 years</p> <p><i>Recruitment dates:</i> December 22 2004 to April 23 2008</p>
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Participant characteristics	CRT-ICD, n= 1089	ICD, n= 731	p value
Age years, mean (SD)	65 (11)	64 (11)	
Gender, n (%) male	814 (74.7%)	553 (75.6%)	
Ethnicity n/N (%)			
- White	979/1083 (90.4%)	657/724 (90.7%)	
- Black	87/1083 (8.0%)	56/724 (7.7%)	
- Other	17/1083 (1.6%)	11/724 (1.5%)	

Participant characteristics	CRT-ICD, n= 1089	ICD, n= 731	p value
Cardiac history & NYHA class, n (%)			
- Ischaemic heart disease NYHA Class I	152 (14.0%)	113 (15.5%)	
- Ischaemic heart disease NYHA Class II	446 (41.0%)	288 (39.4%)	
- Non-ischaemic heart disease NYHA Class II	491 (45.1%)	330 (45.1%)	
NYHA class III or IV >3months before enrolment, n (%)	109 (10.0%)	73 (10.0%)	
Cardiac findings at enrolment			
- blood pressure mm Hg, mean (SD)			
systolic	124 (17)	121 (18)	
diastolic	72 (10)	71 (10)	
- blood urea nitrogen \geq 26 mg/dl (9.3 mmol/litre), n/N (%)	260/1082 (24.0%)	177/721 (24.5%)	
- creatinine mg/dl, mean (SD)	1.2 (0.4)	1.2 (0.4)	
- left bundle-branch block, n/N (%)	761/1088 (69.9%)	520/729 (71.3%)	
- right bundle-branch block, n/N (%)	136/1088 (12.5%)	92/729 (12.6%)	
- QRS duration \geq 150 msec, n (%)	699 (64.2%)	476 (65.1%)	
- LVEF, mean (SD)	0.24 (0.05)	0.24 (0.05)	
- six minute walk distance m, mean (SD)	359 (107)	363 (108)	
Heart rate	Not reported	Not reported	
Echocardiographic or Doppler findings ml, mean (SD)			
Left ventricular end-diastolic volume	245 \pm 60	251 \pm 65	
Left ventricular end-systolic volume	175 \pm 48	179 \pm 53	
Medications, n (%)			
- aldosterone antagonist	352 (32.3)	226 (30.9)	
- amiodarone	78 (7.2)	51 (7.0)	
- angiotensin-converting-enzyme inhibitor	839 (77.0)	563 (77.0)	
- angiotensin-receptor blocker	227 (20.8)	148 (20.2)	
- beta-blocker	1016 (93.3)	681 (93.2)	
- class I antiarrhythmic agent	12 (1.1)	3 (0.4)	
- digitalis	291 (26.7)	177 (24.2)	
- diuretic	824 (75.7)	533 (72.9)	
- lipid-lowering statin	735 (67.5)	491 (67.2)	
Previous treatment	Not reported	Not reported	
Cardiac risk factors, n/N (%)			
- treatment for hypertension	691/1085 (63.7)	461/730 (63.2)	
- atrial fibrillation >1 month before enrolment	118/1063 (11.1)	90/717 (12.6)	
- diabetes mellitus	329/1088 (30.2)	223/729 (30.6)	
- cigarette smoking	122/1069 (11.4)	92/717 (12.8)	
- body-mass index \geq 30	385/1072 (35.9)	263/723 (36.4)	
- coronary-bypass surgery	317/1088 (29.1)	208/730 (28.5)	
Comments:	<ul style="list-style-type: none"> Evidence for some missing baseline data (some Ns differ from total randomised to group) Percentages may not total 100 because of rounding. Baseline characteristics for subgroup who completed the echocardiography protocol reported⁸³ but not extracted. 		
RESULTS			
Outcomes	CRT-ICD, n=1089	ICD only, n=731	HR (95% CI), p value
Death from any cause or non-fatal heart failure event, n/N (%)	187/1089 (17.2%)	185/731 (25.3%)	0.66 (0.52 to 0.84), 0.001
- deaths, n/N (%)	36/1089 (3.3%)	18/731 (2.5%)	nr
- heart failure events only, n/N (%)	151/1089 (13.9%)	167/731 (22.8%)	0.59 (0.47 to 0.74), <0.001
Heart failure events occurring in hospital, n/N	136/151	140/167	
Heart failure events outside the hospital, n/N	15/151	27/167	
Death at any time ^a , n/N (%)	74/1089 (6.8)	53/731 (7.3)	1.00 (0.69 to 1.44), 0.99
Health related quality of life	Not reported	Not reported	

Symptoms and complications related to tachyarrhythmias and/or heart failure	Not reported	Not reported	
Heart failure hospitalisations	Not reported	Not reported	
Change in NYHA class	Not reported	Not reported	
Left ventricular remodelling			
- Change in LVEF	0.11 (n=746)	0.03 (n=620)	<0.001
- Left ventricular end-diastolic volume average change ^b from baseline to 1 year, ml	-52 (n=746)	-15 (n=620)	<0.001
-Left ventricular end-systolic volume average change ^b from baseline to 1 year, ml	-57 (n=746)	-18 (n=620)	<0.001
Exercise capacity outcomes	Not reported	Not reported	
<p>Comments: ^a Total of 127 deaths including those that occurred after the first heart-failure event, annual rate approximately 3% in each group. ^b Average change is not further defined. The 95% CI are represented on a figure but have not been data extracted.</p> <ul style="list-style-type: none"> • Kaplan-Meier estimates of the probability of survival free of heart failure are presented but have not been data extracted. • For the primary outcome of death or heart failure the HR of 0.66 indicates that there was a 34% reduction in the risk of death or nonfatal heart failure (which ever occurred first) among patients in the CRT-ICD group as compared to patients in the ICD-only group. • HRs for heart failure alone and for death at any time for the total population and in the ischemic and nonischemic subgroups (subgroup data below) indicate that the benefit from resynchronisation therapy was driven by a 41% reduction in the risk of heart failure. • An analysis⁸⁷ based on echocardiographic data and construction of a response score to identify predictors of response to CRT-D has not been extracted. • An assessment of the benefit of CRT-D for the prevention of recurring heart failure events HFEs has been published but has not been data extracted.⁸⁵ 			
Adverse effects of treatment	CRT-ICD, n=1089	ICD only, n=731	p value
Death during hospital after device implantation	1 (pulmonary embolus)		
Serious adverse events in the 30 days after device implantation, % of patients			
- pneumothorax	1.7	0.8	
- infection	1.1	0.7	
- pocket haematoma requiring evacuation	3.3	2.5	
Coronary venous dissection with pericardial effusion during CRT-ICD implantation	5 patients (0.5%)	n/a	
Left ventricular coronary-vein lead repositioned during 1 st 30 days	44 patients (4.0%)		
Frequency of serious device-related adverse events during long-term follow-up after the 1 st 30 days	4.5 per 100 device-months	5.2 per 100 device-months	
Removal of device, n (%)	14 (1.3)	5 (0.7)	
Comments:			
Subgroup data			
Patients with ischemic cardio-myopathy (NYHA class I or II)	CRT-ICD, n=598	ICD only, n=401	HR (95% CI), p value
Death from any cause or non-fatal heart failure event, n/N (%)	122/598 (20.4%)	117/401 (29.2%)	0.67 (0.52 to 0.88), 0.003
- heart failure events only, n/N (%)	96/598 (16.1%)	105/401 (26.2%)	0.58 (0.44 to 0.78), p<0.001
Death at any time, n/N (%)	53/598 (8.9)	35/401 (8.7)	1.06 (0.68 to 1.64), 0.80
Patients with nonischemic cardio-myopathy (NYHA class I or II)	CRT-ICD, n=491	ICD only, n=330	HR (95% CI), p value
Death from any cause or non-fatal heart failure event, n (%)	65 (13.2%)	68 (20.6%)	0.62 (0.44 to 0.89), 0.01
- heart failure events only, n(%)	55 (11.2%)	62 (18.8%)	0.59 (0.41 to 0.87), 0.01
Death at any time, n (%)	21 (4.3%)	18 (5.5%)	0.87 (0.44 to 1.70), 0.68
Risk of death or heart failure according to	No. of events/No. of patients		HR (95% CI), p value

selected clinical characteristics					
Age					
< 65 years	142/852		^c 0.80		
≥ 65 years	230/968		^c 0.60		
Sex					
male	294/1367		0.76 (0.59 to 0.97)		
female	78/453		0.37 (0.22 to 0.61), 0.01 for interaction		
NYHA class					
Ischaemic I	53/265		^c 0.76		
Ischaemic II	186/734		^c 0.62		
Nonischaemic II	133/821		^c 0.60		
QRS duration					
<150ms	147/645		1.06 (0.74 to 1.52)		
≥150ms	225/1175		0.48 (0.37 to 0.64), 0.001 for interaction		
LVEF					
≤25%	101/646		^c 0.70		
>25%	271/1174		^c 0.60		
LVEDV					
≤240ml	184/828		^c 0.70		
> 240ml	184/969		^c 0.62		
LVESV					
≤170ml	190/835		^c 0.66		
> 170ml	178/962		^c 0.70		
All patients	372/1820		HR 0.66		
Comments: ^c Hazard ratios estimated from figure but 95% CIs have not been data extracted. <ul style="list-style-type: none"> • Only data from pre-specified subgroups have been extracted. • Patients with ischaemic cardiomyopathy and those with non-ischaemic cardiomyopathy had a similar benefit from CRT-ICD therapy • CRT-ICD therapy was associated with a greater benefit in women than in men, and in patients with a QRS ≥150ms than in those with QRS <150ms. All other interaction p values exceeded 0.10. • No significant interaction effects were identified between the 37 centres with low enrolment (fewer than 10 patients) and the remaining 73 centres with higher enrolment or in patients with an elevated level of blood urea nitrogen (≥26mg/dL [≥9.3 mmol/L]) and those without an elevated level. No data presented. 					
Subgroup analysis					
- by gender⁸⁶	Women, n=453		Men, n=1,367		p value
	CRT-D	ICD	CRT-D	ICD	
Heart failure or death (primary end point)	29/275 (11%)	51/178 (29%)	159/814 (20%)	137/553 (25%)	
	CRT-D:ICD HR 0.31(95% CI 0.19-0.50), p<0.001		CRT-D:ICD HR 0.72(95% CI 0.57-0.92), p<0.01		interaction <0.01
Heart failure only	n=73 events CRT-D:ICD HR 0.30(95% CI 0.18-0.50), p<0.001		n=249 events CRT-D:ICD HR 0.65(95% CI 0.50-0.84), p=0.001		interaction <0.01
Death at any time	n=20 events CRT-D:ICD HR 0.28(95% CI 0.10-0.79), p=0.02		n=107 events CRT-D:ICD HR 1.05 (95% CI 0.70-1.57), p=0.83		interaction <0.03
Comments: <ul style="list-style-type: none"> • Patient characteristics are reported by gender but have not been extracted. • The primary end point included 54 deaths and 322 heart failure events. • A Kaplan-Meier plot of the probability of the primary endpoint in women and men with CRT-D and ICD is presented but has not been data extracted. Overall women receiving CRT-D had a significantly better outcome than women receiving ICD therapy and men receiving either therapy during average follow-up of 2.4 years. • Hazard ratios are also provided separately for men and women by disease etiology, QRS duration, and Conduction disturbance but these data have not been extracted. • Results from the echocardiographic study⁸³ have not been extracted. 					
Methodological comments					

- Allocation to treatment groups: Randomisation, in a 3:2 ratio to CRT-ICD or ICD only, was stratified according to clinical centre and ischaemic status with the use of an algorithm that ensured near balance in each stratum. Random assignment made by the coordinating and data centre and transmitted to the enrolling clinical centre by logging on to a web-based automated program or by telephone with hard copy to follow.⁸²
- Blinding: Treating physicians were aware of study-group assignments. Diagnosis of heart-failure, decisions about therapy or hospital admission for patients with heart failure was made by physicians aware of study-group assignments. Adjudication of end points was carried out by an independent mortality committee and by a heart-failure committee that was unaware of study-group assignments, according to prespecified criteria.
- Comparability of treatment groups: Baseline characteristics and use of cardiac medications at enrolment described as similar in the two groups.
- Method of data analysis: Intention to treat analysis (except for paired volume and ejection fraction studies). Event monitoring was prespecified and involved an independent data and safety monitoring board at up to 20 successive multiples of approximately 35 adjudicated events, precisely specified in terms of variance of the log-rank statistic, with topping boundaries specified for termination of the trial in favour of CRT-ICD therapy, in favour of ICD-only therapy, or for no significant difference. Analysis of the primary end point, based on the statistical log-rank test stratified according to study centre and ischaemic status was used to evaluate statistical significance for the trial. A Cox proportional-hazards regression model (similarly stratified) was used to estimate hazard ratios. These analyses were adjusted for the group-sequential stopping rule and incorporated late reported events that occurred before termination of the trial. Cox proportional-hazards regression was used for additional primary analyses for heart failure alone, for death at any time, and evaluation of 10 prespecified categorical subgroups and treatment interactions. All P values were two-tailed and were not adjusted for the stopping rule (except for the primary end-point analysis). Absolute change in left ventricular volumes and the ejection fraction were evaluated with paired-sample t-tests in patients in each study group who had paired baseline and 12-months recordings. The trial was stopped on the recommendation of the independent data and safety monitoring board when the monitoring statistic reached the prespecified efficacy boundary. The study was then unblinded and analyses were limited to events occurring before trial termination. A plan for secondary analyses related to recurring heart-failure events and a number of tertiary analyses was outlined. Of the tertiary analyses, only echocardiographic changes at 1 year are reported in the paper. Paper states that some caution in the interpretation of the subgroup interactions is needed because of multiple testing, but that given the significance of the comparison, the change of getting two or more false positives is small, and the analyses showed a relatively constant treatment effect over time.
- Sample size/power calculation: A Wang-Tsiatis ($\Delta=0.1$ category) group sequential design (reference provided) was used with a power of 95% to detect a hazard ratio of 0.75 at a two-sided significance level of 0.05.
- Attrition/drop-out: In the CRT-ICD arm 11/1089 patients (1.0%) did not receive a device, in the ICD only arm 19/731 (2.6%) did not receive a device. Overall implantation of a device was achieved in 98.4% of patients, with 95.4% receiving the device to which they had been assigned. During the trial 173 crossovers occurred for the following reasons: in patients assigned to ICD-only 91 (12.4%) received a CRT-ICD device (30 at physicians discretion before reaching an end point and 61 after a heart-failure event); in patients assigned to CRT-ICD 82 (7.5%) received an ICD-only device because of technical difficulties (not further described) in positioning the CRT pacing lead in the coronary vein. During the trial devices were also removed for a variety of reasons (as noted above in the results section, reasons not provided in the paper). In the CRT-ICD group 44 patients (4.0%) declined to continue participating in the study, were withdrawn by a physician, or were lost to follow up in comparison with 55 patients (7.5%) in the ICD-only group. 201 patients in the CRT-ICD group underwent 1-year echocardiographic evaluation with the CRT device switched off. These patients are not included in the paired volume and ejection-fraction studies.

General comments

- Generalisability: The study was designed to investigate the use of a combined ICD-CRT in mildly symptomatic or asymptomatic patients and thus the results are unlikely to be transferable to more severe heart failure patients.
- Outcome measures: The primary end point was a composite measure but the discussion section describes this as appropriate and widely used in heart-failure trials. Other outcomes appear appropriate, however not all were ITT.
- Inter-centre variability: States no significant interaction effects were identified between the 37 centres with low enrolment (fewer than 10 patients) and the remaining 73 centres with higher enrolment.
- Conflict of interests: 11 of the 14 authors named on the publication declared one or more potential conflict

of interest in the form of grant support, lecture fees, consulting fees or institutional fellowship from one or more companies.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^d	Support for Judgement
Selection bias		
Random sequence generation	Unclear	No information provided
Allocation concealment	Low risk	“Random assignment made by the coordinating and data centre and transmitted to the enrolling clinical centre by logging on to a web-based automated program or by telephone with hard copy to follow.”
Performance bias		
Blinding of participants and personnel	High risk	“The treating physicians were aware of study-group assignments”
Detection bias		
Blinding of outcome assessment	High risk	“Members of the heart-failure adjudication committee were unaware of study-group assignments, but the investigators who decided on therapy or hospital admission for patients with heart failure were aware of such assignments. It is possible that the investigators’ knowledge of study-group assignment contributed in some way to the lower frequency of heart failure in the CRT-ICD group.”
Attrition bias		
Incomplete outcome data addressed - Survival/heart failure outcomes	Low risk	“Data analysis was performed according to the intention-to-treat principle” “For the purpose of analysis, subjects will not be censored at withdrawal, and every effort will be made to ascertain the occurrences or non-occurrence of the primary endpoints” ⁸²
Incomplete outcome data addressed - Ventricular remodelling outcomes	High risk	201/1820 participants not included in paired volume and ejection-fraction studies.
Reporting bias		
Selective reporting	Low risk	Paper available describing design and clinical protocol. Outcomes of interest reported as expected.
Other bias		
Other sources of bias	Low risk	

^d ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias

Piccirillo study

Reference and design	Intervention and Comparator	Participants	Outcome measures
Piccirillo <i>et al.</i> , 2006 ⁸⁸ <i>Study design:</i> RCT Italy <i>Number of centres:</i> 1 <i>Funding:</i> not	<i>Intervention:</i> CRT-D <i>Comparator:</i> ICD Biventricular pacemaker (Guidant, St Paul, Minnesota, USA) - the final pace setting was VDD with a lower rate well below patient’s lowest intrinsic heart rate to maintain natural atrial tracking at	<i>Indication for treatment:</i> CHF (with low ejection fraction and prolonged QRS interval) secondary to ischaemic dilated cardiomyopathy <i>Number of randomised participants:</i> n = 31 CRT-D, n=16 ICD, n=15	<i>Not stated if primary or secondary outcome:</i> spectral indexes based on power spectral analysis and changes in spectral indices (not data extracted). Also reported: mortality and

reported	<p>rest (setting essential to allow power spectral analysis of HRV)</p> <p>Both groups were taking standard medications for HF, including ramipril (2.5 to 10 mg/day) or losartan (50 mg/day), furosemide (25 to 250 mg/day), spironolactone (25 mg/day to 50 mg/day), carvedilol (6.25 to 50 mg/day) or bisoprolol (2.5 to 5 mg/day), digoxin (0.125 or 0.250 mg/day) and acetylsalicylic acid (100 mg/day)</p> <p><i>Other interventions used:</i> none reported</p>	<p>Also reported data for healthy, non-randomised control group, n=12. Data not extracted.</p> <p><i>Inclusion criteria:</i> LVEF \leq 35; QRS interval $>$120 msec and sinus rhythm.</p> <p><i>Exclusion criteria:</i> malignancy; primary valve disease; frequent extrasystole ($>$1 per min); atrial fibrillation or other arrhythmias requiring a pacemaker (A-V disturbances) or defibrillator for secondary prevention owing to a history of malignant arrhythmias.</p>	<p>change in NYHA class</p> <p><i>Method of assessing outcomes:</i> details of power spectral analysis and assessment of changes in spectral indices not data extracted. All ICD shocks assessed by 3 experts cardiologist to evaluate appropriateness.</p> <p><i>Length of follow-up:</i> 1 year</p> <p><i>Recruitment:</i> not reported</p>
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Participant characteristics	CRT-D, n=16	ICD, n=15	p value
Age years, mean (SD)	65 (4)	65 (8)	
Gender, M/F	13/3	12/3	
Ethnicity	Not reported	Not reported	
NYHA class III, n	5	5	
NYHA class IV, n	11	10	
LVEF %, mean (SD)	23 (4)	22 (8)	
QRS length (ms), mean (SD)	160 (4)	159 (8)	
Heart rate (beats/min), mean (SD)	79 (4)	81 (8)	
Systolic blood pressure (mm Hg), mean (SD)	112 (12)	109 (19)	
Diastolic blood pressure (mm Hg), mean (SD)	68 (8)	69 (11)	
Electrophysiology findings			
End-systolic diameter (mm), mean (SD)	60 (8)	59 (8)	
End-diastolic diameter (mm), mean (SD)	69 (4)	70 (19)	
Current pharmacological therapy			
Digoxin, n	12	11	
Ramipril, n	16	15	
Furosemide, n	16	15	
Spironolactone, n	9	10	
Carvedilol, n	13	12	
Bisoprolol, n	2	1	
Acetylsalicylic acid, n	16	14	
Cardiac history			
Unstable symptoms of heart failure, n	0	0	
Hospitalisation, n	0	0	
Recent previous treatment			
Coronary angioplasty, n	0	0	
Revascularisation procedures, n	0	0	
Change of therapy during the past 3 months, n	0	0	
Comorbidities	Not reported	Not reported	
Body mass index (kg/m ²), mean (SD)	26 (4)	26 (4)	

Participant characteristics	CRT-D, n=16	ICD, n=15	p value
Comments: data for healthy control group not data extracted; p values for comparison of of CHF patients prior to treatment vs controls not data extracted.			
<ul style="list-style-type: none"> None of the 3 CRT-D ‘non-responders’ received ICD shocks. 			
RESULTS			
Outcomes	CRT-D, n=16	ICD, n=15	p value
Death, n	0	0	
Health related quality of life	Not reported	Not reported	
Received appropriate shocks	2	4	
- Sustained VT	1	3	
- Sustained VF	1	1	
Hospitalisations due to worsening CHF, n	0	2	
NYHA class after 12 months, n ^a			
Class I	1	0	
Class II	3 ^a	1	
Class III	6	1	
Class IV	6 ^a	13	
LVEF %, ^b mean	28	22	
Exercise capacity outcomes	Not reported	Not reported	
Heart rate (beats/min), mean (SD)	75 (4)	76 (4)	
Systolic blood pressure (mm Hg), mean (SD)	115 (4) ^c	108 (11)	
Diastolic blood pressure (mm Hg), mean (SD)	69 (4)	70 (4)	
End-systolic diameter (mm), mean (SD)	55 (4) ^c	61 (4)	
End-diastolic diameter (mm), mean (SD)	66 (8) ^c	72 (11) ^c	
Change in diuretic medication, n	5 reduced	6 increased	
Comments: ^a data for CRT-D group differ between table and text (class 2 amount to 7 in text, class IV are amount to 2 in text, but 3 participants were considered as non-responders as their NYHA class did not change); ^b SDs reported in text and table differ (CRT-D SD 1 in text, 4 in table; ICD SD 1 in text, 8 in table (p-value for within CRT-D group comparison baseline to follow-up not extracted). ^c p-values for within group comparisons baseline to follow-up not extracted.			
<ul style="list-style-type: none"> CRT-D: 3 patients were considered non-responders as their NYHA class did not change; text states that from baseline 4 CRT-D patients improved from NYHA IV to NYHA II, and 5 from NYHA IV to NYHA III, with 3 CRT-D improving from NYHA III to NYHA II and 1 patient from NYHA III to NYHA I. however, these changes do not correspond with the data presented in the table. ICD: 3 patients worsened from NYHA class III to IV and 1 patient improved from class III to II. Results from power spectral analysis for heart rate and blood pressure variability reported, but not extracted. 			
Adverse effects of treatment	CRT-D, n=16	ICD, n=15	p value
	Not reported	Not reported	
Comments: states there were no major complications following implantation.			
Methodological comments			
<ul style="list-style-type: none"> <i>Allocation to treatment groups</i>: patients were randomly assigned in a 1:1 ratio to ICD or CRT-D <i>Blinding</i>: spectral recording assessment blinded (outcomes not extracted), but no other blinding reported. <i>Comparability of treatment groups</i>: states that there were no significant difference in age, BMI, gender distribution or blood pressure between the two CHF groups and the control group, no p values reported (p values were reported for CHF groups vs control, but were not data extracted). <i>Method of data analysis</i>: Linear data express as means ± SD. Non-linear data as median (IQR). ITT analysis not reported. Baseline ICD and CRT-D group data before implantation compared with the control group. The data for ICD and CRT-D groups were then compared at baseline and at 1 year. One-way analysis of variance (ANOVA) was used to compare the general 			

<p>characteristics and other linear data between the study groups. Kruskal–Wallis test and Mann–Whitney test were used for non-normally distributed data. The Wilcoxon test was used for variables with a nonlinear distribution. Event-free survival functions were estimated using the Kaplan–Meier method and differences between the curves were tested for significance by the log-rank statistic; relative risks were computed by Cox proportional-hazards regression model. As spectral analysis outcomes not extracted (because not specified for review) the methods for analysis of these outcomes were also not extracted.</p> <ul style="list-style-type: none"> • <i>Sample size/power calculation</i>: none reported. • <i>Attrition/drop-out</i>: none, all patients completed the study.
<p>General comments</p> <ul style="list-style-type: none"> • <i>Generalisability</i>: sample size too small to generalise, but results would be limited to patients with post-ischaemic dilated cardiomyopathy, excluding primary dilated cardiomyopathy patients. • <i>Outcome measures</i>: extracted outcome measures appear appropriate. • <i>Inter-centre variability</i>: not applicable, one centre only. • <i>Conflict of interests</i>: not reported.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^c	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Only states randomly assigned in a 1:1 ratio, no other details reported.
Allocation concealment	Unclear	No details reported.
Performance bias		
Blinding of participants and personnel	High risk	No blinding reported.
Detection bias		
Blinding of outcome assessment	High risk	Assessment of spectral recordings blinded (outcomes not extracted), but no other blinding reported.
Attrition bias		
Incomplete outcome data addressed	Low risk	No ITT analysis reported, but all data appears to have been reported and states all patients completed the study.
Reporting bias		
Selective reporting	Low risk	No protocol available, but all stated outcomes were reported.
Other bias		
Other sources of bias	Low risk	

^c ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias

Pinter study

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Pinter <i>et al.</i>, 2009¹⁵</p> <p><i>Study design</i>: RCT</p> <p>Canada</p> <p><i>Number of centres</i>: 7</p>	<p><i>All patients</i>: CONTAK CD CHF Device, model 1823 or CONTAC RENEWAL HF Device, model H135 (Guidant Inc, Minneapolis, MN). Standard atrial pacing lead, ventricular defibrillator lead and Easytrak Left</p>	<p><i>Indication for treatment</i>: Mild to moderate heart failure at high risk of sudden death and eligible for an ICD but not candidates for CRT based on guidelines at time of study.</p> <p><i>Number of randomised participants</i>: n = 72</p>	<p><i>Primary outcomes</i>: Left ventricular end-systolic volume (LVESV) change from baseline to 6 months.</p> <p><i>Secondary outcomes</i>: Change in: QoL Stroke volume Cardiac volume</p>

<p><i>Funding:</i> Guidant Inc, Minneapolis, MN</p>	<p>ventricular pacing lead (Guidant Inc).</p> <p><i>Intervention:</i> CRT-D (CRT ON) Pacing programmed to dual-chamber tracking pacing mode (DDD) with lower rate limit at 40 beats/min and maximum tracking rate 20 beats/min less than the tachycardia detect rate. AV delay determined by a proprietary algorithm. RV and LV pacing were simultaneous.</p> <p><i>Comparator:</i> ICD (CRT OFF) Dual chamber non-tracking pacing mode (DDI) 40 beats/min backup biventricular pacing.</p> <p><i>Other interventions used:</i> Not reported, but inclusion criteria state ≥ 2 weeks treatment with maximal tolerated doses of ACE inhibitors or beta-blockers unless adverse effects or contraindicated.</p>	<p>CRT-D, n=36 ICD, n=36</p> <p><i>Inclusion criteria:</i> Heart failure: unequivocal symptoms of dyspnoea or fatigue on climbing ≤ 2 flights of stairs or 6-min walk distance ≤ 450 m; LVEF $\leq 35\%$ within 6 months of implant; QRS interval >120 ms; ≥ 2 weeks treatment with maximal tolerated doses of ACE inhibitors or beta-blockers unless adverse effects or contraindicated. 18-80 years old.</p> <p><i>Exclusion criteria:</i> Pacing for symptomatic bradycardia; not in sinus rhythm; MI or unstable angina within 6 weeks, coronary artery bypass surgery within 4 weeks, Canadian Cardiovascular Society Class 3 or worse angina; typical right bundle branch block morphology in lead V1; pregnant.</p>	<p>Mitral jet area Cardiac output LVEF Serum BNP Average heart rate Standard deviation of adjacent sinus beat intervals (SDANN). Also reports 6 minute walk test, death and hospitalisations.</p> <p><i>Method of assessing outcomes:</i> At baseline and 6 months. LVESV measured by quantitative resting radionuclide angiogram (MUGA), 6-min walk test, 24-hour Holter monitoring for heart rate and SDANN. QoL assessed by Minnesota Living with Heart Failure questionnaire, SF-36, Duke Activity Status Index (DASI), one item Global Visual Analogue Scale.</p> <p><i>Length of follow-up:</i> 6 months</p> <p><i>Recruitment:</i> not reported</p>
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Participant characteristics	CRT ON (CRT-D), n=36	CRT OFF (ICD), n=36	p value
Age years, mean (SD)	66.3 (8.6)	66.1 (8.8)	ns
Gender, % male	77.8	80.6	ns
Ethnicity	nr	nr	
NYHA classification	nr	nr	
LV measurements by MUGA, mean (SD)			
- left ventricular end-systolic volume, ml	242 (96)	251 (147)	ns
- left ventricular end-diastolic volume, ml	314 (108)	335 (156)	ns
- LVEF, %	24.2 (7.5)	26.8 (8.4)	ns
LV measurements by echocardiogram mean (SD)			
- left ventricular end-systolic volume, ml	217 (72)	213 (101)	ns
- left ventricular end-diastolic volume, ml	270 (74)	272 (106)	ns
- LVEF, %	21.2 (7.9)	24.0 (8.3)	ns
Heart rate, bpm	68.1 (12.3)	63.6 (11.0)	ns

Participant characteristics	CRT ON (CRT-D), n=36	CRT OFF (ICD), n=36	p value
Systolic blood pressure, mmHg	113 (19.6)	114.1 (20.8)	ns
Diastolic blood pressure, mmHg	65.7 (10.0)	65.2 (10.7)	ns
Current pharmacological therapy	nr	Nr	
Cardiac history, % of patients			
- coronary artery disease	77.8	80.6	ns
- previous myocardial infarction	66.7	75.0	ns
- coronary artery bypass surgery	38.9	30.6	ns
- coronary angioplasty	8.3	22.2	ns
- dilated cardiomyopathy	16.7	8.33	ns
- valvular disease	16.7	8.33	ns
- mitral regurgitation grade 2/3/4	9/11/1	7/5/1	p=0.09
- atrial fibrillation	16.7	5.6	ns
Primary arrhythmia, %			
- cardiac arrest	25.0	16.7	ns
- sustained VT	58.3	55.5	ns
- prophylactic ICD	16.7	27.8	ns
Hypertension, %	11.1	22.2	ns
Diabetes, %	30.6	25.0	ns
Serum creatinine, μ mol/L, mean (SD)	121 (42)	114 (36)	ns
Assessment of functional status			
- 6-min walk, m, mean (SD)	314 (114)	338 (110)	ns
- Duke Activity Status Index	11.3 (9.8)	12.4 (9.3)	ns
- Global Visual Analogue Scale	6.4 (2.0)	6.5 (1.9)	ns
- Minnesota Living with Heart Failure			
- Complete score	42.3 (20.8)	42.8 (24.9)	ns
- Physical dimension	20.1 (9.2)	17.7 (9.8)	ns
- Emotional dimension	8.5 (6.4)	9.1 (7.6)	ns
- SF-36 health survey subscales			
- Physical functioning	46.7 (24.9)	44.5 (26.5)	ns
- Role physical	14.0 (26.9)	12.4 (23.9)	ns
- Bodily pain	93.0 (11.4)	95.3 (11.0)	ns
- General health	59.4 (12.7)	59.0 (9.6)	ns
- Vitality	43.9 (19.4)	42.8 (25.2)	ns
- Social functioning	59.4 (27.1)	61.7 (29.0)	ns
- Role emotional	46.7 (46.0)	54.0 (47.5)	ns
- Mental health	65.3 (20.0)	69.0 (22.9)	ns
- SF-36 survey component scores			
- Physical component score	39.5 (5.7)	39.1 (5.7)	ns
- Mental component score	43.7 (11.6)	46.0 (13.7)	ns

RESULTS

Outcomes (Unless stated otherwise, it is assumed values are mean (SD) as this is not specified in paper)	CRT ON (CRT-D), n=36	CRT OFF (ICD), n=36	p value
Deaths in 6 months follow-up, n (due to cardiac causes)	1/36 (cardiac causes)	1/36 (cardiac causes)	
LV measurements by MUGA, change from baseline to 6 months, ^a			
- left ventricular end-systolic volume, ml (primary outcome)	-7 (52)	-30 (47)	ns
- left ventricular end-diastolic volume, ml	-7 (61)	-34 (65)	ns
- LVEF, %	1.7 (5.4)	0.6 (6.8)	ns

RESULTS			
Outcomes (Unless stated otherwise, it is assumed values are mean (SD) as this is not specified in paper)	CRT ON (CRT-D), n=36	CRT OFF (ICD), n=36	p value
LV measurements by echocardiogram, change from baseline to 6 months, ^a			
- left ventricular end-systolic volume, ml	-21 (45)	-5 (22)	ns
- left ventricular end-diastolic volume, ml	-16 (44)	-13 (47)	ns
- LVEF, %	3.9 (8.9)	1.9 (6.8)	ns
Cardiac output measured by MUGA, l/min, (SD) ^a			
- baseline	4.5 (1.6)	5.1 (1.9)	
- 6 months	4.8 (1.8)	4.7 (1.8)	
- difference	0.38 (1.5)	-0.56 (1.9)	0.033
Patients hospitalised ^b , %	30.6	36.1	
Jugular venous pressure, cm above the sternal angle ^a			
- baseline	2.1 (2.3)	2.1 (2.1)	ns
- 6 months	2.9 (2.27)	4.3 (2.5)	nr
Bain natriuretic peptide level, ng/l ^a			
- baseline	198.7 (167.2)	200.9 (208.7)	
- 6 months	119.4 (131.7)	107.6 (99.4)	ns
SDANN, ms			
- baseline	83.2 (31.1)	93.7 (29.4)	ns
- 6 months	83.0 (30.6)	109.8 (41.5)	nr
Interventricular dyssynchrony, ms			
- baseline	40 (48)	47 (36)	
- 6 months	13 (40)	48 (34)	
Horizontal extent of the mitral regurgitation jet area, ^a cm ²			
- baseline	4.79 (3.06)	3.58 (3.66)	
- 6 months	3.90 (3.65)	3.00 (2.74)	
QRS duration ^a			
- baseline	169.1 (22.8)	159.5 (17.4)	
- 6 months	163.3 (24.3)	163.8 (22.3)	
Ventricular tachyarrhythmia event requiring therapy from the device, n (%) patients	7 (19.4)	6 (16.7)	ns
Number of treated VT episodes per patient, mean	5.9 (6.1)	3.4 (2.7)	ns
Assessment of functional status, change from baseline to 6 months, ^a			
6-min walk, m	53.3 (113.3)	27.3 (71.1)	ns
Duke Activity Status Index	4.63 (9.20)	1.08 (7.02)	ns
Global Visual Analogue Scale	-0.07 (2.22)	-0.17 (1.64)	ns
Minnesota Living with Heart Failure			
- Total score	-7.8 (20.1)	-0.2 (13.5)	ns
- Physical dimension	-5.0 (12.4)	-0.6 (7.9)	ns
- Emotional dimension	-1.3 (5.0)	0.3 (3.4)	ns
SF 36, change from baseline to 6 months, ^a			
Physical functioning	11.2 (24.2)	6.3 (21.2)	ns
Role physical	19.6 (43.2)	21.6 (38.1)	ns
Bodily pain	-3.3 (16.6)	-2.3 (13.1)	ns
General health	-5.8 (14.9)	-5.8 (13.6)	0.02

RESULTS			
Outcomes (Unless stated otherwise, it is assumed values are mean (SD) as this is not specified in paper)	CRT ON (CRT-D), n=36	CRT OFF (ICD), n=36	p value
Physical component score	1.4 (6.4)	1.3 (4.8)	NS
Vitality	4.7 (22.7)	2.6 (15.7)	NS
Social functioning	12.5 (23.3)	5.4 (32.6)	NS
Role emotional	29.5 (48.4)	3.3 (48.2)	NS
Mental health	4.5 (14.5)	0.1 (21.8)	NS
Mental component score	5.1 (10.1)	0.5 (12.4)	NS
<p>Comments: ^a With group P values reported but not data extracted; ^b States there was no difference in the number of patients hospitalised (statistical significance not reported), the number of hospitalisations, or the reasons for hospitalisations between the two groups (data for the latter two outcomes not reported).</p> <ul style="list-style-type: none"> • States that systolic and diastolic blood pressure, and heart rate were similar at a baseline in the two groups and did not change significantly in either group at 6 months (data not presented). • States no difference in the number of patients receiving shock from the device or the number of shocks per patient, data not presented. • Assume values are mean (SD), but this is not always stated. 			
Adverse effects of treatment	CRT ON (CRT-D), n=36	CRT OFF (ICD), n=36	p value
Not reported			
<p>Methodological comments</p> <ul style="list-style-type: none"> • <i>Allocation to treatment groups:</i> All patients received device. Left ventricular pacing turned off in immediate postoperative period. Patients randomly assigned following completion of baseline procedures 14-28 days post implant. • <i>Blinding:</i> Patients blinded to treatment allocation. All post implant study evaluations were performed by personnel blinded to treatment allocation. • <i>Comparability of treatment groups:</i> no significant differences, although there were more patients with significant mitral regurgitation in the CRT ON group, p=0.09. • <i>Method of data analysis:</i> Primary endpoint analysed according to ITT. Data analysed using unpaired t-test, Wilcoxon signed rank test and repeated measures analysis of variance as appropriate. The difference in change from baseline between groups and within groups analysed using Wilcoxon signed rank test. For some outcomes, data are compared within groups only and not between groups, these p values have not been extracted. • <i>Sample size/power calculation:</i> Allowing for 10% dropout or crossover, estimated 70 patients had to be included to show a clinically meaningful 12% decrease in end-systolic volume with 80% power and two-tailed alpha of 0.05. • <i>Attrition/drop-out:</i> 75/90 (83.3%) attempted implants were successful. 2/75 not randomised due to device-related technical difficulties(double sensing), 1/75 not randomised due to worsening heart failure. 72 randomised. 5/72 missed 6 month visit (1 from each group died due to cardiac causes; 2 crossed over: 1 from OFF to ON due to worsening congestive heart failure, 1 from ON to OFF due to late LV capture failure; 1 CRT ON too ill). 67/72 (93%) completed study (CRT ON = 33; CRT-OFF = 34). 			
<p>General comments</p> <ul style="list-style-type: none"> • <i>Generalisability:</i> Only people with successful implants were randomised. This is a study of prophylactic CRT on patients with mild to moderate heart failure; patients did not meet guidelines for a CRT at the time of the study but may meet indication for CRT by current standards. • <i>Outcome measures:</i> Radionuclide angiography was selected for the measurement of the primary endpoint because of the assumption that it is more accurate than echocardiography in measuring left ventricular outcomes. NYHA Class and adverse events not reported. • <i>Inter-centre variability:</i> Not reported. • <i>Conflict of interests:</i> Two authors have received honoraria and research funding from Guidant Inc. 			

Study was supported by an unrestricted educational grant from Guidant Inc.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^c	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Details not reported
Allocation concealment	Unclear	Details not reported
Performance bias		
Blinding of participants and personnel	Low risk	States that patients were blinded, although not clear how this was maintained.
Detection bias		
Blinding of outcome assessment	Low risk	States that all post implant study evaluations were performed by personnel blinded to treatment allocation
Attrition bias		
Incomplete outcome data addressed	Low risk	Attrition and crossovers reported. ITT analysis performed.
Reporting bias		
Selective reporting	Low risk	No protocol available but outcomes listed in the methods were reported on.
Other bias		
Other sources of bias	Low risk	

^c 'Low risk', 'high risk' or 'unclear risk' of bias

RAFT

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Tang <i>et al.</i>, 2010;¹³ 2009⁸⁹</p> <p>RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial)</p> <p><i>Study design:</i> RCT</p> <p>Canada, Europe, Turkey and Australia</p> <p><i>Number of centres:</i> 34 (Canada 24, Europe & Turkey 8, Australia 2)</p> <p><i>Funding:</i> University-industry peer-</p>	<p><i>Intervention:</i> ICD-CRT (commercially available transvenous leads and devices, Medtronic). Standard implantation technique. Programming standardised to maximise ventricular pacing</p> <p><i>Comparator:</i> ICD Programming standardised to minimise ventricular pacing.</p> <p><i>Other interventions used:</i> OPT for both groups beta-</p>	<p><i>Indication for treatment:</i> initially mild-to-moderate (NYHA Class II or III) heart failure despite OPT, later restricted to NYHA class II, with left ventricular systolic dysfunction and wide QRS complex.</p> <p><i>Number of randomised participants:</i> n =1798 ICD-CRT, n=894 ICD, n=904</p> <p><i>Inclusion criteria:</i> NYHA class: II or III (revised in February 2006 to II only), symptoms despite OPT; LVEF: ≤30% from ischemic or non-ischemic causes; QRS interval: ≥120msec or a paced QRS duration of ≥200msec Sinus rhythm or permanent atrial fibrillation or flutter with a controlled ventricular rate (≤60 beats per minute at rest and ≥90 beats per min during a 6-min walk</p>	<p><i>Primary outcomes:</i> composite outcome of death from any cause or heart failure leading to hospitalisation</p> <p><i>Secondary outcomes:</i> death from any cause at any time during the study, death from any cardiovascular cause, and hospitalisation for heart failure among all patients (those with NYHA class II and NYHA class III heart failure at baseline).</p> <p><i>Method of assessing outcomes:</i> hospitalisation for heart failure was defined as admission to a health care facility lasting >24hrs with symptoms of</p>

<p>reviewed grant from the Canadian Institutes of Health Research. Medtronic of Canada (industry partner) provided funding and CRT components.</p>	<p>blocker, an angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker, spironolactone, aspirin and statins when appropriate; provide uniform arrhythmia detection and therapy.</p>	<p>test) or planned atrioventricular-junction ablation after device implantation) <u>and</u> planned ICD implantation for indicated primary or secondary prevention of sudden cardiac death; Optimal heart failure pharmacological therapy.⁸⁹</p> <p><i>Exclusion criteria:</i> Major coexisting illness; recent cardiovascular event protocol;⁸⁹ life expectancy of <1yr from non-cardiac cause; expected cardiac transplantation within 1yr (status 1); intra-venous inotropic agent in the last 4 days; acute coronary syndrome including MI can be included if the patient has had a previous MI with LV dysfunction (LVEF ≤30%); in hospital patients who have acute cardiac or non-cardiac illness that requires intensive care; uncorrected or uncorrectable primary valvular disease; restrictive, hypertrophic or reversible form of cardiomyopathy; severe primary pulmonary disease such as cor pulmonale; tricuspid prosthetic valve; patients with an existing ICD (inclusion of patients with existing pacemaker if patient satisfies all other inclusion/exclusion criteria); coronary revascularisation (CABG or PCI) <1 month if previous LVEF >30% (more recent revascularisations can be included if previous LVEF ≤30%); patients included in other clinical trial that will affect the objectives of this study; history of noncompliance of medical therapy; unable or unwilling to provide informed consent.</p>	<p>congestive heart failure and subsequent treatment for heart failure (admissions for other medical problems that then developed into heart failure in the hospital were not classified as hospitalisation for heart failure).</p> <p>An adjudication committee reviewed available documents and determined the cause of death and whether hospitalisations lasted >24hrs were due to the exacerbation of heart failure. All adverse events occurring within 30 days after ICD implantation were adjudicated as related or unrelated to the ICD.</p> <p>Follow-up visits 1 month after device implantation and then 6 monthly until ≥18 months until the end of the trial, with clinical assessment and device interrogation at each visit.</p> <p><i>Length of follow-up:</i> minimum of 18mths mean 40 months (SD 20); mean follow-up for surviving patients 44 months (SD 18)</p> <p><i>Recruitment:</i> January 2003 through February 2009</p>
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Participant characteristics	ICD-CRT, n = 894	ICD, n=904	p value
Age years, mean (SD)	66.1 (SD 9.3)	66.2 (SD 9.4)	nr
Gender, male (%)	758 (84.8)	732 (81.0)	nr
Ethnicity	nr	nr	
NYHA classification, n (%)			

Participant characteristics	ICD-CRT, n = 894	ICD, n=904	p value
Class II	708 (79.2)	730 (80.8)	nr
Class III	186 (20.8)	174 (19.2)	nr
LVEF, % mean (SD)	22.6 (5.4)	22.6 (5.1)	nr
Atrial rhythm, n (%)			
Permanent atrial fibrillation or flutter	114 (12.8)	115 (12.7)	nr
Sinus or atrial paced	780 (87.2)	789 (87.3)	nr
QRS duration			
Intrinsic, no of patients	n=826	n=837	nr
Intrinsic - msec, mean (SD)	157 (23.6)	158.3 (24.0)	nr
Paced, no of patients	n=68	n=67	nr
Paced – msec, mean (SD)	206.5 (24.0)	210.3 (18.3)	nr
QRS morphologic type, n (%)			
RBBB	68 (7.6)	93 (10.3)	nr
LBBB	652 (72.9)	643 (71.1)	nr
Nonspecific intraventricular conduction delay	106 (11.9)	101 (11.2)	nr
Ventricular paced	68 (7.6)	67 (7.4)	nr
Peripheral vascular disease, n (%)	88 (9.8)	90 (10.0)	nr
Underlying heart disease, n (%)			
Ischemic	614 (68.7)	587 (64.9)	nr
Non-ischemic	280 (31.3)	317 (35.1)	nr
Hospitalisation for heart failure in prev.6mth, n (%)	238 (26.6)	223 (24.7)	nr
Previous treatment			
Percutaneous coronary interventions, n(%)	220 (24.6)	208 (23.0)	nr
CABG, n(%)	293 (32.8)	313 (34.6)	nr
Comorbidities			
Diabetes mellitus, n (%)	293 (32.8)	313 (34.6)	nr
Hypertension, n (%)	402 (45.0)	397 (43.9)	nr
Current cigarette smoking	121 (13.5)	127 (14.0)	nr
Medication, n (%)			
Beta-blocker	808 (90.4)	805 (89.0)	nr
ACE inhibitor or ARB	859 (96.1)	878 (97.1)	nr
Spirolactone	372 (41.6)	378 (41.8)	nr
Digoxin	301 (33.7)	319 (35.3)	nr
Aspirin	584 (65.3)	622 (68.8)	nr
Warfarin	310 (34.7)	298 (33.0)	nr
Clopidogrel	134 (15.0)	145 (16.0)	nr
Statin	607 (67.9)	618 (68.4)	nr
Diuretic	757 (84.7)	756 (83.6)	nr
Calcium-channel blocker	101 (11.3)	83 (9.2)	nr
Amiodarone	140 (15.7)	124 (13.7)	nr
Other anti-arrhythmia drug	12 (1.3)	8 (0.9)	nr
Distance on 6-min walk test, n	n=789	n=765	nr
Distance on 6-min walk test metres, mean (SD)	351.3 (106.7)	354.9 (110.1)	nr
Estimated glomerular filtration rate, n	n=885	n=897	nr
Estimated glomerular filtration rate, mean % (SD)	59.5 (19.8)	60.8 (21.9)	nr
Rate (ml/min/1.73m ²), n (%)			
<30	57 (6.4)	63 (7.0)	nr
30-59	398 (45.0)	383 (42.7)	nr
≥60	430 (48.6)	451 (50.3)	nr
Comments: Enrolment breakdown: Canada n=1617, Europe and Turkey n=137, Australia n=44;			

RESULTS			
Primary Outcome, n (%)	ICD-CRT, n=894	ICD, n=904	Hazard Ratio (95% CI); p value
Death or hospitalisation for heart failure	297/894 (33.2)	364/904 (40.3)	0.75 (0.64 to 0.87); <0.001
Secondary outcomes, n (%)			
Death from any cause	186/894 (20.8)	236/904 (26.1)	0.75 (0.62 to 0.91); 0.003
Death from cardiovascular cause	130/894 (14.5)	162/904 (17.9)	0.76 (0.60 to 0.96); 0.02
Hospitalisation for heart failure	174/894 (19.5)	236/904 (26.1)	0.68 (0.56 to 0.83); <0.001
Hospitalisation ≥ 1 during follow up (mostly cardiovascular), n	509/894	509	nr
Hospitalisation: cardiac cause, n	423	404	HR 1.04; 0.56
Probability of event-free survival at 5 years, %	57.6	48.7	nr
5-year actuarial rate of death, %	28.6	34.6	nr
Patients in NYHA class II			
	n=708	n=730	
Primary outcome: death or hospitalisation for heart failure	193/708 (27.3)	253/730 (21.1)	0.73 (0.61 to 0.88); 0.001
Secondary outcomes: Death from any cause	110/708 (15.5)	154/730 (21.1)	0.71 (0.56 to 0.91); 0.006
Death from cardiovascular cause	74/708 (10.5)	100/730 (13.7)	0.73 (0.54 to 0.99); 0.04
Hospitalisation for heart failure	115/708 (16.2)	159/730 (21.8)	0.70 (0.55 to 0.89); 0.003
Patients in NYHA class III			
	n=186	n=174	
Primary outcome: death or hospitalisation for heart failure	104/186 (55.9)	111/174 (63.8)	0.76 (0.58 to 0.99); 0.04
Secondary outcomes: Death from any cause	76/186 (40.9)	82/174 (47.1)	0.79 (0.58 to 1.08); 0.14
Death from cardiovascular cause	56/186 (30.1)	62/174 (35.6)	0.77 (0.54 to 1.10); 0.15
Hospitalisation for heart failure	59/186 (31.7)	77/174 (44.3)	0.63 (0.45 to 0.88); 0.006
<p>Comments: 12 patients underwent cardiac transplantation before reaching the primary outcome (ICD-CRT n=7; ICD n=5).</p> <ul style="list-style-type: none"> • 14 patients would be needed to be treated for 5 years with ICD-CRT in order to prevent 1 death • Kaplan-Meier figure reported for composite primary outcome and death from any cause for all patients for NYHA II and III subgroups (not data extracted) • For NYHA class II and III, the 2 interventions were associated with similar reduction for the composite primary outcome (p=0.91 for interaction), death from any cause and hospitalisation for heart failure • Subgroup analysis on 11 pre-specified subgroups showed a significant interaction between treatment and QRS duration (p=0.003). ICD-CRT was more effective in those with intrinsic QRS duration of ≥ 150msec (HR, 0.59; 95% CI, 0.48 to 0.73) than in those with an intrinsic QRS duration of < 150msec (HR, 0.99; 95% CI, 0.77 to 1.27; p = 0.002 for interaction) or those with a paced QRS duration of ≥ 200msec (HR, 1.07; 95% CI, 0.63 to 1.84; p = 0.03 for interaction). • There was a weak interaction between treatment and QRS morphologic type (p = 0.046) such that those with LBBB appeared to have a greater benefit than those with nonspecific intraventricular conduction delay (p = 0.04 for interaction) 			

- Hazard ratios for pre-specified subgroups displayed in a figure only: not data extracted (age: <65 yrs vs ≥ 65, p=0.75; gender: male vs female, p=0.09; NYHA class: II vs III, p=0.91; underlying heart disease: ischemic vs non-ischemic, p=0.90; QRS duration intrinsic QRS <150msec vs intrinsic QRS ≥150msec vs paced QRS ≥200msec, p=0.003; LVEF: <20% vs ≥20%, p=0.05; QRS morphologic features: RBBB vs LBBB vs NIVCD vs paced, p=0.046; atrial rhythm: permanent atrial fibrillations or flutter vs sinus or atrial paced, p=0.14; diabetes: yes vs no, p=0.22; hypertension: yes vs no, p=0.84; estimated GFR (ml/min/1.73m²): <60 vs ≥60, p=0.70)
- States that patients with ischemic or non-ischemic causes of heart failure had a similar benefit from ICD-CRT.

Adverse effects of treatment	ICD-CRT, n=888	ICD, n=899	Hazard Ratio (95% CI); p value
Number of patients (%)			
Death from worsening heart failure within 24hrs after device implantation, no. of patients		1	
Device-related hospitalisation	179 (20%)	110 (12.2)	1.68 (1.32 to 2.13); <0.001
Number of device- or implantation-related complications during the first 30 days after device implantation ^a	118/888	61/899	<0.001
AEs at 30 days after device implantation, n ^a	124/888	58/899	<0.001
Hemothorax or pneumothorax	11 (1.2%)	8 (0.9%)	0.47
Device-pocket hematoma requiring intervention	14 (1.6%)	11 (1.2%)	0.53
Device-pocket infection requiring intervention	21 (2.4%)	16 (1.8%)	0.39
Lead dislodgement requiring intervention	61 (6.9%)	20 (2.2%)	<0.0001
Device-pocket problems requiring revision	4 (0.5%)	1 (0.1%)	0.22
Coronary sinus dissection	11 (1.2%)	0	0.0004
Tamponade	2 (0.23)	2 (0.22)	1
Comments: ^a it is unclear why the number of patients in these categories differ for both groups.			
<ul style="list-style-type: none"> • ICD-CRT group: a left ventricular lead was successfully implanted in 841/888 patients (94.7%); during an initial attempt n=802, in a subsequent attempt n=39. ICD-CRT group: 53 patients (6.0%) did not receive CRT (left ventricular lead failure n=47; lead malfunction n=6); 12 cardiac transplants: ICD-CRT group n=7, ICD group n=5. 			

Methodological comments

- *Allocation to treatment groups*: random assignment in a 1:1 ratio and stratification according to clinical centre, atrial rhythm (atrial fibrillation or flutter or sinus-atrial pacing), and a planned implantation of a single- or dual-chamber ICD.
- *Blinding*: described as double-blind. Patients and general health care providers (including the team responsible for heart failure management and reporting of clinical events) were blinded, as was the adjudication committee responsible for reviewing available documents and determining cause of death. Arrhythmia teams (physicians and caregivers) performing device implantation and device management were not blinded.
- *Comparability of treatment groups*: states baseline clinical characteristic similar between the 2 groups.
- *Method of data analysis*: All analyses were conducted according to the ITT principle. Survival-analysis techniques were used to compare the 2 groups with respect to the primary outcome and principal secondary outcomes. Survival in each of the 2 groups was summarised with the use of Kaplan-Meier product-limit estimates. Survival curves were compared using nonparametric log-rank tests. Hazard ratios and associated 95% CI were calculated with the use of the Cox proportional-hazards model. Primary and secondary outcomes for patients with NYHA class II or III heart failure were analysed separately, as NYHA class III patients were enrolled only during the first part of the study, before protocol revision in February 2006 to include only NYHA class II patients. Cox proportional-hazard models were used to test for interactions in the various

planned subgroups. The protocol states that planned subgroup analyses would include AF vs no AD and NYHA class II vs III (p16).⁸⁹ Chi-square tests were used to compare the Kaplan-Meier (actuarial) rate of event-free survival at 5yrs. Hazard ratio was used to calculate the number needed to treat in order to prevent one death or hospitalisation for heart failure in one patient. Underlying assumptions for these statistical procedures were assessed (in particular, the proportional-hazards assumption). Analyses were conducted with the use of SAS software, version 9.2 (SAS Institute).

- *Sample size/power calculation:* The study had a statistical power of 85% to detect a 25% relative reduction in the primary outcome, given a two-sided alpha value of 0.05 and taking into consideration the expected rate of loss to follow-up and crossover.¹³ In order to detect a 20% relative risk reduction in the primary endpoint for CRT/ICD, at alpha = 0.05 (two-sided) and 90% power, a sample size of 1500 patients will be needed (750 per group. This calculation assumes an exponential survival with all patients followed to the primary endpoint or termination of the study, and allows for a 5% inability to implant the LV lead (based on the most recent data of 96% implant success rate in a world-wide registry), and 3% of crossover from control group (ICD) to experimental group (CRT/ICD).⁸⁹ This sample size will also be able to detect a 25% relative risk reduction of total mortality with the assumption of 11% annual mortality in the control group, at alpha of 0.05 (two-sided) and 80% power.⁸⁹
- *Attrition/drop-out:* ICD-CRT group: 888/ 894 (99.3%) received ICD-CRT; leads successfully implanted n=841/888 (94.7%); 53/888 (60%) did not receive CRT (47 failed, 6 lead malfunctions); non-implantation: death n=4; patient or physician declined to participate n=2. ICD group: 899/ 904 (99.4%) received ICD, non-implantation of ICD: patient or physician declined to participate n=4; lack of venous access n=1. Crossover: ICD to ICD-CRT n =36 (4%) before the occurrence of a primary outcome and 60 (6.6%) after hospitalisation for heart failure. ICD-CRT group: withdrew n=8; lost to follow-up n=2; ICD group: withdrew: n=4; lost to follow-up n=1.
- *Other:* in order to increase recruitment to 34 patients per month, Medtronic sponsored the expansion to more centres in Europe and Turkey from the original 21 centres (Canada 21, Germany 2, Australia 2, New Zealand 1 – see protocol page 16).⁸⁹ However, no enrolment for the centre in New Zealand is reported.
 - Two planned interim analyses were conducted for the data and safety monitoring board and an O'Brien-Fleming alpha spending (1st planned with 33% enrolled and followed for 2yrs; 2nd planned when 66% enrolled and followed for 2yrs⁸⁹) function was used to adjust the sample size for these interim analyses.

General comments

- *Generalisability:* to mild-to-moderate heart failure patients with left ventricular systolic dysfunction and wide QRS complex.
- *Outcome measures:* appear appropriate.
- *Inter-centre variability:* not reported.
- *Conflict of interests:* Medtronic did not participate in the conduct of the trial, the reporting of the data or the decision to submit the manuscript for publication.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Unclear	Random assignment in a 1:1 ratio, with stratification according to centre. No details on sequence generation.
Allocation concealment	Unclear	No details reported.
Performance bias		
Blinding of participants and personnel	Low risk	Double-blind. Patients and general health care providers were blinded, but not device caregivers.
Detection bias		
Blinding of outcome	Low risk	Adjudication committee responsible for reviewing

assessment		available documents and determining cause of death were blinded.
Attrition bias		
Incomplete outcome data addressed	Low risk	ITT analysis, consort flowchart (including numbers analysed) provided in an appendix.
Reporting bias		
Selective reporting	High risk	The protocol ⁸⁹ reported ‘other outcomes’ (e.g. QoL), but no data for these were reported. However, this is a recent study and abstracts are available, possible data will be published in future.
Other bias		
Other sources of bias	Low risk	

^a ‘Low risk’, ‘high risk’ or ‘unclear risk’ of bias

RethinQ

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Beshai <i>et al.</i>, 2007;⁹⁰ Beshai & Grimm, 2007⁹¹</p> <p>RethinQ (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS)</p> <p><i>Study design:</i> RCT</p> <p>USA</p> <p><i>Number of centres:</i> 34</p> <p><i>Funding:</i> Jude St Medical</p>	<p><i>Intervention:</i> CRT-D ON + OPT (CRT device: Epic HF or Atlas+ HF, St.Jude Medical) with a standard right atrial, right ventricular defibrillator and left ventricular leads. Detection and therapy of tachyarrhythmias turned on.⁹¹</p> <p><i>Comparator:</i> ICD + OPT (device as above). Detection and therapy of tachyarrhythmias turned on.⁹¹</p> <p><i>Other interventions used:</i> OPT for both groups defined as beta blockers for min. of 90 days, ACE inhibitor or angiotension receptor blocker (ARBs) for a min. of 30 days, unless contraindicated or not tolerated (for stable medical regimen no more than 100% increase or a 50% decrease in dose).</p>	<p><i>Indication for treatment:</i> standard indication for an ICD, narrow QRS interval and intraventricular mechanical dyssynchrony, ischemic or non-ischemic cardiomyopathy.</p> <p><i>Number of randomised participants:</i> n = 172 CRT-D ON, n= 87 CRT-D OFF, n=85</p> <p><i>Inclusion criteria:</i> NYHA class III caused by either ischemic or non-ischemic cardiomyopathy. LVEF ≤35; QRS interval <130 msec; approved indication for ICD; stable conventional medical regimen; evidence of mechanical dyssynchrony on echocardiography; able to complete exercise stress testing and 6-min walk test (limited only by cardiac fitness).⁹¹</p> <p><i>Exclusion criteria:</i> Standard indication for cardiac pacing or previous treatment with CRT; standard bradycardic indication for pacing; continuous atrial</p>	<p><i>Primary outcomes:</i> proportion of patients with an increase of ≥1.0 ml/kg body weight/ minute in peak oxygen consumption during cardiopulmonary exercise testing⁹⁰ and survival from CRT-D system –related complications⁹¹</p> <p><i>Secondary outcomes:</i> QoL and NYHA class</p> <p><i>Method of assessing outcomes:</i> baseline evaluation 14 days after successful implantation, including cardiopulmonary exercise testing (max. exercise tolerance on treadmill/bicycle ergometry measuring HR, minute ventilation, oxygen uptake and carbon dioxide output). NYHA class assessment, 6-minute walking test, QoL evaluation (Minnesota Living with Heart Failure Questionnaire, scores from 0 to 105, higher scores indicating poorer QoL), assessment of medication stability,</p>

	<p>Also included: aldactone inhibitors, diuretics and cardiac glycosides (i.e. digoxin) as indicated. If intolerant to ace-inhibitors or ARBs or if contraindicated, alternate therapy as appropriate, including afterload reduction agents (e.g. hydralazine) combined with nitrates. Beta-blocker therapy may be absent from OPT if intolerant or contraindicated.⁹¹</p>	<p>fibrillation (AF lasting >1mth) <1 year prior to enrolment; cardioversion for AF in the past month; ability to walk >450 m during the 6-min walk test; NYHA class of I, II or IV; symptomatic COPD; classification of Status 1 for cardiac transplantation or consideration for transplantation in next 6mths; recent MI; unstable angina; cardiac revascularisation (PTCA or CABG) within 40 days of enrolment; recent CVA or TIA within 3mths of enrolment; severe musculoskeletal disorder/s; pregnant or a planned pregnancy in the next 6mths; life expectancy of ≤ 6mths; Age <18 years.⁹¹</p>	<p>echocardiography for optimisation of atrioventricular and interventricular delay and 12-lead electrocardiography. Evaluation repeated at 6 months.</p> <p>Mechanical dyssynchrony definition: an opposing-wall delay of ≥65msec on tissue Doppler imaging or a mechanical dyssynchrony in the septal-to-posterior wall of ≥130msec on M-mode echocardiography)</p> <p>Follow up: cardiopulmonary-exercise testing, NYHA class, 6-minute walking test, QoL and echocardiography.</p> <p><i>Length of follow-up:</i> 6 months</p> <p><i>Recruitment:</i> August 2005 to January 2007</p>
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Participant characteristics	CRT-D ON + OPT, n=87	ICD+OPT, n=85	p value
Age years, mean (SD)	60 (12)	58 (14)	
Gender, male, n (%)	62 (71)	49 (58)	
Ethnicity	Not reported	Not reported	
NYHA class III, n (%)	87 (100)	84 (99)	
LVEF, % (SD)	25 (5)	26 (6)	
End-diastolic diameter, mm (SD)	66 (9) (n=85)	65 (9) (n=84)	
End-systolic diameter, mm (SD)	56 (9) (n=85)	53 (9) (n=84)	
End-diastolic volume, ml (SD)	216 (78)	210 (75)	
End-systolic volume, ml (SD)	163 (65)	156 (64)	
QRS interval, msec, mean (SD)	107 (12)	106 (13)	
<120 msec, n (%)	66 (76)	60 (71)	
≥120 msec, n (%)	21 (24)	25 (29)	
Underlying heart disease, n (%)			
Ischemic	47 (54)	43 (51)	
Non-ischemic	40 (46)	42 (49)	
Indication for ICD, n (%)			
Primary prevention	74 (85)	73 (86)	
Secondary prevention	13 (15)	12 (14)	
Pre-ejection period, msec (SD)	112 (21) (n=86)	112 (22) (n=86)	
Interventricular mechanical delay, msec (SD)	9 (28) (n=85)	8 (31) (n=82)	
Intraventricular mechanical dyssynchrony, msec (SD) ^a			
Septal-to-posterior wall	106 (45) (n=24)	112 (51) (n=33)	
Septal-to-lateral wall	81 (39) (n=85)	86 (38) (n=85)	

Anteroseptal-to-posterior wall	78 (34) (n=83)	81 (45) (n=81)	
Mitral regurgitation, n (%)			
None or mild	59 (68)	55 (66)	
Moderate	25 (29)	23 (28)	
Severe	3 (3)	5 (6)	
Medication at baseline, n (%)			
ACE inhibitors or substitute ^b	77 (89)	77 (91)	
Beta-blockers	84 (97)	79 (93)	
Diuretic	73 (84)	74 (87)	
Antiarrhythmic	7 (8)	10 (12)	
Peak oxygen consumption, ml/kg/min (SD)	12.1 (3.3)	12.4 (4.5)	
Exercise duration, min (SD)	8.9 (3.0)	9.0 (3.8)	
QoL (MLHFQ) score (SD)	54 (24)	57 (26)	
6-min walk test, m (SD)	301 (94)	297 (100)	
Comments: ^a mechanical delays in the septal-to-lateral and anteroseptal-to-posterior walls were measured on tissue Doppler imaging; mechanical delay in the septal-to-posterior wall was measured on M-mode echocardiography. ^b include angiotensin-receptor blockers and hydralazine. <ul style="list-style-type: none"> • States that none of the differences between the groups were significant, but no p values reported. • 97% of left ventricular leads were implanted in a lateral position. 			

RESULTS			
	CRT-D ON + OPT, n=87	ICD+OPT, n=85	p value
Mortality before 6 months, n (%)	5/87 (5.7)	1/85 (1.2)	
Unknown cardiac causes	2/87 (2.3)		
Pump failure	2/87 (2.3)	1/85 (1.2)	
Unknown cause	1/87 (1.2)		
Mortality at 7 months, pump failure, n (%)		1/85 (1.2) ^c	
Cumulative overall survival at 6 months, % (95 % CI)	94.2% (86.7 to 97.6)	98.8% (91.9 to 99.8)	0.11
Cumulative freedom from death caused by worsening HF, % (95 % CI)	97.7% (91.1 to 99.4)	98.9% (91.9 to 99.8)	0.58
Change in Peak VO ₂	(n=76)	(n=80)	0.63
Median change, ml/kg/min (95 % CI)	0.4 (-0.6 to 1.2)	0.5 (-0.3 to 1.1)	
Primary Outcome: increase of ≥ 1.0 ml/kg/min, n (%)	35/76 (46)	33/80 (41)	
Change in QoL (MLHFQ)	(n=76)	(n=80)	
Median change (95 % CI)	-8 (-10 to -1)	-7 (-11 to 3)	0.91
Change in NYHA class	(n=76)	(n=80)	0.006
Improved by 1 class or more, n (%)	41/76 (54)	23/80 (29)	
No change, n (%)	31/76 (41)	51/80 (64)	
Worsened, n (%)	4/76 (5)	6/80 (8)	
Change in 6-min walking test	(n=75)	(n=79)	
Median change (95 % CI), m	26 (0 to 46)	6 (-17 to 30)	0.23
Change in ejection fraction	(n=68)	(n=74)	
Median change (95 % CI), %	1.2 (-0.4 to 4.4)	2.0 (0.3 to 4.2)	0.83
Change in end-diastolic volume	(n=68)	(n=74)	
Median change (95 % CI), ml	-16 (-29 to -8)	-11 (-30 to -2)	0.71
Change in end-systolic volume	(n=68)	(n=74)	
Median change (95 % CI), ml	-19 (-34 to -12)	-18 (-28 to -8)	0.81
Change in end-diastolic diameter	(n=72)	(n=77)	
Median change (95 % CI), mm	0 (-2 to 0)	-1 (-2 to 1)	0.49
Change in end-systolic diameter	(n=72)	(n=77)	

Median change (95 % CI), mm	-1 (-3 to 0)	0 (-2 to 2)	0.34
Change in degree of mitral regurgitation, n (%)	(n=76)	(n=80)	>0.99
Improved by 1 or more grade	8/76 (11)	9/80 (12)	
No change	60/76 (81)	61/80 (80)	
Worsened by 1 or more grade	6/76 (8)	6/80 (8)	
Comments: ^c not included in survival analysis (included in efficacy analysis);			
Adverse effects of treatment, n /N (%)	CRT-D ON + OPT, n=87	ICD+OPT, n=85	p value
HF events requiring intravenous therapy	24 events in 14/87 patients (16.1)	41 events in 19/85 patients (22.3)	
Lead dislodgement	13/172 (7.6)		
Left ventricular lead	5/172 (2.9)		
Infection	6/172 (3.5)		
Bleeding or hematoma	2/172 (1.2)		
Loss of pacemaker-lead capture	2/172 (1.2)		
Phrenic-nerve stimulation	3/172 (1.7)		
Deep venous thrombosis	3/172 (1.7)		
Pneumothorax	2/172 (1.2)		
Pericarditis	2/172 (1.2)		
Coronary sinus perforation	1/172 (0.6)		
Comments: states that the numbers of AEs did not differ significantly between the two study groups, but no p value reported.			
Subgroup analysis according to QRS interval at 6 months, change from baseline^d	CRT-D ON + OPT, QRS ≥120, n=17 QRS <120, n=59	ICD+OPT, QRS ≥120, n=25 QRS <120, n=55	p value
Peak Oxygen Consumption, increase of at least 1 ml/kg body weight/min from baseline			
QRS ≥120	58.9	19.7	0.02
QRS <120	42.2	51.2	0.45
NYHA class, proportions of patients whose condition improved by at least 1 class from baseline			
QRS ≥120	70.7	28.0	0.01
QRS <120	49.4	29.3	0.04
QoL, median changes from baseline, %			
QRS ≥120	0	-3.7	0.24
QRS <120	-8.9	-7.0	0.63
6-min walk distance, median changes from baseline, m			
QRS ≥120	0.0	-19.1	0.86
QRS <120	33.7	10.3	0.31
Subgroup analysis according to cardiomyopathy classification at 6 months, change from baseline^d	CRT-D ON + OPT, Ischemic, n=40 Non-ischemic, n=36	ICD+OPT, Ischemic, n=41 Non-ischemic, n=39	p value
Peak Oxygen Consumption, increase of at least 1 ml/kg body weight/min from baseline			
Ischemic	40.0	44.2	0.82
Non-ischemic	52.6	38.4	0.25
NYHA class, proportions of patients whose condition improved by at least 1 class from baseline			
Ischemic	55.3	29.5	0.02
Non-ischemic	53.2	28.4	0.04

QoL, median changes from baseline, %			
Ischemic	-5.9	-3.6	0.68
Non-ischemic	-10.6	-6.5	0.60
6-min walk distance, median changes from baseline, m			
Ischemic	4.2	5.8	0.57
Non-ischemic	55.0	2.5	0.01
Comments: ^d all values estimated by reviewer using Engauge. P values extracted from paper.			

Methodological comments

- *Allocation to treatment groups*: random assignment in a 1:1 ratio according to centre and stratified according to the cardiomyopathy classification and the QRS interval (<120 msec and ≥120 msec) within each centre. Randomisation assignments created in S-plus software (Insightful) and provided to site personnel (aware of study group assignments) with the use of an interactive voice-response system at the baseline visit. Participants were randomised after successful implantation and once all baseline evaluations were completed.
- *Blinding*: states double-blind, but site personnel provided with randomisation assignments were aware of study-group assignments. Site personnel unaware of study-group assignments administered all evaluations at 6 months. Independent committees whose members were unaware of study-group assignments and investigational centre adjudicated all deaths and adverse events.
- *Comparability of treatment groups*: States that none of the differences between the groups were significant, but no p values were reported.
- *Method of data analysis*: all end points were analysed according to ITT principle; patients who crossed over were analysed according to their original treatment group. Secondary end points were each evaluated at a significance level of 0.025 and were considered significant only if the primary efficacy end point was met with the use of the gatekeeper method. All p values were calculated with the use of a two-sided test. Survival curves were constructed according to the Kaplan-Meier method and the differences between curves were examined by the log-rank statistic. Data for all patients were censored at 196 days, the last day of the 6-month window for clinical visits. CIs for survival were computed on a log-log scale. For continuous variables, data are presented as median changes between baseline and 6 months. CIs for the median were computed with the use of a distribution-free approach. Comparisons of changes from baseline to 6 months between the CRT-D OFF (control) and the CRT-D ON were evaluated for significance by the Wilcoxon rank-sum test. Mean (SD) values are presented. For categorical variables, differences in the distribution of responses to treatment at 6 months in the 2 groups were compared by Fisher's exact test. CIs for proportions were computed by exact methods. The protocol specified that end-point analyses be performed for patients with data available at 6 months and for those who died, withdrew, or were unable to perform the evaluation at 6 months owing to worsening heart failure. The latter patients were included in the analysis with their worst values imputed as follows: 0 ml per kilogram per minute for peak oxygen consumption, a score of 105 on the QoL scale, NYHA class IV, and 0 m for the 6-minute walking test.
- *Sample size/power calculation*: the study was powered to detect a difference of 23% in the proportion of patients who achieved the primary end point in the CRT-D ON group as compared with the CRT-D OFF group (control). The proportion that improved in the control group was assumed to be 25%. The sample size required to detect this difference with a statistical power of 80% at the 0.05 significance level was 76 patients in each group, with the use of Fisher's exact test. On the basis of an attrition rate of 40%, the study required a total enrolment of 250 patients.
- *Attrition/drop-out*: total recruitment n=250, total randomised n=172 (unsuccessful implantation: n=4, deaths: n=2, withdrawals: n=3, did not meet inclusion criteria: n=69).

CRT-D ON: death from other causes than HF: n=3, withdrew for reasons other than worsening HF: n=3; had <6mths follow-up: n=3; no exercise test at follow-up: n=2. 76 participants included in efficacy analyses, 2 died from HF. CRT-D OFF: had <6mths follow-up: n=4; no exercise test at 6mths: n=1. 80 participants in efficacy analyses, 2 died from HF and 2 did not have an exercise test due to worsening HF.

Crossovers: 3 participants crossed from CRT-D OFF to CRT due to worsening HF (included in

control group analysis). No crossovers from CRT-D ON group.

General comments

- *Generalisability*: limited to participants with successful implantation, QRS interval <130 and NYHA class III and evidence of mechanical dyssynchrony (states only 4% of patients were eligible to participant in the study solely on the basis of mechanical dyssynchrony criteria on M-mode echocardiography). 96% qualified on the basis of the tissue Doppler criterion (i.e., an opposing-wall delay of ≥ 65 msec, rather than the mechanical dyssynchrony in the septal-to-posterior wall of 130 msec or more on M-mode echocardiography).
- *Outcome measures*: appear to be appropriate. Primary outcome measure was proportion of patients with an increase of ≥ 1.0 ml/kg body weight/ min in peak oxygen consumption during cardiopulmonary exercise testing. The study was not powered for mortality.
- *Inter-centre variability*: not reported.
- *Conflict of interests*: Dr. Beshai, Dr. Grimm, Dr. Nagueh, Dr. Greenberg and Dr. Pires received lecture/consulting fees, support and /or grants from St. Jude Medical, Medtronic, GE, and/or Boston Scientific. Authors state that there was no other potential conflict of interest relevant to the publication. States that investigators had full access to all data and performed analyses without restrictions or limitation from the sponsor.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^a	Support for Judgement
Selection bias		
Random sequence generation	Low risk	Random assignment in a 1:1 ratio according to centre and stratified according to the cardiomyopathy classification and the QRS interval within each centre. Randomisation assignments created in S-plus software (Insightful).
Allocation concealment	Low risk	Allocation provided to site personnel with the use of an interactive voice-response system at the baseline visit.
Performance bias		
Blinding of participants and personnel	Unclear risk	States double blind, but unclear who was blinded. Randomisation assignments were provided to site personnel who were aware of study-group assignment, unclear if these personnel continued to be involved in care of participants.
Detection bias		
Blinding of outcome assessment	Low risk	Site personnel conducting evaluations at 6 months were unaware of treatment assignment, as were independent committee members adjudicating all deaths and adverse events.
Attrition bias		
Incomplete outcome data addressed -Peak oxygen consumption (primary outcome). QoL, NYHA class, 6-min walk, mortality before 6 months	Low risk	States that all end points were analysed according to ITT principle. The protocol specified that end-point analyses be performed for patients with data available at 6 months and for those who died, withdrew, or were unable to perform the evaluation at 6 months owing to worsening heart failure. However, analysis were performed on CRT-D ON + OPT n=66 and ICD+OPT n=80, due to participants not having completed a

		cardiopulmonary exercise test for reasons other than worsening HF. Numbers and reasons given.
- Other endpoints	High risk	Missing data, reasons not given.
Reporting bias		
Selective reporting	Low risk	All protocol outcomes reported.
Other bias		
Other sources of bias	Low risk	

^a 'Low risk', 'high risk' or 'unclear risk' of bias

RHYTHM-ICD

Reference and design	Intervention and Comparator	Participants	Outcome measures
<p>Summary of Safety and Effectiveness 2004^{87;92}</p> <p>RHYTHM-ICD (Resynchronization for Hemodynamic Treatment for Heart Failure Management)</p> <p><i>Study design:</i> RCT</p> <p>Country not stated</p> <p><i>Number of centres:</i> 50</p> <p><i>Funding:</i> not stated but presumed to be the device manufacturer, St. Jude medical, Sunnyvale, CA</p>	<p><i>Intervention:</i> CRT-D St. Jude Medical[®] Epic[™] HF model V-338 (maximum output 30 J) CRT-D with Aescula LV leads.</p> <p><i>Comparator:</i> ICD</p> <p><i>Other interventions used:</i> not stated</p>	<p><i>Indication for treatment:</i> patients indicated for ICD therapy with NYHA Class III/IV heart failure and a prolonged QRS duration.</p> <p><i>Number of randomised participants:</i> n = 205 enrolled, n=182 successful implants, baseline visit n=179. CRT-D, n= 119 ICD, n= 60</p> <p><i>Inclusion criteria:</i> LVEF ≤ 35%; QRS interval ≥ 150ms; ICD indication for treatment of life-threatening VT; symptomatic HF for ≥ 6 months; NYHA class III or IV despite ≥90 days appropriate pharmacological therapy; receiving OPT for CHF (including ACE inhibitor & β-blocker as tolerated) stable for 30 days before enrolment; ability to complete cardiopulmonary exercise stress test & 6-minute walk test; able to consent and comply with follow-up tests and evaluations.</p> <p><i>Exclusion criteria:</i> Standard bradycardic indication for pacing; chronic atrial fibrillation (continuous AF lasting > I</p>	<p><i>Primary outcomes:</i> LVs lead-related complications at 6 months; EPIC HF system-related complications at six months; defibrillation system effectiveness: VF detection/redetection times; cardiac resynchronisation therapy efficacy (Peak V_{O2}).</p> <p><i>Secondary outcomes:</i> Improvement at 6-months in: NYHA class; QoL; six minute walk test. Aescula LV lead performance and lead pacing capture threshold.</p> <p><i>Method of assessing outcomes:</i> Baseline visit approximately 2 weeks after implant. Follow up at 1, 3 & 6 months. After 6 months cross over to CRT-D permitted & follow-up every 3 months. Complications defined as adverse events that required invasive intervention. Observations defined as adverse events managed without invasive intervention (e.g. reprogramming of the</p>

		month) within 1 year or cardioversion for AF in the past month, able to walk > 450 meters in 6-Minute walk test; NYHA class I or II; contraindication for an emergency thoracotomy; candidate for cardiac transplantation in next 6 months, recent (within 1 month) MI, unstable angina or cardiac revascularisation; CVA or TIA in last 3 months; severe musculoskeletal disorder(s); pregnancy; participation in other clinical investigations, life expectancy < 6 months.	pulse generator). QoL - Minnesota living with heart failure questionnaire. <i>Length of follow-up:</i> Average 12.1 (3.4) months, range 0.3 to 20.3 patient months. Outcomes reported at 6 months. <i>Recruitment:</i> July 2002 to October 2003
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Participant characteristics	CRT-D, n= 119	ICD, n=59	p value
Age years, mean (SD)	nr	nr	
Gender	nr	nr	
Ethnicity	nr	nr	
NYHA class			0.61
NYHA class I, n (%)	1 (0.8)	2 (3.4)	
NYHA class II, n (%)	6 (5.0)	4 (6.8)	
NYHA class III, n (%)	104 (87.4)	50 (84.7)	
NYHA class IV, n (%)	8 (6.7)	3 (5.1)	
LVEF %, mean (SD) and range	25.6 (8.3) Range 9 to 48	23.3 (6.4) Range 11 to 43	0.07
Heart rate	nr	nr	
QRS duration, ms, mean (SD) and range	169 (16) Range 120 to 210)	167 (15) Range 130 to 200	0.40
Left ventricular end diastolic dimension, mm, mean (SD) and range	66.2 (8.5) Range 44.7 to 85.9	66.0 (9.4) Range 50.1 to 84.2	0.88
Left ventricular end systolic dimension, mm, mean (SD) and range	57.1 (9.4) Range 37.1 to 76.2	56.9 (10.5) Range 37.9 to 78.2	0.93
Quality of life score, mean (SD) and range	48 (24) Range 0 to 103	46 (24) Range 4 to 100	0.53
Six minute walk distance, meters, mean (SD) and range	275 (103) Range 37 to 561	291 (89) Range 31 to 480	0.30
Cardiopulmonary exercise test			
- peak VO ₂ , ml/kg/min, mean (SD) and range	10.8 (3.0) Range 4.3 to 26.9	12.3 (3.5) Range 6.0 to 23.1	0.006
- exercise time, minutes, mean (SD) and range	8.0 (3.2) Range 0.7 to 16.5	8.9 (3.6) Range 2.3 to 19.8	0.08
Baseline medications, n (%)			
- ACE inhibitors/substitutes	85 (71.4)	44 (74.6)	0.79
- β- blockers	95 (79.8)	52 (88.1)	0.24
- angiotensin receptor blockers	24 (20.2)	10 (16.9)	0.76
- diuretics	103 (86.6)	54 (91.5)	0.47
- positive inotropics/glycoside	73 (61.3)	39 (66.1)	0.65
- nitrates	39 (32.8)	23 (39.0)	0.51
- anti-coagulants and anti-platelets	102 (85.7)	48 (81.4)	0.59

Participant characteristics	CRT-D, n= 119	ICD, n=59	p value
- calcium channel blockers	11 (9.2)	9 (15.3)	0.35
- anti-arrhythmics	29 (24.4)	13 (22.0)	0.87
RESULTS			
Outcomes	CRT-D, n= 83	ICD, n= 43	p value
Total deaths ^a at 6-month visit, average 12.1 (3.4) patient months of follow-up	9	3	
- cardiac arrhythmic	0	0	
- cardiac non-arrhythmic	1	1	
- cardiac unknown	0	0	
- non-cardiac	7	2	
- unknown	1	0	
Additional deaths after the 6-month visit ⁸⁷ at average of 15.1 (4.1) patient months of follow-up			
- cardiac arrhythmic	0	0	
- cardiac non-arrhythmic	1	0	
- cardiac unknown	1	0	
- non-cardiac	1	1	
- unknown	1	0	
Quality of life score, mean (SD)			
- baseline	48.3 (24)	42.0 (23)	
- 6-month follow-up	40.4 (22)	45.4 (31)	
- change	-7.8 (22)	3.4 (31)	0.009
NYHA class, mean (SD)			
- baseline	3.01 (0.33)	2.86 (0.52)	
- 6-month follow-up	2.53 (0.69)	2.58 (0.73)	
- change	-0.48 (0.65)	-0.28 (0.63)	0.048
Peak VO ₂ ^b , ml/kg/min, mean (SD) (primary outcome)			
- baseline	11.2 (3.0)	12.8 (3.7)	
- 6-month follow-up	11.7 (3.2)	11.4 (5.6)	
- change	0.52 (2.5)	-1.41 (4.6)	0.001
Per-protocol analysis of change in peak VO ₂ , ml/kg/min, mean (SD) at 6-months	n=85 0.52 (2.5)	n=41 -1.47 (4.7)	0.001
6 minute walk distance, mean (SD)			
- baseline	284 (105)	298 (94)	
- 6-month follow-up	197 (122)	283 (150)	
- change	13 (74)	-15 (142)	0.07
Improvement in echocardiography parameters at 6-months, mean (SD)	n=82	n=40	
- left ventricular end diastolic diameter, mm	-4.3 (5.4)	-2.4 (6.5)	
- left ventricular end systolic diameter, mm	-4.6 (7.0)	-3.0 (6.4)	
- left ventricular end diastolic volume, ml	-43 (69)	-37 (53)	
- left ventricular end systolic volume, ml	-43 (58)	-36 (47)	
- LVEF, %	4.3 (9.9)	2.9 (6.2)	
- MR (grade) ^c	-0.06 (0.74)	0.10 (0.50)	
- E/A wave point ratio	-0.08 (0.8)	-0.02 (1.2)	
- sphericity index	-0.02 (0.1)	0.02 (0.1)	
- pre-ejection time, ms	-1.5 (52)	7.3 (33)	
- intraventricular mechanical delay, ms	-14.5 (52)	-6.4 (48)	
- Tei Index	-0.4 (0.8)	-0.05 (0.5)	
- contraction interval, ms	-94 (124)	-55 (103)	
Discontinuations and withdrawals (excluding withdrawals)			

due to deaths and after unsuccessful implants) at average of 15.1 (4.1) patient months of follow-up ⁸⁷		
- system explant	^d , day 1 after implant	
- heart transplant	1, 75 days after implant	
- patient request	1, 28 days after implant 1, 397 days after implant	
- patient's family request	1, 293 days after implant	
<p>Comments: ^a - an additional 5 deaths (4 cardiac non-arrhythmic + 1 non-cardiac) occurred in patients who did not have a successful implant or death occurred before baseline visit and randomisation. Total deaths therefore 17 as detailed in methodological comments, Attrition. ^b - patients who crossed over from ICD to CRT-D were analysed according to their original treatment group ^c - MR not defined, presumed to be mitral regurgitation. ^d - 1 patient withdrawn before baseline visit and randomisation therefore not assigned to either group.</p> <ul style="list-style-type: none"> • Mean detection and redetection times for induced VF episodes, Aescula LV lead performance, and Aescula LV lead pacing capture threshold at 6-months have not been extracted because they were not analysed by treatment group. • States that the average percentage of biventricular pacing at 6-months in the CRT-D cohort (n=83) was 95% (6%), range 70-100%. 		
Adverse effects of treatment	Reported for the whole study group prior to randomisation n=205	p value
Total complications, n patients ^e (%) & n events at average 12.1 (3.4) patient months of follow-up ⁹²	21 (10.2), 29 events	
- coronary sinus perforation/dissection	2 (1.0), 2 events	
- diaphragmatic/phrenic nerve stimulation	3 (1.5), 3 events	
- lead dislodgement or migration	8 (3.9), 9 events	
- bleeding/hematoma ^f	6 (2.9), 6 events	
- blood clot/ thrombosis	1 (0.5), 1 event	
- high defibrillation/cardioversion requirements	2 (1.0), 2 events	
- infection	1 (0.5), 1 event	
- noise on EGM post shock (non-SJM RV lead) ^g	1 (0.5), 1 event	
- pneumothorax	2 (1.0), 2 events	
- retained foreign body (surgical sponge)	1 (0.5), 1 event	
- elevated pacing threshold - LV lead	1 (0.5), 1 event	
Total observations, n patients ^e (%) & n events at average 12.1 (3.4) patient months of follow-up ⁹²	57 (27.8), 68 events	
- asystolic episode during LV lead placement	1 (0.5), 1 event	
- bleeding/hematoma ^f	10 (4.9), 10 events	
- blood clot/ thrombosis	2 (1.0), 2 events	
- coronary sinus perforation/dissection	6 (2.9), 6 events	
- diaphragmatic/phrenic nerve stimulation - LV lead	10 (4.9), 10 events	
- diaphragmatic/phrenic nerve stimulation - RV lead	2 (1.0), 2 events	
- elevated pacing thresholds - LV lead	10 (4.9), 10 events	
- elevated pacing thresholds - RV lead	2 (1.0), 2 events	
- heart block at implant	2 (1.0), 2 events	
- high defibrillation/cardioversion requirements	1 (0.5), 1 event	
- hypotension requiring ventilator support	1 (0.5), 1 event	
- inappropriate therapy for SVT	10 (4.9), 13 events	
- infection	3 (1.5), 3 events	

- possible pulmonary embolism	1 (0.5), 1 event	
- T-Wave sensing	2 (1.0), 3 events	
- pocket inflammation/seroma	1 (0.5), 1 event	
LV lead-related complications at 6 months	11/155 patients, 13 complications	
Epic HF system-related complications at 6 months	13/182 patients, 16 complications	
Total complications, n patients ^e (%) & n events at average of 15.1 (4.1) patient months of follow-up (only those complications with added data detailed below) ⁸⁷	22 (10.7), 31 events	
- lead dislodgement or migration	9 (4.4), 10 events	
- infection	2 (1.0), 2 events	
Total observations, n patients ^e (%) & n events at average of 15.1 (4.1) patient months of follow-up (only those observations with added data detailed below) ⁸⁷	59 (28.8), 76 events	
- diaphragmatic/phrenic nerve stimulation - LV lead	14 (6.8), 14 events	
- elevated pacing thresholds - LV lead	12 (5.9), 12 events	
- inappropriate therapy for SVT	11 (5.4), 14 events	
- infection	4 (2.0), 4 events	
Comments: ^e - some patients experienced more than one event therefore the number of patients is less than the number of events. ^f 15 of the 16 patients with bleeding/hematoma related events were on active anticoagulation therapy. ^g abbreviations not defined in the publication.		
<ul style="list-style-type: none"> • A total of 97 adverse events (29 complications and 68 observations) were reported in 70 patients. 		

Methodological comments

- *Allocation to treatment groups:* States randomised, 2:1 (CRT-D: ICD)
- *Blinding:* States double blind
- *Comparability of treatment groups:* Report does not comment on this, groups appear broadly comparable the only significant difference appears to be in peak VO₂ for the exercise test where the ICD group performed significantly better than the CRT-D group. Note that this measure is a primary outcome.
- *Method of data analysis:* Not stated. Analysed data set was smaller than the randomised set due to attrition (see below).
- *Sample size/power calculation:* Not reported.
- *Attrition/drop-out:* 17 (increasing to 22 with additional follow-up⁸⁷) patients were withdrawn due to death (3 deaths patients with unsuccessful implant; 2 deaths between implant and baseline visit, 8 deaths between baseline and 6-month visit; 4 deaths after 6-month visit). 5 of 17 deaths not attributed to a treatment group as they occurred in patients who did not have a successful implant (unrelated to implant procedure) or death occurred before baseline visit and randomisation. From 205 enrolled patients 23 implants were unsuccessful [unable to cannulate coronary sinus (CS) n=7; unable to obtain distal lead placement n=6; unable to obtain stable lead position n=3; high pacing thresholds n=3; CS dissection n=3; high defibrillation threshold n=1]. Therefore 182 patients successfully implanted, of these 1 patient withdrew before baseline, and 2 (as noted above) died before the baseline visit, leaving 179 patients. One further patient attended baseline visit but refused randomisation and baseline evaluations except device interrogation and electrical measurements. Thus baseline evaluations for 178 patients are presented. Of the 179 patients who attended for baseline visit a flow chart shows 119 assigned to CRT-D and 60 assigned to ICD. A further 36 in CRT-D were not included in the analysable patient group for the effectiveness analysis [1 refused baseline cardiopulmonary exercise test (CPET), 2 withdrawn, 2 could not complete baseline/6-month CPET due to non-cardiac reasons, 6 died, 4 had invalid baseline/6-month CPET and 21 had < 6-months follow up], and 17 were not analysable in the ICD group (1 refused baseline CPET, 2 died, 4 invalid baseline/6-month CPET, 10 <6-months follow-up). Consequently the analysed data set was CRT-D n=83 and ICD n=43.

General comments

- *Generalisability*: Uncertain - no indication of age, gender or ethnicity of the participants. Country in which trial took place not reported. Patients had an indication for ICD therapy plus NYHA Class III/IV heart failure and a prolonged QRS duration. Those with chronic atrial fibrillation were excluded. Baseline evaluation occurred 14 days post-implant, followed by randomisation, only those with successful implants randomised.
- *Outcome measures*: Primarily this was a study of safety, effectiveness outcomes were on the whole secondary measures. Outcomes seem appropriate.
- *Inter-centre variability*: Not commented on in the report.
- *Conflict of interests*: Not stated in the report but the study appears to have been funded and conducted by the device manufacturers.

Criteria for assessment of risk of bias in RCTs⁴

	Judgement ^h	Support for Judgement
Selection bias		
Random sequence generation	Unclear	No information provided
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	Unclear	States double blind but no detail about how this was achieved reported
Detection bias		
Blinding of outcome assessment	Unclear	States double blind but no detail about how this was achieved reported
Attrition bias		
Incomplete outcome data addressed	Low risk	Although there was a high degree of attrition this has been clearly documented and appears similar (numbers and reasons) between groups.
Reporting bias		
Selective reporting	Unclear	Report is a submission to the FDA and it is not clear whether only selected outcome have been presented to meet the needs of the FDA approvals process.
Other bias		
Other sources of bias	Unclear	Due to a lack of details e.g. methodological & regarding patient characteristics, the risks of other sources of bias are unclear.

^h 'Low risk', 'high risk' or 'unclear risk' of bias

Appendix 11: SHTAC peer review of manufacturers' submission

Comprehensiveness of ascertainment of published studies

Clinical effectiveness:

The MS contains a systematic review of clinical effectiveness. In addition, a network meta-analysis (NMA) of individual patient level data (IPD) is presented (see Table below). Details and results of studies included in the systematic review were tabulated. Risk of bias was assessed and tabulated in MS Appendix 3, but no narrative discussion of risk of bias was provided. The studies were not presented according to the population groups specified in the NICE scope, and the inclusion criteria for the systematic review and NMA differ from the NICE scope. The statement of the decision problem (MS p44) defines the population of interest as 'adults with heart failure (NYHA I to IV) and LVEF \leq 35%, and/or at risk of sudden cardiac death'. The population inclusion criteria for the systematic review (MS p51) are defined as: 'adults with LVEF \leq 40% or those who may not have (LVEF) \leq 40% but are considered to be secondary prevention patients according to TA 95 criteria' or 'adults who have experienced prior myocardial infarction or coronary revascularisation; this must have occurred more than 45 days prior to enrolment'. In addition, for the IPD NMA, the four interventions of interest (OPT, ICD, CRT-P, and CRT-D) were not all included as comparators in all the patient subgroups (rationale MS Table 6 p45). The MS states this was either based on contraindication (e.g. CRT not being recommended for patients with a QRS duration $<$ 120ms), or on a paucity of IPD data (described as 'proxy for non-use in routine clinical practice'). This differs from the NICE scope.

- *Were databases and dates of searches specified?* Yes. Searches were conducted on 27th and 28th June 2011), no update searches were reported. MS states that timelines initially provided by NICE to all technology sponsors were followed. Medline and Medline in Process, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. MS stated that searches were restricted to English language and start publication date of 1990. Reference lists of full text retrieved papers were also scanned.
- *Were search strategies supplied?* Yes, search strategies for the three databases are presented in Appendix 1.
- *Was enough detail provided to be reproducible?* Yes.
- *Did they search/report on ongoing studies?* No.
- *Did they search for conference proceedings?* No, there were no specific searches for conference abstracts and the MS states that abstracts were excluded from the assessment.

- *How much of the data is CIC/AIC?* There are no CIC/AIC data in the SR, but the vast majority of the IPD are marked CIC (no AIC data).

Cost effectiveness:

The MS did not report any additional searches for cost-effectiveness studies.

Searches identified

- *Clinical trials (details):* 22 RCTs trials reported in 46 publications (total records identified by MS: 4749, total records identified by SHTAC: 4169), plus 5 trials (reported in 11 publications) of secondary prevention that were not data extracted.
- *Did any meet our inclusion criteria which we have not already included?* No additional trials were identified in the MS. However, there are differences in included/excluded trials:
 - People at risk of sudden cardiac death: MS did not describe or report data for secondary prevention studies (listed in MS Appendix 4) and provided justification for this (reduction in implant costs, absence of new studies since TA 95; MS states that they believe this patient group lies outside the scope of the current appraisal). SHTAC included four secondary prevention studies (AVID, CASH, CIDS, DEBUT). Of the primary prevention trials, SHTAC included three trials that were not included by the MS: DINAMIT, IRIS and CABG Patch. The MS excluded DINAMIT and IRIS for ‘inappropriate population’ and one paper linked to CABG Patch was excluded for ‘endpoint’ although other papers from this trial were not mentioned.
 - People with heart failure: SHTAC excluded three of the trials included by the MS:
 1. RESPOND (participants did not have cardiac dyssynchrony);
 2. REVERSE (mixed population receiving interventions CRT-P or CRT-D with the comparators OPT or ICD, and results not presented separately).
 3. VECTOR (FDA report with insufficient information to allow the assessment of methods and results, no baseline characteristics reported).
 - MS excluded ‘patients with familial cardiac conditions with a high risk of SCD, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and following surgical repair of Tetralogy of Fallot’ (MS p54). SHTAC did not exclude these patients and therefore included the DEBUT study.

A list of excluded studies with reasons for exclusion was provided in response to a request from SHTAC.

Clinical Analysis:

- *Any major differences in evidence reported?* Despite having mixed population, intervention and comparators, the MS presents the REVERSE trial in tables as patients randomised to CRT-D versus ICD for simplicity, and notes this on MS p55. The 22 trials are tabulated together and not

according to the groups defined in the NICE scope. The narrative synthesis of results often does not refer to the different populations in the studies, e.g. cardiomyopathy or myocardial infarction. The MS does not undertake meta-analyses of outcomes reported by studies included in the systematic review, but reports the meta-analyses undertaken by Fox and colleagues in 2007² and others.

- *Are the MS conclusions similar to the SHTAC review?* The MS does not explicitly report their conclusions from their systematic review in the main body of the submission. The MS executive summary states ‘there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF’ (MS p4). There is no comment regarding the comparative effectiveness of the interventions for the NICE defined populations. Further conclusions are presented based on the IPD NMA.
- *Any indirect comparisons?* No indirect comparisons of included studies were undertaken by the MS. However, the MS presents a NMA of IPD combining data from 13 of the 22 included studies.
- *Any differences in outcome measures?* The MS reports the same outcome measures as the SHTAC review.
- *Any extra adverse event info?* A narrative overview of adverse events in the included studies and information from previous meta-analyses is presented.

Interpretation:

- *Does their interpretation of the clinical data match their analyses?* The MS does not explicitly provide interpretation for the systematic review. Interpretation of IPD NMA assessed below.

Questions:

- *Any areas of uncertainty/discrepancy compared with the SHTAC review?*
 - Inclusion of the REVERSE trial.
 - Population not defined according to NICE scope.

SHTAC critical appraisal of the ABHI Individual Patient Data (IPD) Network Meta-Analysis (NMA)

Appraisal criteria	Criteria met?
A. CONCEPTUAL BASIS	
1. Is a justification given for conducting an MTC?	Yes. The MS correctly identifies that an IPD NMA would be beneficial in helping to understand the effects of ICDs, CRT-P and CRT-D on health outcomes for patients with heart failure. It is particularly important given the limited direct evidence for some comparisons. Also it is helpful in identifying sub-groups within a heterogeneous patient population, providing the opportunity to capture baseline risks and relative treatment effects. With published evidence at an aggregate level, the effectiveness for sub-groups is not addressed by most trials and inconsistently reported in others. Provision of confidential IPD by the manufacturer's made such an analysis possible.
B. SYSTEMATIC PROCESSES	
2. Is a comprehensive and transparent search strategy reported?	Yes. There was a comprehensive and transparent search strategy for the systematic review (SR) (not separate searches for the NMA) that provided the basis for the evidence network. The IPD was based on 14 RCTs from 22 trials included in the network of evidence from the SR (reported by the MS as 13 as 2 trials were combined). IPD were supplied by the manufacturers.
3. Are inclusion / exclusion criteria adequately reported?	Yes. RCTs were from the SR, for which IPD could be obtained. The criteria do not strictly accord with the decision problem specified in the NICE scope for the appraisal (refer to SHTACs assessment of MS).
4. Is the number of included /excluded studies from the MTC reported, with reasons for exclusions?	Yes. The number (13/22 RCTs, dated 1996-2010) and reasons for exclusions from the evidence network are reported. Justifications for exclusion include: 2 studies because the manufactures' IPD data were not available; 2 studies because the available data sets could not be reconciled with the published data; 2 manufacturer sponsored studies that the SR searches failed to identify until after the database for the NMA had been assembled (Vector: started in 2000 and details published in 2005 FDA report; RESPOND: journal article published February 2011);

	and 2 trials were not sponsored by the manufacturers contributing to submission. In addition to these trials, SHTAC also included 7 trials (DINAMIT, IRIS and CABG Patch and 4 secondary prevention RCTs) that were not included in the MS. While the excluded studies only account for 5.3% of the data (n=712/13350), it is unclear what impact their exclusions has on the results. A flowchart is presented for the SR and numbers excluded from the NMA are reported.
5. Is a visual representation of the data networks provided?	Yes. A visual network diagram was provided for the SR (MS Section 4, page 103). An explanation is provided for handling the different trials within the network. The REVERSE trial was treated as 2 trials (CRT-P and CRT-D, as well as split into EU and US due to different protocol-specific duration of follow up (24 months and 12 months respectively)). CONTAK-CD was also treated as 2 trials, as the cross-over design was changed to a 6-month parallel group trial half way through (phase 2). The MIRACLE ICD trial was combined with the MIRACLE ICD-II trial, as the MS states these were effectively a single trial. In addition, the MS pooled the data of the Amiodarone and the placebo arm in the SCD HeFT trial.
6. Are the data from included studies extracted and tabulated?	Yes. Baseline information was presented in the SR for the individual trials (see MS, Tables 7-11, p57-72). A summary table for the IPD trials with combined participant's baseline characteristics per device (Table 35, p.110) is presented for comparison with UK summary data (Table 36, p.111). The MS suggests that differences between the two tables in NYHA class are distorted due to previous NICE decisions about the devices and differences in other data due to high levels of missing data in the UK National Audit data. The MS suggests that despite this, the IPD is broadly reflective of the UK population. Comparison is further complicated by QRS being presented as mean (ms) in the MS table, but as percentage (prolonged) in the UK summary table. A cross-check with the original trial publications is not possible, as this is based on a large database of IPD.
7. Is the quality of the included studies assessed?	Yes. All the NMA trials were critically appraised in the SR. Risk of bias for all 22 studies is presented in Appendix 3 of the MS, but there is no discussion of this. No studies were excluded because of any potential risk of bias and the MS fails to address any of the issues arising from the assessment.

C. STATISTICAL ANALYSIS	
<p>8. Are the statistical procedures adequately described and executed?</p>	<p>No. Overall procedures used are reported, but specific details of the analyses for the outcomes of all-cause mortality, all-cause hospitalisation and health related quality of life (HRQoL) are omitted. This limits the opportunity to appraise the NMA. Published sources are referred to for the methods employed in statistical analysis.</p> <p>Analysis of the 3 outcomes follows a similar 2 stage approach, although different types of regression were used. First, baseline rates were estimated independent of treatment effect using pooled data from the IPD trials on OPT (the comparator). Second, device specific treatment effects were estimated using relevant IPD trials measuring the specific outcome in question. Both stages used patient characteristics as covariables to incorporate baseline risk and treatment effect modifiers. This allowed sub-groups of patients to be identified for whom the devices may have a differential effect.</p> <p>All-cause mortality</p> <p>For all-cause mortality, a parametric survival analysis was undertaken to generate estimates of baseline mortality. Parametric distributions assessed included exponential, Gompertz, log-logistic, log-normal and Weibull. Covariables were assessed for inclusion and, where necessary, transformation undertaken (e.g. age as a time-dependent co-variable). Models were assessed using fitted and Kaplan Meier survival curves within trial follow-up, visual review of the extrapolations and of the shape of the instantaneous hazard over time, Akaike Information Criteria (AIC), Cox Snell residuals, tests of acceptability of the proportional hazards assumption or accelerated failure time assumption, comparison against external data and review by clinical experts. Results of the tests are not presented. The Weibull distributions were the basis for the final baseline model.</p>

IPD NMA using meta-regression were undertaken with and without covariables to estimate relative treatment effects (i.e. hazard ratios) comparing devices and OPT. Comparisons were made between the NMA, pairwise meta-analyses and aggregate trial data to judge whether representative and the type of analyses that should be undertaken (see appendix 7). The MS reports that caterpillar plots, Brooks Gelman-Rubin statistics, autocorrelation and deviance information criteria were assessed, although few results are reported. Covariables were selected through univariate analyses, multivariate stepwise procedures and exploratory analyses. Final fixed effects models using a Cox proportional hazards approach and stratified for study were estimated and assessed using proportional hazards tests (see appendix 8) and Schoenfeld residual tests (not reported).

All-cause hospitalisations

The analysis focused on ‘expected number of events per month’ and ‘expected number of days per month spent in hospital’ (excluded events within 60 days post randomisation as included in economic model). Negative binomial regression was used to estimate baseline rates for OPT patients and the effects of treatment for all devices. Approach decided through measures of goodness of fit (i.e. Bayesian Information Criteria (BIC), AIC and two times log-likelihood score (2LL)) and the covariates incorporated into the analyses through a stepwise process (included at a significance level of $p=0.05$), although details not reported. Limited data resulted in pooling of some categorical variables (e.g. NYHA groups). Justifications were provided for decisions and comparisons with previous evaluations.

HRQoL

HRQoL was assessed using EQ-5D, adjusting UK age and gender specific utilities with disease and treatment specific decrements/increments estimated from the IPD trials reporting EQ-5D. Baseline HRQoL estimated using similar process to all-cause hospitalization. Prior to analysis raw data were transformed as were skewed. Derived

	values were checked against population norms and trial values. Treatment impact was estimated through mean difference from baseline to first follow-up (180 days). Limited and skewed data resulted in counter-intuitive results, so Minnesota Living with Heart Failure Questionnaire 6 month IPD data and evidence from the SR were used to adjust final values (justifications provided). Duration of effect was estimated when mean device versus OPT values showed no difference.
9. Is there a sufficient discussion of heterogeneity?	The MS recognises the heterogeneous nature of the trials included in the IPD NMA. This is reflected in the approach taken - use of meta-regression to try to take account of the variation, the process for including covariables and the presentation and discussion of results for different sub-groups. There is some limited discussion of measure of goodness of fit associated with the NMA, however this is not related specifically to taking account of heterogeneity. Some comparisons are made between the NMA, individual trial results and pairwise meta-analyses, highlighting differences related to heterogeneous studies.
10. Is the type of model used (i.e. fixed or random effects) reported and justified?	Yes. Comparisons of network meta-analysis results from IPD trials and all trials using both fixed and random effects models are reported and said to be broadly similar (p.123), although random effects confidence intervals are wider. The MS states for all-cause mortality that the deviance information criteria (DIC) assessment of model fit supported the use of the fixed effect model: all trials (FE DIC = 59.0 vs. RE DIC = 60.8) and IPD trials (FE DIC = 1.4 vs. RE DIC = 3.0). Although modelling of all-cause hospitalisation and HRQoL used a fixed effects approach and it is indicated that goodness of fit statistics were assessed, no data or discussion are presented.
11. Was sensitivity analysis conducted?	Yes, in relation to the inclusion of covariables included in the baseline and treatment effect models through univariate and multivariate stepwise analyses. (MS, appendix 9). No sensitivity analyses were undertaken on trials included or the quality of studies.
12. Is any of the programming code used in the statistical programme provided?	The MS did not provide any programming codes used in the statistical programme.

D. PRESENTATION AND INTERPRETATION OF THE EVIDENCE	
13. Is there a tabulation/ illustration of results for each intervention and for each outcome?	<p>Results are presented through a series of tabulations and illustrations, specifically:</p> <p>All-cause mortality</p> <p>Baseline model results were presented through Kaplan Meier plots of parametric curves and tabulation of risk models. Treatment effects from the NMA were presented through Forest plots for different devices and covariables and tabulation of the preferred model.</p> <p>All-cause hospitalisation</p> <p>Baseline model results were presented through Kaplan Meier plots and tabulation of the baseline risk model. Treatment effects from the NMA were presented through tabulation of the preferred model and effects on events per month by device.</p> <p>HRQoL</p> <p>Outcomes are baseline disease severity on HRQoL, treatment effect on HRQoL , explorative analysis of change in MLEHF at 6 months, HRQoL treatment benefit duration and addition IPSD analyses (long-term MLWHF data from all studies and devices) – results were presented in tables, histograms and line graphs.</p>
14. Is there a narrative commentary on the results?	<p>Yes. The MS presents narrative comments on the results, putting them into the context of other research and providing comments on the main limitation (i.e. dichotomisation may miss some of the heterogeneity in response to therapy in the 120-150ms QRS category, p.128; lack of power in analysis to detect modest effect modifiers, p.137) or uncertainties (i.e. treatment effect beyond the included number of years, p.137).</p> <p>The MS provides a cautionary note regarding not over-interpreting individual subgroups since anomalies may arise as a result of participant level characteristics not accounted for (p130).</p>
15. Does the discussion of the results	<p>The discussion of results for the 3 outcomes does reflect the results presented and provides warnings about the</p>

reflect the data presented?	limitations of the IPD available and the analyses undertaken. It also places them in the context of other evidence.
16. Have the authors commented on how their results compare with other published studies (e.g. MTCs), and offer any explanation for discrepancies?	Partly. The MS comments on how some of the results compare to other reviews, meta-analyses, studies or to routinely collected data. It also undertakes additional analyses to check outcomes. In some instances, the MS provides alternative values due to uncertainties in the results, providing justifications. Importantly the MS recognizes the limitations in the IPD and NMA undertaken, providing a note of caution.
17. Have the authors discussed whether or not there are any differences in effects between the direct and indirect evidence?	The MS reports that good concordance between pairwise MA and network MA results suggest reasonable concordance between the indirect and direct data (p.124). Unable to establish if there were any discrepancies in IPD data.

Study Characteristics

Reference

Association of British Healthcare Industries (2012)⁹³

Health technology

Implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT)

Interventions and comparators

ICD and CRT for the treatment of cardiac arrhythmias and heart failure

Was a no treatment/ supportive care strategy included?

Optimal pharmacological medical therapy (OMT)

Describe interventions/ strategies

As above

Research question

For adults with heart failure and LVEF $\leq 35\%$, and/or at risk of sudden cardiac death, which patients should receive ICD, CRT-P, or CRT-D device, based upon their clinical parameters.

Study type

Cost utility analysis

Study population

For adults with heart failure (NYHA I to IV) and LVEF $\leq 35\%$, and/or at risk of sudden cardiac death

Institutional setting

Secondary care

Country/ currency

UK pounds

Funding source

Biotronik, Boston Scientific, Medtronic, Sorin and St Jude Medical

Analytical perspective

NHS and PSS

Effectiveness

The clinical effectiveness estimates were based upon a network meta-analysis of individual patient level data (IPD) from 13 clinical trials (12,638 patients, followed up for up to 7.5 years). The clinical trials were: CARE-HF, COMPANION, CONTAK-CD, DEFINITE, MADIT, MADIT II, MADIT-CRT, MIRACLE ICD, RAFT, RethinQ, REVERSE AND SCD-HeFT. These trials were identified through a systematic review of the clinical effectiveness for all the interventions. A further nine trials were also identified in the review, but IPD were not available for these trials.

The network meta-analysis enabled the combination of trials that compared different sets of treatments within a single analysis, and to use available direct and indirect evidence to inform a comparison between possible treatments.

All cause-mortality

The network meta-analysis found CRT-D to have the strongest effect on all-cause mortality with a hazard ratio of [REDACTED]. Treatment effects for the individual devices were

[REDACTED].

The parameters used in the cost effectiveness model are shown in the Table below. It shows the predicted treatment effect for each subgroup.

MS Table 1: Preferred model for IPD network meta-analysis

Variable ^a	Hazard ratio	P-value
ICD	[REDACTED]	[REDACTED]
CRT-P	[REDACTED]	[REDACTED]
CRT-D	[REDACTED]	[REDACTED]
QRS<120	[REDACTED]	[REDACTED]
QRS>=120	[REDACTED]	[REDACTED]
LBBB	[REDACTED]	[REDACTED]
AGE>=60	[REDACTED]	[REDACTED]
GENDER=M	[REDACTED]	[REDACTED]
ICD*QRS<120	[REDACTED]	[REDACTED]
ICD*QRS>=120	[REDACTED]	[REDACTED]
ICD*LBBB	[REDACTED]	[REDACTED]
ICD*GENDER=M	[REDACTED]	[REDACTED]

ICD*AGE>=60	■	■
CRTP*QRS>=120	■	■
CRTP*LBBB	■	■
CRTP*GENDER=M	■	■
CRTP*AGE>=60	■	■
CRTD*QRS>=120	■	■
CRTD*LBBB	■	■
CRTD*GENDER=M	■	■
CRTD*AGE>=60	■	■

a – Reference category is a patient receiving OMT, <60 years of age, female, QRS duration ≥ 150 ms and non-LBBB conduction abnormality. NB: main effects for covariables greyed out as not included in cost-effectiveness model.

All cause hospitalisation

Across all NYHA classes, device therapy was associated with a reduction in admission rates. In NYHA classes I to III, ICD was associated with a ■ reduction in monthly admission rates, and CRT with a ■ reduction. The effect in NYHA class IV was even more pronounced with CRT offering a ■ reduction in monthly admission rates.

Intervention Costs

IPD from the trials were used to estimate the mean number of all cause hospitalisation events per month and the mean number of days per month. The hospital costs were derived from the NHS Schedule of Reference Costs (SRC) and combined with the average mean length of stay. The HF hospitalisation event costs was £2,295 and the non HF hospitalisation event cost was £2,448.

Device costs were sourced from the average selling prices from the manufacturers via the Association of British Healthcare Industries (ABHI). These prices are an aggregate across all sponsors (manufacturers) for ICD, CRT-P and CRT-D devices and leads sold in the UK to the NHS. The implantation costs were taken from the HRG tariff values. Device related infection costs were derived by inflating value in Fox et al to £3,139. Device costs, with implantation costs are shown in the table below.

MS Table 2: Device costs used in the model

Item	Cost	Components
Initial implant operation (ICD)	£15,248	ABHI system costs (incl. leads) and UK tariff EA12Z
Initial implant operation (CRT-P)	£8,281	UK Tariff E07Z
Initial implant operation (CRT-D)	£17,849	ABHI system costs (incl. leads) and UK tariff EA12Z
Replacement (ICD)*	£14,705	ABHI system costs (excl. leads) and UK tariff EA12Z
Replacement (CRT-P*)	£8,281	UK Tariff E07Z
Replacement (CRT-D)*	£17,308	ABHI System costs (excl. leads) and UK tariff EA12Z

Device related infection (ICD)	£18,964	See section 5.5.3.3
Device related infection (CRT-P)	£12,541	See section 5.5.3.3
Device related infection (CRT-D)	£21,568	See section 5.5.3.3
Battery replacement (ICD)	£12,004	ABHI generator costs (excl. leads) and UK tariff EA39Z
Battery replacement (CRT-P)	£8,381	UK Tariff
Battery replacement (CRT-D)	£14,672	ABHI generator costs (excl. leads) and UK tariff EA39Z

Medication cost

Heart failure medication cost was included for the patients in the model. The proportion of patients using a range of heart failure, by NYHA class, was derived through a systematic review and expert opinion. Common values are applied to all four interventions in each month of the model, on the basis of baseline NYHA values. Recommended doses and purchases costs of the medication were from the BNF. The total cost of treatment per 1 month model cycle was £14.28 for NYHA I and between £22.13 and £22.30 for NYHA II – IV.

Indirect Costs

NA

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)

The approach taken for health related quality of life was i) to estimate UK specific age and gender population utilities, ii) derive a disease specific decrement using IPD EQ-5D data, iii) derive treatment specific increment associated with each device at first follow up visit by NYHA class.

UK specific age and gender population utilities were taken from a study of 3,395 individuals resident in the UK. Disease specific decrements were taken from the CARE-HF, MADIT-CRT and RAFT trials. For the impact of treatment, the utility decrement was calculated as the difference between baseline and first follow-up period.

The HRQoL benefit observed at six months is maintained up to five years and thereafter begins to recede in a linear manner over the time period five to ten years. After ten years, the model assumed that the individual with a CRT or ICD device will have no additional HRQoL benefit over an identical person receiving OPT.

List the utility values used in the evaluation

Individuals in NYHA I/II have the same HRQoL as an age equivalent member of the general public. Patients in NYHA class III and NYHA class IV has extra decrements by sex and ischaemic aetiology.

MS Table 3: Age and gender specific UK EQ-5D population norms (mean, SD.) reproduced from Kind et al.

Age band	Male	Female
Under 25	0.94 (0.12)	0.94 (0.12)
25-34	0.93 (0.16)	0.93 (0.15)
35-44	0.91 (0.17)	0.91 (0.15)
45-54	0.84 (0.27)	0.85 (0.23)
55-64	0.78 (0.28)	0.81 (0.26)
65-74	0.78 (0.28)	0.78 (0.25)
75+	0.75 (0.28)	0.71 (0.27)

MS Table 4: NBRM Coefficients used to predict baseline utility decrement

Covariable	β Coefficient	Std. error	Z score	e^{β}
NYHA = III	████	████	████	████
NYHA = IV	████	████	████	████
Age	████	████	████	████
Ischaemic aetiology	████	████	████	████
Gender= Male	████	████	████	████
Constant	████	████	████	██

* Variable included despite not being significant on the basis of the underlying disease. Lack of significance likely to have arisen due to small patient counts.

MS Table 5: Treatment specific utility increments used in the economic model

	NYHA I/II	NYHA III	NYHA IV
OPT	████	████	████
ICD	████	████	██
CRT-P	██	████	████
CRT-D	████	████	████

Modelling

A survival model with two states for alive and dead. Death is modelled via a series of covariate based regression equations for baseline risk and treatment effect using long term individual patient data.

There is also a state for all cause hospitalisation that is aligned to mortality.

The baseline probability of death is for patients who receive OMT but no device, based on a range of clinical covariates. These probabilities are used in combination with device-specific treatment effects, derived from the network meta-analyses. A similar approach is taken to estimate the probability of all-

cause hospitalisation. HRQoL utility is applied to patients in the model according to their treatment and clinical characteristics.

The model does not include short term device related adverse events as the costing approach used to derive total implant costs covers additional costs such as short term adverse events.

Results were generated in a two stage process. In the first, both for patients with and without LBBB, cost and QALY estimates were derived for all relevant comparators in all 4,992 patient profiles (4 NYHA * 2 aetiology status (ischaemic/ non-ischaemic) * 3 QRS categories * 4 LVEF categories* LBBB status (yes/no)* 2 gender groups * 13 age categories). In the second stage, these were collapsed to 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology. Results were aggregated over LVEF and age and gender categories.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

Mortality

For the model the baseline survival curve was derived using the following formulae:

$$h(t) = \exp(-(\log(\text{scale}) - \beta \cdot X) \cdot \text{shape}) \cdot \text{shape} \cdot t^{\text{shape}-1}$$

$$S(t) = \exp\left(-\int_0^t h(t) dt\right)$$

where h(t) is the instantaneous hazard, S(t) is the survival curve, β are the coefficients on the covariables and the X are the set of covariables (which can be time-dependent).

MS Table 6: Preferred baseline risk model

Variable	Coefficient	Hazard ratio for prognostic variable ^a	P-value
Age (per year)	████	████	████
Male gender	████	████	████
NYHA III	████	████	████
NYHA IV	████	████	████
Ischaemic aetiology	████	████	████
QRS duration <120ms	████	████	████
LVEF>20% and <=25%	████	████	████
LVEF>25% and <=30%	████	████	████
LVEF>30%	████	████	████
log(scale)	████	██	████
log(shape)	████	██	████

(a) Hazard ratio = $\exp(\beta/\text{shape})$; Na = not applicable

All-cause hospitalisation

The derived monthly probabilities are shown in Table 41, using a starting age of 66 years.

MS Table 7: Monthly probability of hospitalisation by covariate pattern (OPT)

	NYHA I/II	NYHA III	NYHA IV
Non-Ischaemic aetiology			
QRS <120ms	████	████	████
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████

Ischaemic aetiology			
QRS <120ms	████	████	████
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████

Device lifetime

UK device longevity estimates were derived from an analysis of all implants with verified life status from 2000 to 2011 (~ 40,000 implants). Device specific median survival estimates were used to inform transition probabilities of device failure in the model. Median time to device failure in the model was 7.1 years for ICD, 10.4 years for CRT-P and 5.8 years for CRT-D.

What is the model time horizon?

Lifetime

What discount rates have been applied in the model?

3.5% for costs and benefits.

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

The model estimates the total lifetime QALYs for various patient subgroups, but these values are not presented in the report.

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

The model estimates the total lifetime costs for various patient subgroups, but these values are not presented in the report.

Synthesis of costs and benefits.

Results of the base case deterministic cost-effectiveness analysis are presented for 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology (24 subgroups for patients with LBBB and 24 subgroups for patients without). All individuals are assumed to have LVEF $\leq 35\%$. The authors stated that ischemia did not substantively impact on cost-effectiveness and so the results presented below are therefore applicable to both ischemic and non-ischemic patients.

Deterministic base case results (patients without LBBB)

NYHA Class	Etiology	QRS Duration	N	C-E Sequence				ICERs			
				1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	66	OPT	ICD	N/A	N/A	Referent	£24,304	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	11	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,619	N/A
I	Non-Ischemic	>=150ms	8	OPT	ICD	CRTD	N/A	Referent	£18,074	£1,080,057	N/A
I	Ischemic	<120ms	272	OPT	ICD	N/A	N/A	Referent	£24,016	N/A	N/A
I	Ischemic	>=120, <150 ms	216	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,234	N/A
I	Ischemic	>=150ms	106	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,086	N/A
II	Non-Ischemic	<120ms	710	OPT	ICD	N/A	N/A	Referent	£25,110	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	232	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,016	N/A
II	Non-Ischemic	>=150ms	141	OPT	ICD	CRTD	N/A	Referent	£20,312	£27,175	N/A
II	Ischemic	<120ms	788	OPT	ICD	N/A	N/A	Referent	£23,884	N/A	N/A
II	Ischemic	>=120, <150 ms	756	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,749	N/A
II	Ischemic	>=150ms	470	OPT	ICD	CRTD	N/A	Referent	£20,697	£22,777	N/A
III	Non-Ischemic	<120ms	255	OPT	ICD	N/A	N/A	Referent	£29,402	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	150	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£19,760	£27,336
III	Non-Ischemic	>=150ms	109	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,227	£24,350
III	Ischemic	<120ms	438	OPT	ICD	N/A	N/A	Referent	£26,923	N/A	N/A
III	Ischemic	>=120, <150 ms	426	OPT	CRTP	ICD	CRTD	Referent	£19,670	Ext Dominated	£24,796
III	Ischemic	>=150ms	192	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,392	£25,734
IV	Non-Ischemic	<120ms	5	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	12	OPT	CRTP	CRTD	N/A	Referent	£17,324	£30,624	N/A
IV	Non-Ischemic	>=150ms	9	OPT	CRTP	CRTD	N/A	Referent	£16,304	£33,901	N/A
IV	Ischemic	<120ms	42	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	52	OPT	CRTP	CRTD	N/A	Referent	£24,366	£43,500	N/A
IV	Ischemic	>=150ms	10	OPT	CRTP	CRTD	N/A	Referent	£18,065	£37,802	N/A

Deterministic base case results (patients with LBBB)

NYHA Class	Etiology	QRS Duration	N	C-E Sequence				ICERs			
				1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	21	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,021	N/A
I	Non-Ischemic	>=150ms	33	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,118	N/A
I	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	76	OPT	ICD	CRTD	N/A	Referent	£19,989	£24,343	N/A
I	Ischemic	>=150ms	165	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,335	N/A
II	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	385	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,608	N/A
II	Non-Ischemic	>=150ms	1,308	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,794	N/A
II	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	477	OPT	ICD	CRTD	N/A	Referent	£20,640	£21,277	N/A
II	Ischemic	>=150ms	982	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,479	N/A
III	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	189	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,550	£23,831
III	Non-Ischemic	>=150ms	775	OPT	ICD	CRTD	CRTD	Referent	Dominated	£9,798	£27,592
III	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	355	OPT	ICD	CRTD	CRTD	Referent	Dominated	£15,449	£25,540
III	Ischemic	>=150ms	773	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,408	£29,912
IV	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	22	OPT	CRTD	CRTD	N/A	Referent	£14,715	£31,920	N/A
IV	Non-Ischemic	>=150ms	81	OPT	CRTD	CRTD	N/A	Referent	£12,076	£35,660	N/A
IV	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	38	OPT	CRTD	CRTD	N/A	Referent	£22,340	£41,695	N/A
IV	Ischemic	>=150ms	97	OPT	CRTD	CRTD	N/A	Referent	£17,722	£46,445	N/A

Summary of results

NYHA class I/II

- QRS duration < 120ms: the ICERs for ICD vs. OPT are below £25,200 per QALY gained.
- QRS duration 120-149ms: ICD is a cost-effective treatment option (ICER < £17,000 / QALY) patients with no LBBB. For CRT-D all ICERs are below £25,000 per QALY gained in LBBB patients (£20,608 to £24,343).
- QRS duration ≥ 150ms, CRT-D is cost effective treatment with ICER is less than £28,000 per QALY for all options.

NYHA class III

- QRS duration <120ms: ICD vs. OPT generates ICERs below £30,000 per QALY.
- QRS duration 120-149ms: CRT-P is cost-effective. CRT-D generates ICERs between £23,900 and £27,400 per QALY gained relative to CRT-P.
- QRS duration >150ms: CRT-P is cost-effective vs. OPT (ICER < £20,000 per QALY). Compared to CRT-P, CRT-D generates ICERs below £30,000 per QALY gained. ICD is either dominated or extended dominated.

NYHA class IV

- QRS duration < 120ms: no comparative analysis was possible in this patient group.
- QRS duration ≥120ms: For CRT-P compared to OPT, all ICERs are close to or below £20,000 per QALY gained. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

The authors reported that in many cases, there is little difference between the best and second best options (when viewed in terms of incremental cost-effectiveness ratios), and there may be other issues that clinicians wish to take into account, and conclude that there seems to be a reasonable case for building clinical flexibility into the recommendations in those cases where the ICER differences between technologies are small and the uncertainty as to which is the preferred device is high.

Give results of any statistical analysis of the results of the evaluation.

NA

Was any sensitivity analysis performed

Yes deterministic sensitivity analyses.

What scenarios were tested in the sensitivity analysis?

The following scenarios were tested in sensitivity analyses: removal of treatment effect tapering (mortality and HRQoL), use of alternative NYHA based IPD results, increase in device longevity.

Give a summary of the results of the sensitivity analysis

The following scenarios were tested in sensitivity analyses: removal of treatment effect tapering (mortality and HRQoL), use of alternative NYHA based IPD results, increase in device longevity. The base case assumed that treatment effects on mortality or HRQoL are not constant but diminish over time. When constant treatment effects for mortality and quality of life were explored, ICERs in all patient groups were lower than in the base case.

According to the MS, there may be a lower mortality treatment effect in patients with NYHA class IV compared to NYHA classes I/II/III for CRT-D. The economic model was run using the estimated all-cause mortality treatment effects based on the grouping of NYHA class IV vs. NYHA class I-III patients. This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups are lower than in the base case.

Device longevity was investigated by increasing time to device failure by 10%. There were only minimal changes to the ICERs.

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

This analysis reconfirms the clinical and economic value of ICD, CRT-P, CRT-D in NYHA class I-IV heart failure patients.

What are the implications of the evaluation for practice?

The recommendations from the ABHI analysis would lead to a widening of the eligibility criteria for an ICD or CRT device and consequently an increase in implant rates. The ABHI analysis estimates that the additional annual expenditure incurred by the NHS ranges from £41.6 million to £230.2 million, depending on the choice of scenario and year of interest,.

SHTAC Commentary

Selection of comparators:

The interventions compared in the MS consist of those comprised in NICE's scope. However, not all of them were included as comparators for all patient subgroups in the MS:

- ICD excluded for NYHA class IV
- CRT-P excluded for NYHA class I/II and QRS <120ms
- CRT-D excluded for QRS <120ms

These exclusions seem to conflict with NICE scope, for example some patients of the scoped population with HF and ventricular arrhythmia considered eligible for ICD are likely to be NYHA class IV.

Validity of estimate of measure of benefit:

Device-specific increments seem similar to those in previous models but the magnitude of the HF-related decrements is not clear from the regression coefficients reported in the MS.

Validity of estimate of costs:

Overall, the derivation of costs and assumptions presented in the MS seem appropriate and consistent with previous approaches. However, specific searches for resource use or cost studies in the UK are not reported in the MS, and the impact of changes to the values and assumptions used was not analysed in the MS. The estimates in the model seem to cover the relevant resource use, including complications, non-HF hospitalisations, and outpatient visits.

Appendix 12: List of excluded economic evaluations

Alcaraz A, Gonzalez ZJ, Augustovski F. Cost-effectiveness of implantable cardioverter-defibrillator in patients with risk factors for sudden death in Argentina. *Value in Health* 2011; **Conference**:7.

Reason for exclusion: Language

Anderson MH, Camm AJ. Implications for present and future applications of the implantable cardioverter-defibrillator resulting from the use of a simple model of cost efficacy. *British Heart Journal* 1993; **69(1)**:83-92.

Reason for exclusion: No comparator

Bryant J, Brodin H, Loveman E, Clegg A. Clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators for arrhythmias: a systematic review and economic evaluation.

International Journal of Technology Assessment in Health Care 2007; **23(1)**:63-70.

Reason for exclusion: Abstract has limited details

Feingold B, Arora G, Webber SA, Smith KJ. Cost-effectiveness of implantable cardioverter-defibrillators in children with dilated cardiomyopathy. *Journal of Cardiac Failure* 2010; **16(9)**:734-741.

Reason for exclusion: Population

Groarke J, Orfali N, Nolan P, Heerey A, Kasim S, Crowley J et al. Cost effectiveness of Implantable Cardioverter Defibrillator (ICD) therapy in clinical practice. *European Heart Journal* 2010;

Conference:225.

Reason for exclusion: Abstract

Groeneveld PW, Farmer SA, Suh JJ, Matta MA, Yang F. Outcomes and costs of implantable cardioverter-defibrillators for primary prevention of sudden cardiac death among the elderly. *Heart Rhythm* 2008; **5(5)**:646-653.

Reason for exclusion: No economic evaluation

Hauer RN, Derksen R, Wever EF. Can implantable cardioverter-defibrillator therapy reduce healthcare costs? *American Journal of Cardiology* 1996; **78(5A)**:134-139.

Reason for exclusion: Comparator

L'Agence Nationale d'Accreditation d'Evaluation en Sante (ANAES). Implantable cardioverter defibrillators: update. *Paris: L'Agence Nationale d'Accreditation d'Evaluation en Sante (ANAES)* 2001;**4**.

Reason for exclusion: No economic evaluation

Kutyifa V, Aidelsburger P, Schauer S, Merkely B, Klein H, Kuniss M et al. Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator in mild heart failure based on Markov modeling using UK cost approach in MADIT CRT. *European Heart Journal* 2012; **33**:896.

Reason for exclusion: Abstract

Linde C, Mealing S, Hawkins N, Eaton J, Brown B, Daubert JC et al. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction). *European Heart Journal* 2011; **32(13)**:1631-1639.

Reason for exclusion: Population

Maniadakis N, Ekman M, Calvert MJ, Freemantle N, Karamalis M, Vardas P. Cost effectiveness of cardiac resynchronization therapy in Greece: an analysis based on the CARDiac RESynchronization in Heart Failure trial. *Europace* 2011; **13**(11):1597-1603.

Reason for exclusion: Abstract

Medical Advisory Service. *Internet-based device-assisted remote monitoring of cardiovascular implantable electronic devices*. 2012.

Reason for exclusion: Intervention

Mushlin AI, Zwanziger J, Gajary E, Andrews M, Marron R. Approach to cost-effectiveness assessment in the MADIT trial. *American Journal of Cardiology* 1997; **80**:F33-F41.

Reason for exclusion: No economic evaluation

Neyt M, Stroobandt S, Obyn C, Camberlin C, Devriese S, De LC et al. Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure. *Value in Health* 2011; **Conference**:7.

Reason for exclusion: Abstract

NHS Quality Improvement Scotland. Evidence Note Number 10. *The use of cardiac resynchronization therapy (CRT) for heart failure*. 2005.

Reason for exclusion: No economic evaluation

Pons JM, Granados A. *Implantable cardioverter defibrillator: experience in Catalonia (1989-1995) and elements of its evaluation*. 1997.

Reason for exclusion: Unobtainable

Pozzolini A. *Cost-effectiveness of ICD therapy in the prevention of sudden death in CAD and/or HF patients*. MILAN: SPRINGER-VERLAG ITALIA; 2007.

Reason for exclusion: Unobtainable

Shah P, Rongione A, Hewitt P, Rosner C, May C, Burton N et al. Is Cardiac Resynchronization Therapy a Cost-Effective Strategy in Patients Whose Ultimate Destination Is a Left Ventricular Assist Device? *Journal of Heart and Lung Transplantation* 2012; **31**(4, Suppl. S):S50-S51.

Reason for exclusion: Abstract

Taylor R. *The clinical and cost effectiveness of biventricular pacing for patients with severe heart failure*. A West Midlands Health Technology Assessment Collaboration Report. 2006.

Reason for exclusion: No economic evaluation

Wells GA, Coyle D, Nichol G, Coyle K, Talajic M, Tang A. Cost effectiveness of cardiac resynchronization therapy (CRT) for mild to moderate heart failure. *Heart Rhythm* 2012; **Conference**:5.

Reason for exclusion: Unobtainable

Wever EF, Hauer RN, Schrijvers G, van Capelle FJ, Tijssen JG, Crijns HJ et al. Cost-effectiveness of implantable defibrillator as first-choice therapy versus electrophysiologically guided, tiered strategy in postinfarct sudden death survivors. A randomized study. *Circulation* 1996; **93**(3):489-496.

Reason for exclusion: Comparator

Appendix 13: Data extraction: cost-effectiveness

Study	Buxton, 2006 ⁹⁴
Country	UK
Analysis type	CUA/CEA
Study type	Markov model
Perspective	UK NHS
Time horizon	20 year
Discounting (rate)	Base-case discount rates were 6% for costs and 1.5% for benefits.
Costing year, currency	2001/02 prices
Population	Secondary prevention patients at risk of SCD with previously documented cardiac arrest or VT.
Intervention(s), Comparator(s)	ICD vs. OPT (amiodarone)
Intervention effect	Transition probabilities were estimated using IPD from the CIDS trial (for OPT patients) and UK sampled observational data (for ICD patients).
Health Outcomes	A cross sectional survey collected HRQoL data (using Nottingham Health Profile, Short Form 36, Hospital Anxiety and Depression questionnaire, EuroQoL 5 dimensions) on a sample of 229 patients.
Device cost	Cost of ICD (with leads) £16,402.
Results Over a 20-year horizon, mean discounted incremental costs were £70,900. Mean discounted incremental gain was 1.24 years or 0.93 QALYs for ICD compared to OPT. The ICER for an average UK patient was £76,139 per QALY gained.	
Sensitivity analysis Sensitivity analyses suggested that targeting those patients at greatest risk of SCD, through either age or poor LVEF would increase the overall cost effectiveness of ICD.	
Author's conclusions	The results suggest that ICDs, as currently applied in the UK, are not cost-effective by conventional standards.
Reviewer's comments	Sound UK study that included QoL and costing studies for ICD patients.

Quality Assessment Form for Economic Evaluations

Item	Y/ N/ ?
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y
2. Is the setting comparable to the UK?	Y
3. Is the analytical and modelling methodology appropriate?	Y
4. Are all the relevant costs and consequences for each alternative identified?	Y
5. Are the data inputs for the model described and justified?	Y
6. Are health outcomes measured in QALYs?	Y
7. Is the time horizon considered appropriate?	Y
8. Are costs and outcomes discounted?	Y
9. Is an incremental analysis performed?	Y
10. Is uncertainty assessed?	Y
<i>Y – yes, N – no, ? - unclear</i>	
Comments	

Study	Bond, 2009 ⁹⁵ derived from Fox, 2007 ²					
Country	UK					
Analysis type	CUA					
Study type	Markov model					
Perspective	UK NHS					
Time horizon	Lifetime					
Discounting (rate)	Costs and QALYs (3.5%)					
Costing year, currency	2005 GBP (£) for all costs except for drug costs (2006 GBP (£))					
Population	A mixed age cohort of patients with NYHA class III and IV heart failure (HF), evidence of left ventricular systolic dysfunction (left ventricular ejection fraction ≤35%) and evidence of electrical dyssynchrony (QRS duration >120 ms).					
Intervention(s), Comparator(s)	CRT <i>versus</i> OPT ^a CRT-D ^b <i>versus</i> CRT OPT <i>versus</i> CRT <i>versus</i> CRT-D ^a referred to as medical therapy, ^b referred to as CRT-ICD					
Intervention effect	Source: Fox, 2007 ² Relative risk of death due to HF with device: - CRT and CRT-D: HR 0.68 (95% CI: 0.46 to 0.98) - ICD: HR 0.95 (95% CI: 0.74 to 1.21) Relative risk of sudden death with device: - CRT: HR 0.75 (95% CI: 0.45 to 1.18) - CRT-D: HR 0.44 (95% CI: 0.23 to 0.86) - ICD: HR 0.37 (95% CI: 0.27 to 0.50)					
Health Outcomes	Mean model survival was 4.7, 5.8, and 6.2 years for medical therapy, CRT and CRT-D respectively. NYHA class-specific estimates of QoL were used to derive time-dependent utility estimates (derived from CARE-HF trial ⁹ and Kirsch and McGuire ⁹⁶ that used the EQ-5D and UK population values) and utility of hospitalisation due to heart failure (from McAlister et al ⁹⁷).					
Device cost	Surgery to implant new system (includes cost of the device): CRT £5,074; CRT-D £17,266; ICD £11,596.					
Results						
Discounted	Mean Cost, £	Mean QALYs	Incremental Cost, £	Incremental QALYs	ICER, £/QALY (95% CI)	P(CE)* %
OPT	9,367	3.10	-	-	-	-
CRT	20,997	3.80	-	-	-	-
CRT-D	32,687	4.09	-	-	-	-
CRT vs OPT	-	-	11,630	0.70	16,738 (14,630 – 20,333)	91.3
CRT-D vs CRT	-	-	11,689	0.29	40,160 (26,645 – 59,391)	26.3
*P(CE) - Probability of being cost-effective at a willingness to pay threshold of £30,000/QALY						
Sensitivity analysis						
Deterministic univariate and probabilistic sensitivity analyses were conducted.						
One-way sensitivity analyses show results sensitivity to structural parameters, event probabilities and risk ratios. In comparison to CRT, CRT-D devices were most likely to be cost-effective when implanted in younger individuals and in those with a high risk of sudden cardiac death.						
A cost-effectiveness probability frontier shows that CRT is most likely the most cost-effective						

option at WTP thresholds between £17,000 and £39,000. Above the WTP threshold of £40,000, CRT-D would be the option with highest expected net benefit (approximately 50% probability of being cost-effective).	
Author's conclusions	CRT-D is not cost-effective for left ventricular dysfunction. Instead CRT alone remains the most cost-effective policy option in this population. CRT-D is more likely to be cost-effective in the subgroups of younger patients or those with high risk of sudden cardiac death who would qualify for CRT.
Reviewer's comments	PenTAG's CUA in UK setting using clinical effectiveness data from alongside systematic review and meta-analysis of RCTs.

Quality Assessment Form for Economic Evaluations

Item	Y/ N/ ?
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y
2. Is the setting comparable to the UK?	Y
3. Is the analytical and modelling methodology appropriate?	Y
4. Are all the relevant costs and consequences for each alternative identified?	Y
5. Are the data inputs for the model described and justified?	Y
6. Are health outcomes measured in QALYs?	Y
7. Is the time horizon considered appropriate?	Y
8. Are costs and outcomes discounted?	Y
9. Is an incremental analysis performed?	Y
10. Is uncertainty assessed?	Y
<i>Y – yes, N – no, ? - unclear</i>	
Comments	

Appendix 14: List of excluded QoL studies

Almenar-Pertejo M, Almenar L, Martinez-Dolz L, Campos J, Galan J, Girones P et al. Study on health-related quality of life in patients with advanced heart failure before and after transplantation. *Transplantation Proceedings* 2006; **38(8)**:2524-2526.

Reason for exclusion: Format of measure

Austin J, Williams WR, Ross L, Hutchison S. Five-year follow-up findings from a randomized controlled trial of cardiac rehabilitation for heart failure. *European Journal of Cardiovascular Prevention & Rehabilitation* 2008; **15(2)**:162-167.

Reason for exclusion: Format of measure

Austin J, Williams WR, Hutchison S. Multidisciplinary management of elderly patients with chronic heart failure: five year outcome measures in death and survivor groups. *European Journal of Cardiovascular Nursing* 2009; **8(1)**:34-39.

Reason for exclusion: Format of measure

Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *European Journal of Heart Failure* 2005; **7(3)**:411-417.

Reason for exclusion: Format of measure

Cooper TJ, Dickstein K, Hasselberg N, Comin-Colet J, Filippatos G, Lainscak M et al. Changes in symptom and quality-of-life assessments correlate strongly and consistently with changes in functional capacity in patients with heart failure. *European Journal of Heart Failure* 2011; *Supplement*:S162.

Reason for exclusion: Abstract

de Rivas B, Permanyer-Miralda G, Brotons C, Aznar J, Sobreviela E. Health-related quality of life in unselected outpatients with heart failure across Spain in two different health care levels. Magnitude and determinants of impairment: the INCA study. *Quality of Life Research* 2008; **17(10)**:1229-1238.

Reason for exclusion: Spanish tariff for EQ-5D

Flynn KE, Lin L, Ellis SJ, Russell SD, Spertus JA, Whellan DJ et al. Outcomes, health policy, and managed care: relationships between patient-reported outcome measures and clinical measures in outpatients with heart failure. *American Heart Journal* 2009; **158(4)**:Suppl-71.

Reason for exclusion: EQ-5D VAS

Iqbal J, Francis L, Reid J, Murray S, Denvir M. Quality of life in patients with chronic heart failure and their carers: a 3-year follow-up study assessing hospitalization and mortality. *European Journal of Heart Failure* 2010; **12(9)**:1002-1008.

Reason for exclusion: Format of measure

Kaplan RM, Tally S, Hays RD, Feeny D, Ganiats TG, Palta M et al. Five preference-based indexes in cataract and heart failure patients were not equally responsive to change. *Journal of Clinical Epidemiology* 2011; **64(5)**:497-506.

Reason for exclusion: Format of measure

Kirsch J, McGuire A. Establishing health state valuations for disease specific states: an example from heart disease. *Health Economics* 2000; **9(2)**:149-158.

Reason for exclusion: Time Trade off measure

Kontodimopoulos N, Argiriou M, Theakos N, Niakas D. The impact of disease severity on EQ-5D and SF-6D utility discrepancies in chronic heart failure. *European Journal of Health Economics* 2011; **12(4)**:383-391.

Reason for exclusion: Format of measure

Linde C, Mealing S, Hawkins N, Eaton J, Brown B, Daubert JC et al. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction). *European Heart Journal* 2011; **32(13)**:1631-1639.

Reason for exclusion: Utility not reported

Marti B, Delgado J, Oliva J, Llano M, Pascual P, Comin J et al. Quality of life in chronic symptomatic heart failure patients in Spain. *Value in Health* 2010;**7**:A363.

Reason for exclusion: Abstract

Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. *American Heart Journal* 2005; **150(4)**:707-715.

Reason for exclusion: Format of measure

Spiraki C, Kaitelidou D, Papakonstantinou V, Prezerakos P, Maniadakis N. Health-related quality of life measurement in patients admitted with coronary heart disease and heart failure to a cardiology department of a secondary urban hospital in Greece. *Hjc Hellenic Journal of Cardiology* 2008; **49(4)**:241-247.

Reason for exclusion: Format of measure

Sullivan MD, Newton K, Hecht J, Russo JE, Spertus JA. Depression and health status in elderly patients with heart failure: a 6-month prospective study in primary care. *American Journal of Geriatric Cardiology* 2004; **13(5)**:252-260.

Reason for exclusion: EQ-5D VAS

Appendix 15 Parameters included in the probabilistic sensitivity analyses

Population 1

Parameter type	Parameter	Source Estimate				Distribution
		Mean	SE	LL	UL	
All-cause mortality	LN(λ)	-3.381	0.0257	-3.431	-3.330	Normal
	γ	0.696	0.0092	0.678	0.714	Normal
	HR ICD	0.75	0.0816	0.61	0.93	Lognormal
All causes multiplier	HR 18-59	0.62	0.0459	0.54	0.72	Lognormal
	HR 75+	1.41	0.0051	1.40	1.42	Lognormal
Due to surgery	ICD	0.0034	0.0262	-0.0479	0.0548	Normal
Probability of perioperative death	Transplant	0.122	0.007	0.109	0.136	Normal
Event Probabilities (per cycle)						
Hospitalisation due to HF	OPT	0.0082	0.0061	-0.0036	0.0201	Beta
	RR ICD	1	0.1	0.804	1.196	Beta
Probability of transplant following HF hospitalisation	Transplant	0.0014	0.0025	-0.0034	0.0062	Beta
Non-fatal arrhythmia requiring hospitalisation	OPT	0.0075	0.0037	0.00016	0.0148	Beta
	ICD	0.0075	0.0037	0.00016	0.0148	Beta
Probability of surgical failure	ICD	0.011	0.0441	-0.07659	0.0962	Beta
Device replacement interval	LN(λ)	-15.784	0.203	-16.182	-15.385	Normal
	γ	1.942	0.0273	1.889	1.996	Normal
Upgrade after HF hospitalisation	OPT to ICD	0.0018	0.002	-0.0023	0.0059	Beta

Parameter inputs for population 2 model

	Parameter	Source Estimate				Distribution
		Mean	SE	LL	UL	
Death due to HF(HDTH) OPT 65-74	LN(λ)	-6.115	0.070	-6.253	-5.977	Normal
	γ	1.223	0.022	1.180	1.265	Normal
	HR CRT-P	0.67	0.094	0.51	0.88	Lognormal
	HR CRT-D	0.73	0.163	0.47	1.11	Lognormal
	HR ICD	1.14	0.153	0.88	1.48	Lognormal
Post-transplant mortality	RR Transplant	0.35	0.035	0.281	0.419	Lognormal
Death due to SCD	LN(λ)	-6.069	0.053	-6.173	-5.964	Normal
	γ	1.140	0.017	1.107	1.173	Normal
	HR CRT-P	1	0.1505	0.54	1.13	Lognormal
	HR CRT-D	0.44	0.1607	0.23	0.86	Lognormal
	HR ICD	0.44	0.0765	0.31	0.61	Lognormal

All cause mortality	18-64	0.62	0.05	0.54	0.72	Lognormal
RR by age	75+	1.41	0.01	1.4	1.42	Lognormal
Event Probabilities (per cycle)						
Surgical mortality	ICD	0.003	0.026	0.000	0.055	Beta
	CRT-P	0.005	0.002	0.001	0.008	
	CRT-D	0.005	0.003	0.000	0.011	
	Transplant	0.122	0.007	0.109	0.136	
Hospitalisation due to HF	OPT	0.037	0.006	0.025	0.049	Beta
	RR ICD	1	0.1	0.804	1.196	
	RR CRT-P	0.58	0.1556	0.35	0.96	
	RR CRT-D	0.77	0.0765	0.63	0.93	
Transplant following	Transplant	0.001	0.002	-0.003	0.006	Beta
Non-fatal arrhythmia requiring hospitalisation	OPT	0.007	0.004	0.000	0.015	Beta
	ICD	0.007	0.004	0.000	0.015	
	CRT-P	0.007	0.004	0.000	0.015	
	CRT-D	0.007	0.004	0.000	0.015	
Probability of Upgrade after HF hospitalisation	OPT to ICD	0	0	0	0	Beta
	OPT to CRT-P	0.003	0.003	0.000	0.009	
	OPT to CRT-D	0.002	0.002	0.000	0.006	
	CRT-P to CRT-D	0.001	0.001	0.000	0.003	
Surgical failure	ICD	0.011	0.001	0.009	0.013	Beta
	CRT-P	0.084	0.007	0.070	0.097	
	CRT-D	0.087	0.012	0.064	0.109	

Parameter inputs for population 3 model

Parameter		Source Estimate				Distribution
		Mean	SE	LL	UL	
All-cause mortality	LN(λ)	-6.334	0.068	-6.467	-6.202	Normal
	γ	1.234	0.018	1.199	1.270	Normal
Baseline - CRT-D	HR CRT-P	1	0.100	0.804	1.196	Log-normal
	HR ICD	1.190	0.084	1.042	1.370	Log-normal
	HR OPT	1.563	0.235	1.163	2.083	Log-normal
All cause mortality RR	18-64	0.621	0.046	0.54	0.72	Log-normal
	75+	1.410	0.005	1.4	1.42	
Event	CRT- D	0.008	0.003	0.003	0.013	Beta
Hospitalisation due to HF	RR ICD	1.333	0.133	1.136	1.563	Log-normal
	RR CRT-P	1	0.1000	0.804	1.196	
	RR OPT	1.67	0.0893	1.51	1.86	
Non-fatal arrhythmia requiring hospitalisation	CRT- D	0.029	0.007	0.015	0.042	Log-normal
	ICD RR	1.111	0.111	0.880	1.410	
	CRT-P RR	1	0.1	0.804	1.196	
	OPT RR	1	0.1	0.804	1.196	
Probability of Upgrade after HF hospitalisation	OPT to ICD	0.002	0.002	0	0.006	Beta
	OPT to CRT-P	0.003	0.003	0	0.009	
	OPT to CRT-D	0.002	0.002	0	0.006	
	CRT-P to CRT-D	0.001	0.001	0	0.003	

	ICD to CRT-D	0.007	0.003	0.001	0.013	
Surgical	ICD	0.003	0.026	0	0.055	Beta
	CRT-P	0.005	0.002	0.001	0.008	
	CRT-D	0.005	0.003	0	0.011	
Surgical failure	ICD	0.011	0.001	0.009	0.013	Beta
	CRT-P	0.084	0.007	0.070	0.097	
	CRT-D	0.087	0.012	0.064	0.109	
Device lifetime	ICD	-15.784	0.203	-16.182	-15.385	Normal
		1.943	0.027	1.889	1.996	
	CRT-P	-14.222	0.242	-14.697	-13.747	
		1.677	0.032	1.613	1.740	
	CRT-D	-15.465	0.273	-16	-14.931	
		1.935	0.036	1.863	2.006	

For all populations

Utilities

per NYHA class	No HF	0.855	0.0048	0.845	0.864	Beta
	NYHA I	0.855	0.0048	0.845	0.864	
	NYHA II	0.771	0.0051	0.761	0.781	
	NYHA III	0.673	0.0097	0.727	0.765	
	NYHA IV	0.532	0.0265	0.48	0.584	
HF hospitalisation	Hospitalisation with HF	0.57	0.0570	0.458	0.682	
Utility decrement	Surgery	0.05	0.0255	0	0.1	Beta
	Infection	0.1	0.0255	0.05	0.15	
Proportion of month hospitalised for HF		25%	0.0255	20%	30%	Beta

Costs and resource use (£)

Total costs of treating device-related complications

Implantation	CRT-P	8,281	1,479	6,098	11,895	Gamma
	CRT-D	17,849	4,521	15,246	32,969	
	ICD	15,248	4,261	13,155	29,858	
Lead Displacement/ Implantation failure	CRT-P	5,681	1,219	4,008	8,786	Gamma
	CRT-D	6,097	3,346	5,798	18,914	
	ICD	6,099	3,346	5,799	18,916	
Battery Failure / Device malfunction	CRT-P	5,348	788	3,884	6,974	Gamma
	CRT-D	17,308	1,704	14,811	32,322	
	ICD	14,705	4,207	12,718	29,209	
Infection	CRT-P	12,553	2,036	7,285	15,265	Gamma
	CRT-D	21,580	5,552	17,202	38,966	
	ICD	18,977	5,292	15,109	35,853	

Operative complications	CRT-P	4,884	1,869	2,442	9,768	Gamma
	CRT-D	6,634	2,539	3,317	13,268	
	ICD	3,432	1,313	1,716	6,864	
Hospitalisation Non-elective hospitalisation	HF hospitalisation	2,308	232	1,669	2,578	Gamma
	Arrhythmia hospitalisation	1,372	173	922	1,601	
Transplant	Heart transplant	35,606	5,578	21,449	43,315	Gamma
Outpatient appointments 6 monthly	Outpatient cardiology specialist FU	123	14	94	148	Gamma
OPT drugs Average monthly cost per class	NYHA class I	5.78	2.21	2.89	11.56	Gamma
	NYHA class II	19.39	7.42	9.695	38.78	
	NYHA class III	19.56	7.48	9.78	39.12	
	NYHA class IV	19.73	7.55	9.865	39.46	

Appendix 16 Regression analyses for deriving model parameters

Kaplan-Meier curves for overall survival were used to derive approximate hazard functions using a Weibull distribution. Transition probabilities, used in the model, can be calculated from the estimated hazard functions.⁹⁸ The Weibull distribution is defined according to two parameters: the scale parameter (λ) and the shape parameter (γ). These parameters were fitted using linear regression of transformations of the Kaplan-Meier estimates. To do this, scanned images of the Kaplan-Meier curves were imported in Engauge software (Engauge Digitizer - Digitizing software, <http://digitizer.sourceforge.net/>) and the extracted data points were then exported to Microsoft Excel for further analysis.

For a Weibull distribution the survival function is given by

$$S(t) = \exp(-\lambda t^\gamma)$$

with scale parameter λ and shape γ . Taking the log of both sides gives

$$\log(S(t)) = -\lambda t^\gamma$$

Taking the log of both sides again, gives

$$\log(-\log(S(t))) = \log(\lambda) + \gamma \log(t)$$

which is a linear function and can be fit using least squares methods to provide estimates of λ and γ .

Population 1

Table 1 below shows the parameters derived for estimation of all-cause mortality for the OPT arm in the model.

Table 8. Weibull model parameters for all-cause mortality

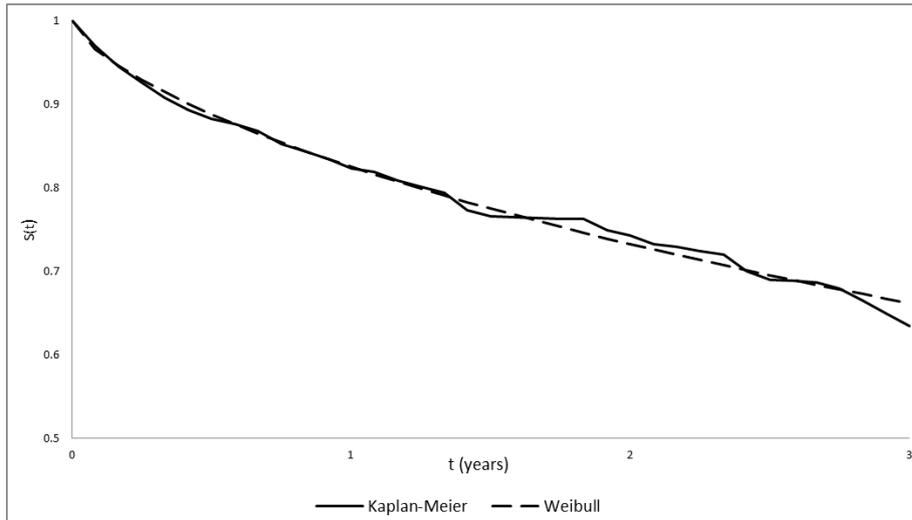
Parameter	Mean (SE)			
	AVID ¹⁸ ($R^2 = 0.994$)	MADIT II ⁵⁵ ($R^2 = 0.9903$)	SCD-HeFT ⁹⁹ ($R^2 = 0.993$)	SCD-HeFT ^{99;100} non-ischaemic CHF subgroup ($R^2 = 0.985$)
$\ln(\lambda)$	-3.380 (0.026)	-4.628 (0.047)	-5.288 (0.039)	-4.821 (0.037)
γ	0.696 (0.009)	1.007 (0.017)	1.083 (0.011)	0.883 (0.011)

Weibull model: $\ln(-\ln(S)) = \ln(\lambda) + \gamma \ln(t)$; $S(t) = \exp(-\lambda t^\gamma)$

Secondary prevention

Figure 1 shows the Weibull approximation fitted to the Kaplan-Meier curve for overall survival of patients in the AVID trial¹⁸ – who survived ventricular fibrillation or sustained ventricular tachycardia that had caused hemodynamic compromise. Goodness-of-fit can be inspected visually as well as indicated by the R^2 measure close to 1 (R^2 0.994). The shape parameter ($\gamma = 0.70$) for the Weibull approximation for the AVID trial is less than 1, indicating that the hazard rate decreases with time.

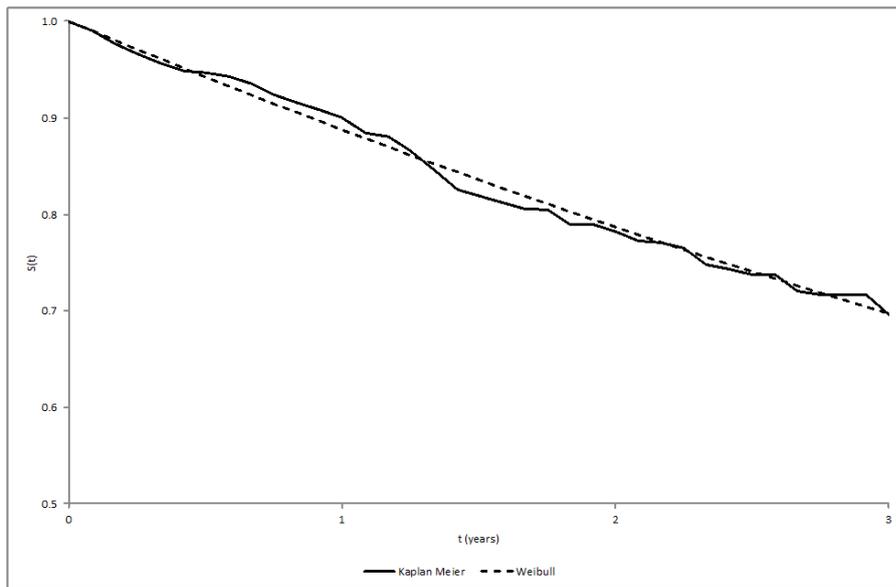
Figure 1. Kaplan-Meier survival estimates for all-cause mortality from the AVID trial¹⁸



Primary prevention – remote MI

Figure 2 illustrates the curve fitting process for patients with remote MI and reduced LVEF using data extracted from the MADIT II trial,⁵⁵ showing the fitted Weibull approximation. Visual inspection suggests that the curve fits the data well (R^2 from the regression is 0.99). The shape parameter ($\gamma = 1.01$) is close to 1, which would indicate that the distribution could potentially be reduced to the exponential form.

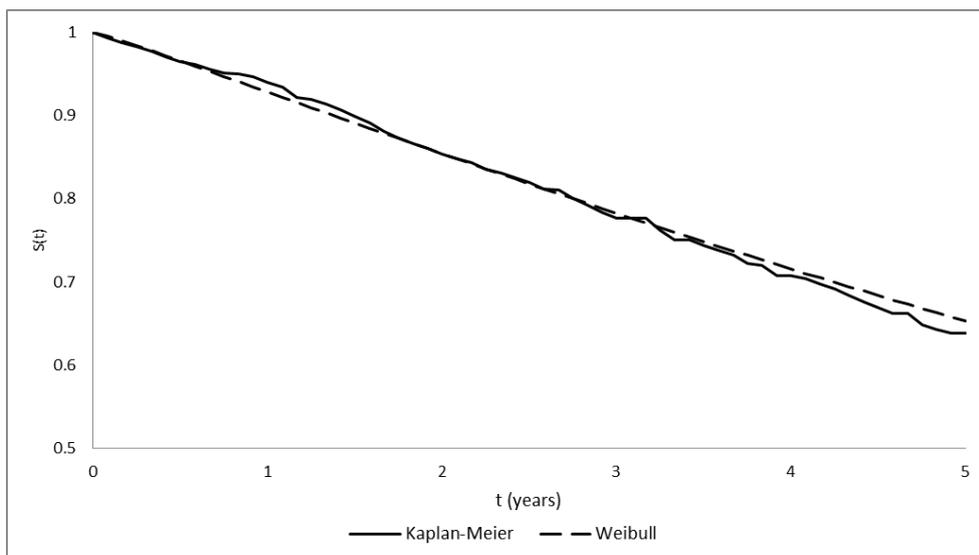
Figure 2. Kaplan-Meier survival estimates for all-cause mortality in patients with remote MI and reduced LVEF (MADIT II population) ⁵⁵



Primary prevention – mild-moderate heart failure

The Kaplan-Meier curve for overall survival of patients in the control group with mild to moderate heart failure at increased risk of SCD from the SCD-HeFT trial⁹⁹ is shown in Figure 3 below, as well as its derived Weibull approximation. The R^2 of 0.993 confirms the goodness-of-fit of the Weibull model to the Kaplan-Meier curve of the trial. For the SCD-HeFT the shape parameter ($\gamma = 1.08$) is slightly greater than 1, indicating that the hazard rate slightly increases with time.

Figure 3. Kaplan-Meier survival estimates for overall survival in patients with mild to moderate heart failure (SCD-HeFT population)⁹⁹



Primary prevention – cardiomyopathy

The SCD-HeFT⁹⁹ reported all-cause mortality for the subgroup of patients with non-ischaemic congestive heart failure. The Kaplan-Meier curve for the placebo arm was used to derive the baseline mortality for the subgroup analysis of patients with cardiomyopathy (Figure 4). The R² from the regression (0.99) and visual inspection of the Weibull approximation suggest that the model fits the Kaplan-Meier estimates well.

Figure 4. Kaplan-Meier estimates and Weibull approximation for all-cause mortality in patients with non-ischaemic congestive heart failure (SCD-HeFT population)⁹⁹

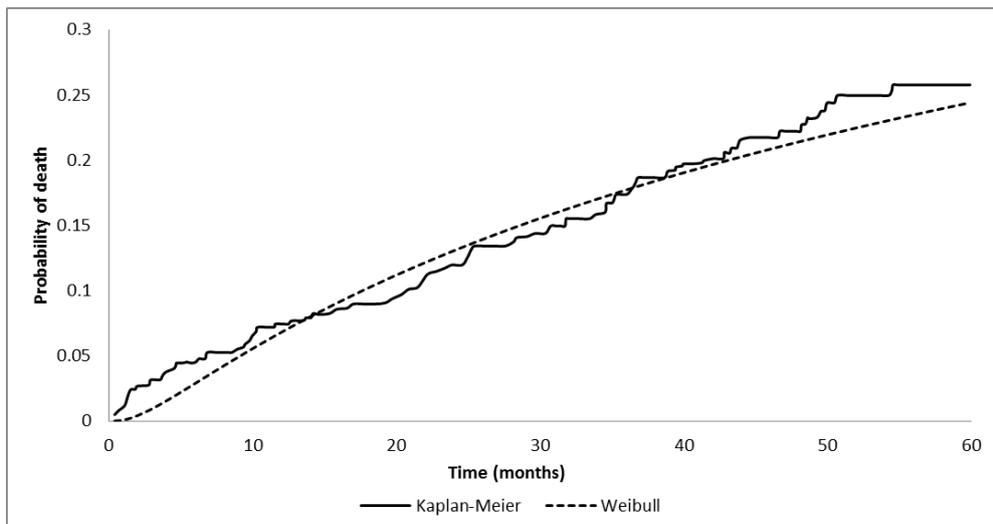


Table 2 reports a comparison of observed survival at given years reported for each trial against model predictions.

Table 9. Regression results and comparison of observed survival against Weibull model predictions – all-cause mortality in the AVID, MADIT-II, and SCD-HeFT trials

AVID: (R² = 0.994) λ = 0.0340 γ = 0.6962				
Year	Trial report¹⁸		Weibull approximation	
	AAD	ICD	AAD	ICD^a
1	0.823	0.893	0.825	0.881
2	0.747	0.816	0.733	0.814
3	0.641	0.754	0.662	0.762
MADIT II: (R² = 0.9903) λ = 0.0098 γ = 1.0068				
Year	Trial report⁵⁵		Weibull approximation	
	Conventional medical therapy	ICD	Conventional medical therapy	ICD^b

1	0.90	0.91	0.89	0.92
2	0.78	0.84	0.79	0.85
3	0.69	0.78	0.70	0.78
SCD-HeFT: ($R^2 = 0.993$) $\lambda = 0.0051$ $\gamma = 1.0831$				
Year	Trial report^{99 c}		Weibull approximation	
	Placebo	ICD	Placebo	ICD^d
1	0.940	0.938	0.928	0.944
2	0.854	0.885	0.854	0.885
3	0.777	0.827	0.783	0.828
4	0.708	0.777	0.716	0.773
5	0.639	0.711	0.653	0.720

^a Hazard ratio (defibrillator vs antiarrhythmic drug) for total mortality is not reported in the AVID trial publication.¹⁸

Survival probability with defibrillator was calculated by applying risk ratio (0.66) calculated in the systematic review.^b

Survival probability with defibrillator was calculated by applying hazard ratio of 0.69 from trial report⁵⁵ to the Weibull

approximation. ^c Survival probabilities for year not reported in SCD-HeFT trial publication⁹⁹ – these values were estimated

from the scanned Kaplan-Meier curves. ^d Survival probability with defibrillator was calculated by applying hazard ratio of 0.77 from trial report⁹⁹ to the Weibull approximation.

Population 2

Cardiac mortality

CARE-HF is the trial with longest follow-up period from those included in SHTAC's clinical effectiveness review for people with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT. Hence, baseline time-dependent probabilities of SCD and death due to worsening heart failure were derived from CARE-HF survival curves.⁶⁴ Table 3 below shows the parameters derived for estimation of SCD and HF deaths for the OPT arm.

Table 10: Weibull model parameters for sudden cardiac death and heart failure mortality

Parameter	Mean	95% CI	
		Lower limit	Upper limit
Sudden cardiac death			
$\ln(\lambda)$	-6.069	-6.173	-5.964
γ	1.140	1.107	1.173
Heart failure			
$\ln(\lambda)$	-6.115	-6.256	-5.974
γ	1.223	1.179	1.266

Weibull model: $\ln(-\ln(S)) = \ln(\lambda) + \gamma \ln(t)$; $S(t) = \exp(-\lambda \cdot t^\gamma)$

Population 3

Mortality and relative risks

Estimates of survival over time were derived from Kaplan-Meier curves reported for relevant trials included in the systematic review. The two largest trials reporting the longest follow-up and comparing events between groups statistically (MADIT-CRT⁸⁶) and RAFT¹³) were included in this analysis.

Kaplan-Meier curves for all-cause mortality were used to derive approximate hazard functions using a Weibull distribution. Parameters for the Weibull distribution were fit in Microsoft Excel using linear regression of transformations of the Kaplan-Meier estimates obtained using Engauge software. Table 4 presents the regression results using data extracted from both trials.^{13;86}

Table 11: Regression results - Parameters used to fit the Weibull models

Parameter	Mean	95% CI	
		Lower limit	Upper limit
<i>RAFT</i>			
ICD-CRT arm ($R^2 = 0.9894$)			
$\ln(\lambda)$	-6.334	-6.202	-6.467
γ	1.243	1.20	1.27
<i>MADIT -CRT</i>			
Men CRT-D arm ($R^2 = 0.989$)			
$\ln(\lambda)$	-6.935	-7.005	-6.865
γ	1.287	1.266	1.308

R^2 statistics reported for the regressions on Table 4 above confirm that the Weibull models fit data well. Figure 5 shows the Weibull approximation to the Kaplan-Meier estimates obtained from the curve published for the ICD-CRT arm of the RAFT trial. The γ value (1.24, 95% CI 1.20 to 1.27) is greater than 1, indicating that the probability of death increases over time.

Figure 5. Weibull approximation to Kaplan-Meier survival for all-cause mortality of patients with CRT-D in the RAFT trial

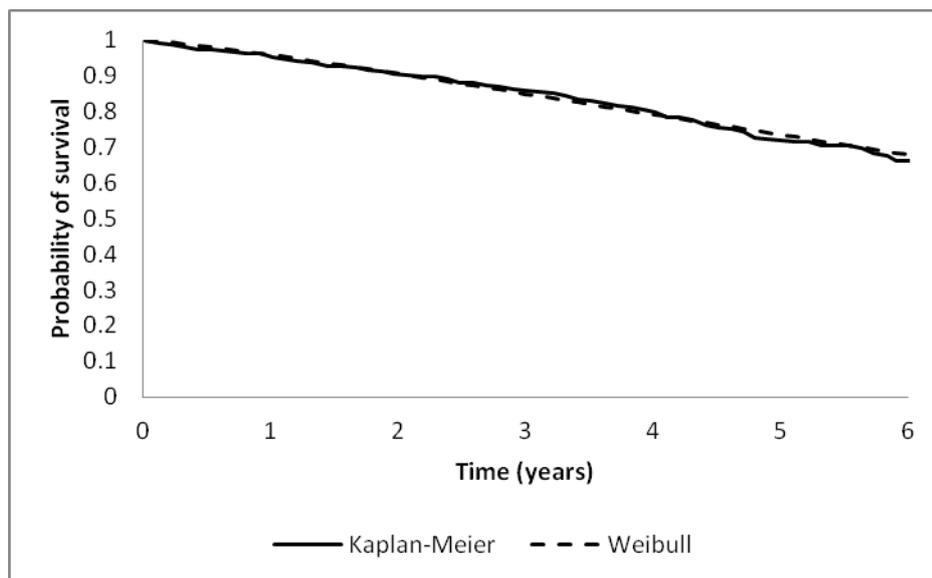


Table 5 reports a comparison of observed survival at times reported for the trial against model predictions.

Table 12: Comparison of observed survival against Weibull model predictions – all-cause mortality in the RAFT and MADIT-CRT trials

RAFT				
Year	Trial report ^a		Weibull approximation	
	ICD-CRT	ICD	ICD-CRT	ICD^c
1	0.954	0.937	0.959	0.945
2	0.902	0.877	0.906	0.876
3	0.860	0.811	0.849	0.804
4	0.797	0.718	0.792	0.733
5	0.714 ^b	0.654 ^b	0.736	0.664
6	0.663	0.553	0.681	0.599
MADIT-CRT men				
Year	Trial report ^a		Weibull approximation	
	CRT-D	ICD	CRT-D	ICD^d
1	0.974	0.976	0.974	0.975
2	0.946	0.939	0.938	0.941
3	0.889	0.929	0.897	0.901
4	0.855	0.851	0.854	0.858

^a Survival probabilities for year not reported in the trial publication – these values were estimated from the scanned Kaplan-Meier curves. ^b Survival probabilities reported in the RAFT trial publication. ^c Survival probability with defibrillator was calculated by applying reverse hazard ratio of 0.75 from trial report for ICD-CRT¹³ to the Weibull approximation. ^d Survival probability with defibrillator was calculated by applying reverse hazard ratio of 1.05 from trial report for men in the ICD-CRT arm⁸⁶ to the Weibull approximation

Appendix 17 Validation of the independent economic model

Validation against the model developed by Fox and colleagues² for TA120

At an early stage of model development, the OPT arm of the model developed by Fox and colleagues² for TA120 was replicated. The OPT arm consisted of a cohort of patients with heart failure initially managed with OPT alone who are eligible for ICD implantation. Table 1 below summarises the output of the original model and the replica in terms of life years and respective discounted QALYs spent in each health state. The same state occupancy was obtained with both versions of the model.

Table 1. Models output for an average 70-year old patient with HF initially managed with OPT

Health state	Life years		Discounted QALYs	
	Fox et al.	Replica	Fox et al.	Replica
Stable with OPT	3.42	3.42	2.17	2.17
Hospitalised with OPT	0.13	0.13	0.08	0.08
ICD implantation	0.03	0.03	0.02	0.02
Peri-operative complications	0.01	0.01	0.00	0.00
Stable with ICD	1.56	1.56	0.98	0.98
Hospitalised with ICD	0.06	0.06	0.04	0.04
Device replacement	0.02	0.02	0.01	0.01
Device-related infection	0.00	0.00	0.00	0.00
Lead displacement	0.00	0.00	0.00	0.00
Transplanted	0.03	0.03	0.02	0.02
<i>Total</i>	5.26	5.26	3.31	3.31

Having reproduced this model arm, the model was adapted according to clinical advice to reflect disease progression for the populations defined in the scope¹⁰¹ developed by NICE for this assessment.

Validation against trial data

Population 1

The model was validated against the trial data for all-cause mortality for the AVID, MADITII and SCD-Heft trial. The model used the all-cause mortality regression parameters calculated for these trials and the trial RR for ICD, i.e. 0.66 for AVID, 0.71 for MADITII and 0.77 for SCD-HEFT. The

figures 1 to 3 show the results from these analyses. The model generated results show a good fit against the AVID RCT. The model results show a reasonable fit against the MADIT II and SCD-HeFT, although the model appears to slightly underestimate the benefit of ICD compared OPT, and therefore may be a conservative fit.

Figure 1 Overall survival curves for OPT and ICD compared to the AVID RCT data

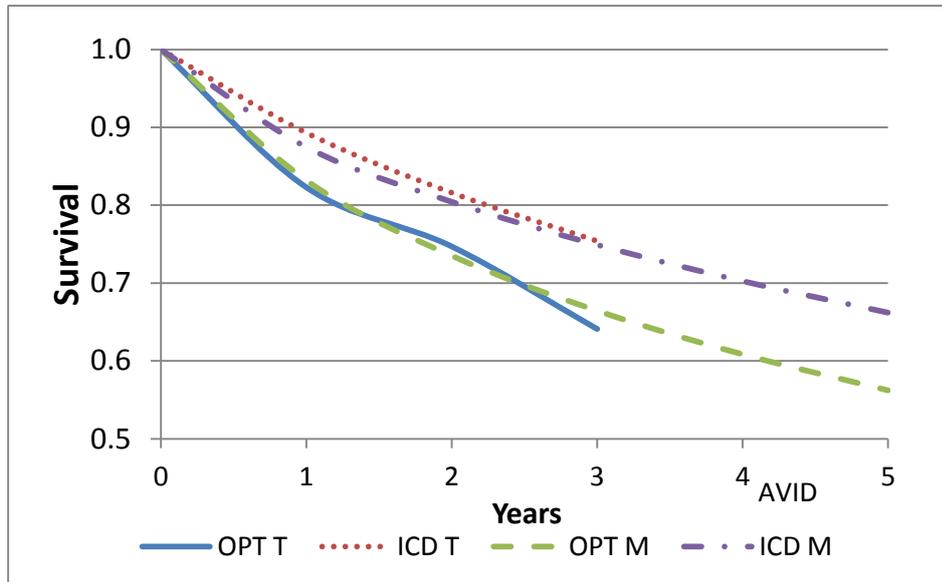


Figure 2 Overall survival curves for OPT and ICD compared to the MADIT II RCT data

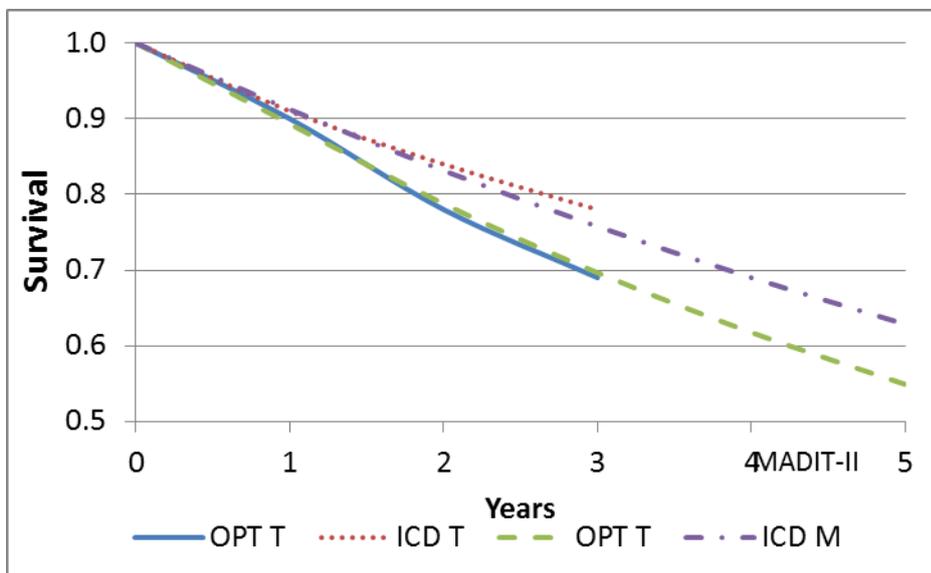
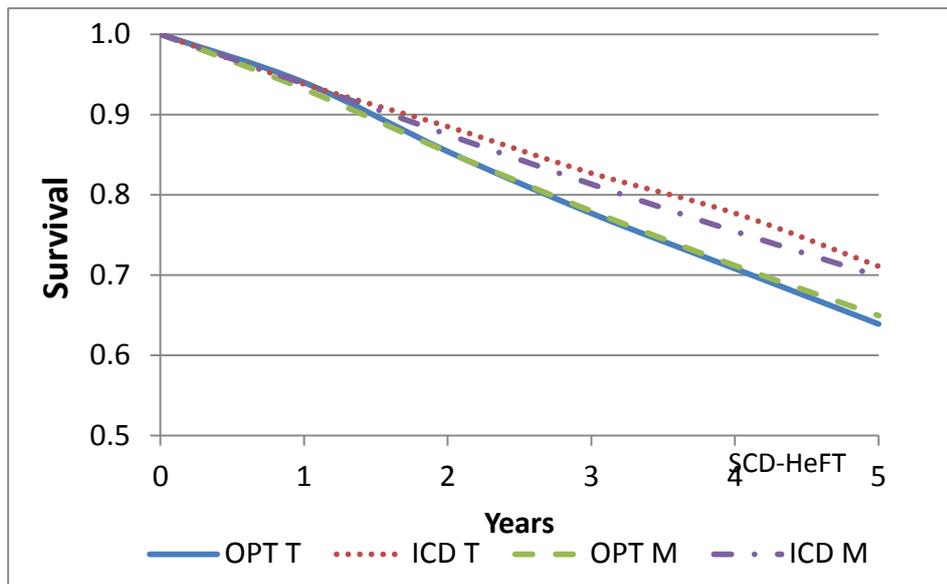


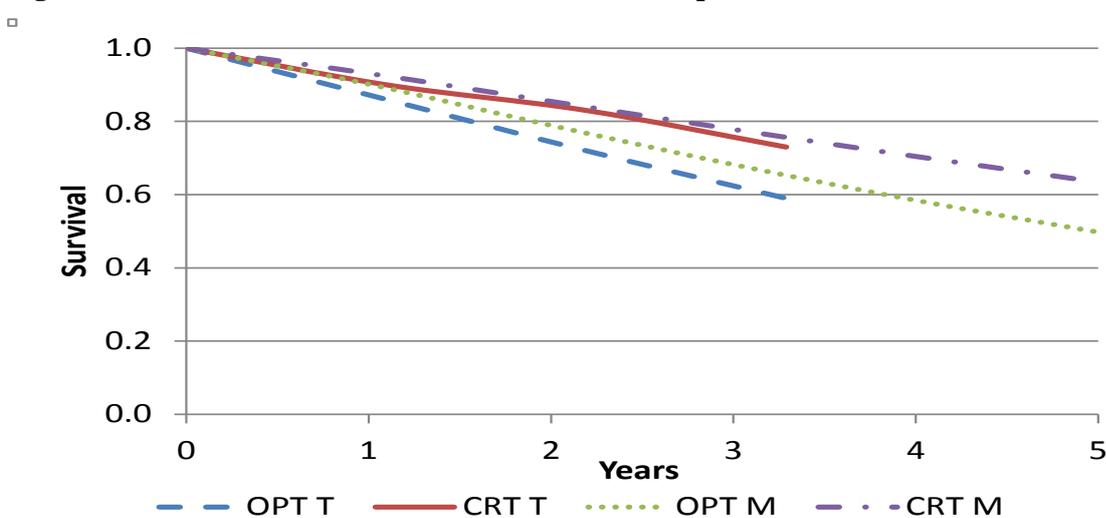
Figure 3 Overall survival curves for OPT and ICD compared to the SCD-HeFT RCT data



Population 2

The model was validated against the trial data for all-cause mortality for the CARE-HF trial. The model used the SCD and HF mortality regression parameters calculated for these trials and the trial RR for ICD, i.e. 0.55 for HF, 0.54 for SCD. Figure 4 shows the results from this analysis. The model generated results show a reasonable fit against the CARE-HF, although the model underestimates all-cause mortality for the OPT arm. This is likely to be an underestimate of non-cardiac mortality for this group. The model results show a reasonable fit against the CRT arm from CARE-HF although the model appears to underestimate the benefit of CRT compared OPT, and therefore may be a conservative fit.

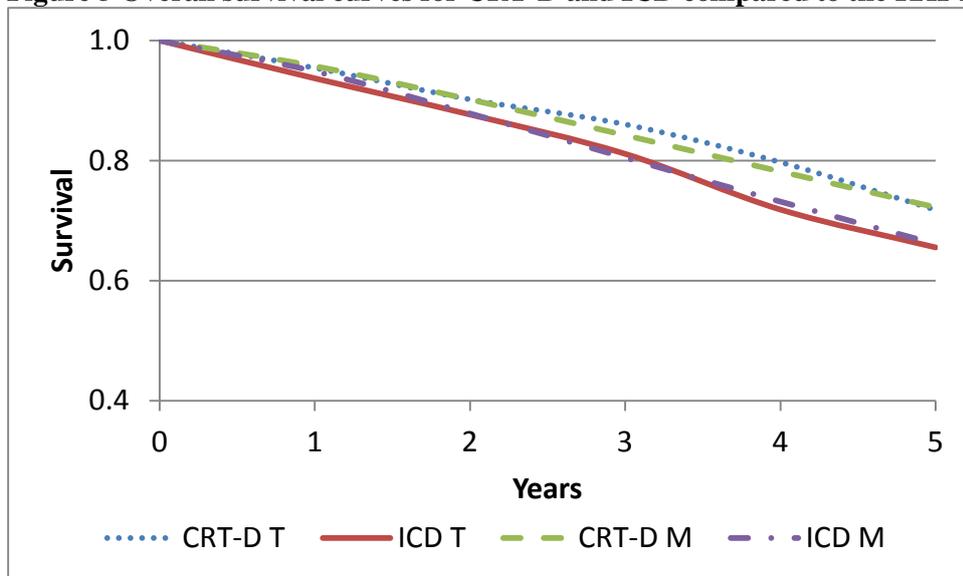
Figure Overall survival curves for CRT and OPT compared to the CARE-HF RCT data



Population 3

The model was validated against the trial data for all-cause mortality for the RAFT trial. The model used the all-cause mortality regression parameters calculated for this trials and the trial RR for CRT-D vs ICD, i.e. 0.75. Figure 5 shows the results from this analysis. The model generated results show a good fit against the RAFT RCT data.

Figure 5 Overall survival curves for CRT-D and ICD compared to the RAFT RCT data



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Additional scenario analysis

Southampton Health Technology Assessments Centre (SHTAC)

March 2013

'OPT only' scenario analysis

Scenario analysis was performed to estimate the impact of an alternative comparator arm with patients being managed with OPT only (i.e. no upgrades to a device) on the cost-effectiveness results for the three populations.

Population 1

Results for P1 patients' base case analysis and 'OPT only' scenario are summarised in Table 1. A P1 patient assumed to be managed with 'OPT only' over a lifetime is estimated to have lower lifetime costs (-£10,802), shorter life expectancy (-0.41 life-years), and hence lower QALY gain (-0.36 QALYs) than a patient modelled allowing for ICD implantation as clinically necessary (i.e. base case OPT). The incremental cost and incremental health benefits of managing patients with an 'ICD plus OPT' compared with 'OPT only' become higher than in the base case analysis, resulting in a slightly higher ICER of £22,710 (an additional £3,231 per QALY gained) compared to an ICER of £19,479 per QALY gained in the base case analysis.

Table 1. OPT only scenario analysis results for Population 1

Intervention	Cost (£)	Life-years	QALYs	Incremental cost (£)	Incremental life-years	Incremental QALYs	ICER (£/QALY gained)
<i>Base case^a</i>							
OPT	15,890	7.32	5.95	-	-	-	-
ICD + OPT	31,382	8.25	6.75	15,492	0.93	0.80	19,479
<i>OPT only scenario</i>							
OPT only	5,088	6.91	5.59	-	-	-	-
ICD + OPT	31,382	8.25	6.75	26,294	1.34	1.16	22,710

^a replicated from report Table 118; Discounted costs and benefits; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio

Population 2

Table 2 presents the results for the 'OPT only' scenario and the base case in P2 patients. A small decrement of estimated lifetime costs and benefits (-£314 and -0.01 QALYs) is estimated for the OPT only arm compared to the base case OPT arm in Population 2. These small differences for not having patients upgrading to CRT-P + OPT (reduced costs and health benefits) had a minor impact on the ICERs, as only a small proportion of patients were estimated to have an upgrade in the base case analysis.

Table 2. OPT only scenario analysis results for Population 2

Strategy	Cost (£)	Life-years	QALYs	Incremental Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
Base case^a							
<i>vs next best option^b</i>							
OPT	7,615	4.86	3.48	-	-	-	-
CRT-P + OPT	26,460	5.51	4.17	18,845	0.66	0.68	27,584
CRT-D + OPT	38,163	7.21	4.58	11,703	1.69	0.41	28,420
<i>vs OPT</i>							
CRT-D + OPT	38,163	7.21	4.58	30,548	2.35	1.09	27,899
OPT only scenario							
<i>vs next best option^b</i>							
OPT only	7,300	4.85	3.47	-	-	-	-
CRT-P + OPT	26,430	5.51	4.17	19,129	0.67	0.69	27,644
CRT-D + OPT	38,162	7.21	4.58	11,733	1.70	0.41	28,429
<i>vs OPT</i>							
CRT-D + OPT	38,162	7.21	4.58	30,862	2.36	1.10	27,937

^a replicated from report Table 128, ^b Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated; Discounted costs and benefits; QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio

Population 3

Table 3 shows the results for P3 base case analysis and OPT only scenario. A reduction of costs and benefits is estimated for P3 'OPT only' arm (-£30,580, -1.18 life-years, and -0.88 QALYs) compared with the base case OPT (and subsequent upgrades) arm. Managing patients with OPT only becomes therefore considerably cheaper and less effective than ICD + OPT (ICER of £39,169/QALY gained), in contrast with the base case results (where OPT was more expensive and effective than ICD + OPT, ICER = £2,824 per QALY gained). The incremental cost and QALY gain of managing patients with CRT-D + OPT increased substantially as well, however the ICER obtained is quite similar (£35,010/QALY gained).

Table 3. OPT only scenario analysis results for Population 3

Strategy	Cost (£)	Life-years	QALYs	Incremental			ICER (£/QALY gained)
				Cost (£)	Life-years	QALYs	
Base case^a							
<i>vs next best option^b</i>							
ICD + OPT	39,719	7.45	5.57	-	-	-	-
OPT	40,006	7.59	5.67	287	0.14	0.10	2,824
CRT-P + OPT	51,202	7.96	5.94	11,196	0.37	0.27	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	10,906	0.42	0.31	35,193
OPT only scenario							
<i>vs next best option^b</i>							
OPT only	9,426	6.41	4.79	-	-	-	-
ICD + OPT	39,719	7.45	5.57	30,292	1.04	0.77	Extendedly dominated
CRT-P + OPT	51,202	7.96	5.94	11,483	0.51	0.37	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	41,485	1.60	1.18	35,010

^a replicated from report Table 141, ^b Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated; Discounted costs and benefits; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

As suggested by the expert methodologist advisor, using an OPT only arm leads to significantly increased incremental costs of the comparators versus OPT. This change was accompanied by a significant gain in incremental QALYs and therefore to similar ICERs as the base case analyses.

Subgroups in the ABHI submission: clinical opinion

**Southampton Health Technology Assessments Centre (SHTAC)
March 2013**

We sought the opinion of four clinical experts regarding how the 48 subgroups in the ABHI submission relate to the three populations defined in the NICE scope. Only two experts replied, and their responses were conflicting.

Clinical Expert 1:

"I remain unsure as to exactly what NICE mean by their first category. I am assuming it implies the individual is at risk of SCD by virtue of the fact that they have previously experienced ventricular arrhythmia, rather than being destined to die specifically from ventricular arrhythmia (i.e. a secondary prevention group)

If so, and assuming the manufacturers submission does not stipulate presence or absence of prior arrhythmia, then all the manufacturers groups fit in to category 'B' (heart failure etc) in as much as they are referring to a primary prevention population with left ventricular dysfunction. They are appropriately subdividing the groups on clinical criteria in an attempt to define the group that is most cost-effective. As I'm sure you realise, the 150ms QRS cut-off is increasingly being recognised as discriminating between high and low rates of CRT response. The non-ischaemic group was ducked by NICE last time around.

Strictly speaking those in NYHA I don't have heart failure per se as they are asymptomatic. This matters more for the CRT groups than the ICD population as the device was initially envisaged as a symptomatic treatment and has only recently been shown to benefit prognosis in a more mildly symptomatic group.

In essence what the manufacturers seem to be doing is providing a more rational basis for resource allocation than the arbitrary and irrational structure [imposed by the NICE appraisal]"

Clinical Expert 2:

"I guess for some it is - I have labelled them A, B & C and put in table below.

Some groups are tricky though

Non-ischemic NYHA Class 1 - no trials covering this group

All Class IV - really not good for ICD even though at increased risk of SCD, but can have CRT so can be B. If QRS < 120ms then labelled n/a as no device indicated. As a clinician one will implant a CRT in a Class IV pt with a QRS of >120ms as a last chance treatment - if they have no other option and are in hospital.

The 120-150ms groups with LBBB are to some extent debatable between groups A & C, but I have labelled as C as its so annoying to implant a device appropriate for A only to change it within a couple of years because they are group C. For non LBBB most now do not advise CRT so have left as A."

Populations defined in NICE scope	Clinical Expert 2
People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment	A
People with heart failure as a result of LVSD and cardiac dyssynchrony despite optimal pharmacological treatment	B
People with both conditions described above	C

Table

Subgroups defined in ABHI submission			Clinical Expert 2
NYHA Class	Etiology	QRS duration	
Without LBBB			
I	Non-ischemic	<120 ms	n/a
I	Non-ischemic	≥120, <150 ms	n/a
I	Non-ischemic	≥150 ms	n/a
I	Ischemic	<120 ms	A
I	Ischemic	≥120, <150 ms	A
I	Ischemic	≥150 ms	A
II	Non-ischemic	<120 ms	A
II	Non-ischemic	≥120, <150 ms	A
II	Non-ischemic	≥150 ms	A
II	Ischemic	<120 ms	A
II	Ischemic	≥120, <150 ms	A
II	Ischemic	≥150 ms	A
III	Non-ischemic	<120 ms	A
III	Non-ischemic	≥120, <150 ms	A
III	Non-ischemic	≥150 ms	A
III	Ischemic	<120 ms	A
III	Ischemic	≥120, <150 ms	A
III	Ischemic	≥150 ms	A
IV	Non-ischemic	<120 ms	n/a
IV	Non-ischemic	≥120, <150 ms	B
IV	Non-ischemic	≥150 ms	B
IV	Ischemic	<120 ms	n/a
IV	Ischemic	≥120, <150 ms	B
IV	Ischemic	≥150 ms	B
With LBBB			
I	Non-ischemic	<120 ms	n/a
I	Non-ischemic	≥120, <150 ms	n/a
I	Non-ischemic	≥150 ms	n/a
I	Ischemic	<120 ms	A
I	Ischemic	≥120, <150 ms	C
I	Ischemic	≥150 ms	C
II	Non-ischemic	<120 ms	A
II	Non-ischemic	≥120, <150 ms	C
II	Non-ischemic	≥150 ms	C
II	Ischemic	<120 ms	A
II	Ischemic	≥120, <150 ms	C
II	Ischemic	≥150 ms	C
III	Non-ischemic	<120 ms	A
III	Non-ischemic	≥120, <150 ms	C
III	Non-ischemic	≥150 ms	C
III	Ischemic	<120 ms	A
III	Ischemic	≥120, <150 ms	C
III	Ischemic	≥150 ms	C
IV	Non-ischemic	<120 ms	n/a
IV	Non-ischemic	≥120, <150 ms	B
IV	Non-ischemic	≥150 ms	B
IV	Ischemic	<120 ms	n/a
IV	Ischemic	≥120, <150 ms	B
IV	Ischemic	≥150 ms	B

Summary of differences between population 2 and population 3 results

SHTAC

22nd April 2013

In response to some of the consultees comments we have examined in more detail the differences between the results from the population 2 (P2) and population 3 (P3) results.

Baseline risk for population 2 and population 3

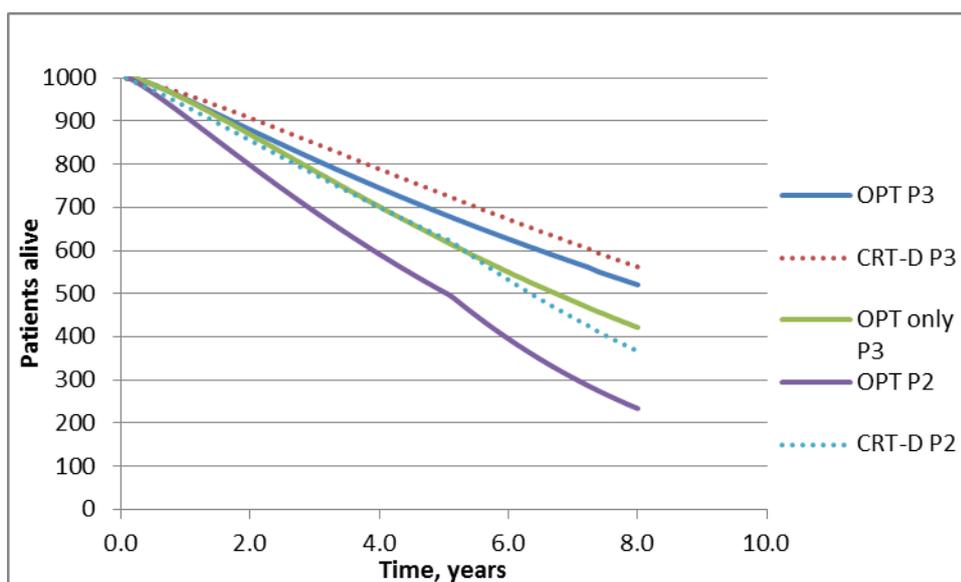
The baseline risk for population P2 is higher than for P3, as shown in Table 1, but the relative risk improvement with CRT-P compared to OPT is similar in the two populations.

Table 1 Summary of baseline risk for population 2 and population 3

	P2	P3
Starting age	70	66
All-cause mortality (yearly probability) OPT	0.108	0.067
All-cause mortality CRT-D	0.07	0.043

Figure 1 shows the survival functions for population 2 and 3. In the original analyses, there is a greater benefit in terms of survival for P2 than P3 because of the high numbers of crossovers to CRT-D in OPT in P3. This can be seen by considering the OPT only scenario for P3.

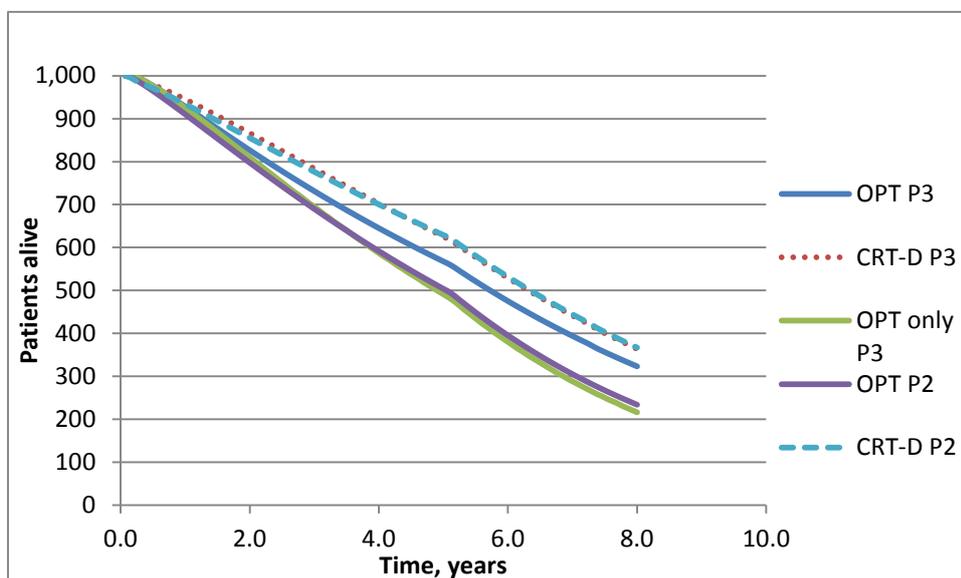
Figure 1 Survival of OPT, CRT-D arms for P2 and P3 in original analysis



The baseline risk for P3 was from the RAFT trial. A scenario analysis was run using the upper and lower confidence intervals of baseline mortality data from the RAFT trial (see SHTAC responses to comments from consultees). The ranges used were the confidence intervals from the RAFT trial (yearly probability all-cause mortality CI range 0.033 – 0.053 for CRT-D). Thus even with the upper CI from the RAFT trial, the baseline risk was greater in P2, than P3.

A new scenario for P3 was run with a higher baseline risk similar to all-cause mortality for P2. All-cause mortality for P3 was 50% higher (All-cause mortality yearly probability OPT 0.105, CRT-D 0.065). This gives a similar ICER to the baseline (£34,964 vs. £35,193). Figure 2 shows the survival functions of population 2 and with a higher baseline risk for P3 compared to P2.

Figure 2 Survival of OPT, CRT-D arms for P2 and P3 with higher baseline risk for P3



Quality of life

We have discovered an error for our scenario analysis for changes to quality of life (Table 145 of assessment report, p370) for P3. Quality of life has more of an impact on the model results than reported in this Table (see SHTAC responses to comments from consultees, p5).

Furthermore, the scenario differs from the data used for HF progression in P2:

P2 model assumes a given initial distribution of patients per NYHA class (initially more severe than that in P3 model). At 9 months and 18 months, different distributions per NYHA class (derived from CARE-HF and Curnis et al 2003 – BRESCIA study) are assumed capturing the effect of CRT on patients HRQoL.

In P3 model, HRQoL of patients was kept constant over time assuming the initial distribution of patients per NYHA class as that reported for the RAFT trial at baseline.

The net effect of these differences is that in P2, there is more QoL benefit for patients receiving CRT-D than in P3. In our view, these differences in the HF progression between P2 and P3 explain some of the differences between P2 and P3 results.

We have conducted a new scenario in P3 replicating the HF progression used in P2.

Scenario analysis for P3 – “P2 HRQoL”

This scenario assumes P3 has the same heart failure progression as P2 to provide an estimate of the impact of the assumptions made for HRQoL in P2 model on P3 model results.

In this scenario, we assume the same utility values over time for P3 as those for P2 (assuming same HF baseline condition and same progression over time).

Table 1 below shows the cost-effectiveness results for this scenario and for the base case analysis. Results show an ICER of £27,396/QALY gained for CRT-D versus OPT, similar to that from P2 model (£27,899/QALY).

Table 1. P2 HRQoL scenario results for Population 3

Strategy	Cost (£)	Life-years	QALYs	Incremental			ICER (£/QALY gained)
				Cost (£)	Life-years	QALYs	
Base case^a							
vs next best option^b							
ICD + OPT	39,719	7.45	5.57	-	-	-	-
OPT	40,006	7.59	5.67	287	0.14	0.10	2,824
CRT-P + OPT	51,202	7.96	5.94	11,196	0.37	0.27	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	10,906	0.42	0.31	35,193
P2 HRQoL scenario							
vs next best option^b							
ICD + OPT	39,719	7.45	5.37	-	-	-	-
OPT	40,006	7.59	5.68	287	0.14	0.31	936
CRT-P + OPT	51,202	7.96	6.04	11,196	0.37	0.36	Extendedly dominated
CRT-D + OPT	50,911	8.01	6.08	10,906	0.42	0.40	27,396

^a replicated from report Table 141, ^b Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated; Discounted costs and benefits; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120)

ICERs for ICD in intermediate QRS group (120-149 ms)

Context: The effectiveness of cardiac resynchronisation therapy in patients with slightly prolonged QRS duration has been questioned in recent publications (Cleland et al., 2013 and Ruschitzka et al 2013). The Committee agreed that subgroups with a QRS duration between 120 and 149 ms, as defined in the manufacturers' analysis, may include patients in whom CRT may be inappropriate and clinical opinion on other factors that affect the decision about CRT devices would need to be taken into consideration. The Committee considered that there were subgroups for whom CRT devices could not be clearly recommended and took into consideration the ICERs when CRT was excluded.

The ICERs for ICD compared with OPT were not available for following subgroups in the manufacturers' additional analysis:

- NYHA class II with LBBB
- NYHA class III without LBBB

Subsequently, the Assessment Group was asked to explore these ICERs with the Committee's preferred assumption of a 5 year duration of constant effect on mortality followed by tapering up to 20 years. The results are presented below:

ICER of ICD for QRS duration between 120 and 149 ms

Subgroup	OPT		ICD		ICER (£/QALY)
	QALYs	Costs (£)	QALYs	Costs (£)	
NYHA II with LBBB	5.47	6,512	6.38	27,558	23,144
NYHA class III without LBBB	2.73	5,630	3.52	25,006	24,514

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; NYHA, New York Heart Association; OPT, optimal pharmacological therapy.

Reproduced from an email from the Assessment Group (dated 27/11/2013)

Summary

We would like to thank NICE for the opportunity to respond to the dossier prepared by Southampton Health Technology Assessment Centre (SHTAC).

We would like to raise two major areas of concern we have regarding the approach taken by SHTAC to the clinical evidence and the cost-effectiveness modelling. We believe that these issues may make it very difficult for the appraisal committee to make specific recommendations based on the analyses presented by SHTAC.

Firstly, SHTAC separates the patient population in to three subgroups specified in the scope.

1. Population 1 - patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite OPT
2. Population 2 - patients with heart failure as a result of LVSD and cardiac dyssynchrony despite receiving OPT
3. Population 3 – patients with both conditions described above.

The criteria by which patients and thereby clinical trial populations are attributed to each of the groups have not been objectively defined by SHTAC. The ABHI group, including two UK clinical specialists, believe that there are no accepted *a priori* clinical criteria which allow most of the trials in this review to be categorised as a whole to the groups defined in the scope. Indeed, the cross-over between the target populations for defibrillation and cardiac resynchronisation therapy was a key driver of the merging of the ICD and CRT appraisals by NICE for this review. If the most cost-effective technology were to be selected based on the SHTAC analysis in each population, it is therefore unclear what specific guidance could be issued.

The ABHI group therefore worked from the original individual patient data in the pivotal clinical trials back to the scope's categories to determine which patients benefit on clinical and cost effectiveness criteria from the treatments being assessed, defibrillation and cardiac resynchronisation.

Using the IPD we have been able to identify patient characteristics that define these populations i.e. Population 1 (patients with an increased risk of sudden cardiac death but without dyssynchrony who have been shown to benefit from ICD therapy); those in Population 2 (patients with dyssynchrony but without significantly elevated risk of sudden cardiac death who have been shown to benefit from CRT-P therapy) and those in Population 3 (patients with increased risk of sudden cardiac death and with dyssynchrony who have been shown to benefit from CRT-D therapy).

Based on the ABHI analysis, group definitions and treatment recommendations are as follows (all patients with LVEF \leq 35%):

- Patients with NYHA I/II and QRS $<$ 150ms without left bundle branch block (LBBB) and those with NYHA III and QRS $<$ 120ms are at elevated risk of sudden cardiac death. ICD is cost-effective in this population.

- Patients with NYHA class I/II QRS \geq 150ms without LBBB, NYHA I/II QRS \geq 120ms with LBBB, and NYHA III QRS \geq 120ms are at elevated risk of both sudden cardiac and heart failure death. CRT-D is cost-effective in this population.
- Patients in NYHA class IV with QRS \geq 120ms are at elevated risk of heart failure death. CRT-P is cost-effective in this population.

Table 1 summarises these recommendations. Summary and detailed cost-effectiveness results to support these conclusions are reproduced in Appendix 1 of this document.

Table 1: Treatment recommendations resulting from ABHI IPD-based cost-effectiveness model (all patients with severe left ventricular systolic impairment, LVEF \leq 35%)

LBBB	NYHA	QRS (ms)	Treatment recommendation
No	I/II	<150	ICD
		\geq 150	CRT-D
	III	<120	ICD
		\geq 120	CRT-D
	IV	\geq 120	CRT-P
Yes	I-III	\geq 120	CRT-D
	IV	\geq 120	CRT-P

This issue is discussed in detail in Part 1 of this response.

Secondly, in the SHTAC analysis the comparators comprise “treatment pathways” in which patients start on a given therapy (OPT, ICD, CRT-P or CRT-D) and may subsequently cross-over to a different device. We do not believe this comparison of treatment pathways can inform decision making in this appraisal. If a device is not recommended, patients will obviously not be able to switch to it in clinical practise. This issue is discussed in detail in Part 2 of this response. Although SHTAC have provided a revised analysis (“Additional scenario analysis, Southampton Health Technology Assessments Centre (SHTAC), March 2013”) this only partially addresses this concern, as documented in Part 2.

The ABHI analysis included individual patient data from over 12,000 patients, representing 95% of the relevant randomised controlled trial evidence. The ABHI analysis responds to the difficult decision of how to select appropriate devices in a heterogeneous patient population. This has been achieved by identifying measurable patient characteristics that could be used to define when patients would benefit most from a device delivering defibrillation or resynchronisation treatment, or both. Part 3 of our response discusses the critique of our analysis by SHTAC which we do not think recognised the full value of this analysis of such a large volume of individual patient data.

In addition, Appendix 2 documents substantive technical errors in the SHTAC analysis. This appendix focuses largely on Population 2 and 3 where the concerns are greatest. Population 1 represents a simpler population both in terms of comparators and the selection of relevant clinical data. Furthermore, the revised analysis from SHTAC for Population 1 fully addresses the concern regarding cross-over documented above. Both the ABHI group and SHTAC analyses suggest ICERs under £30,000/QALY in this group (ICD vs. medical therapy).

The ABHI group would like to emphasise that even if the technical flaws in the SHTAC model are addressed (both the removal of cross-over and the large number of flaws noted in Appendix 2); the

group believes that there are significant limitations to using a model based on summary trial data to inform the current appraisal. We therefore suggest that the committee use the SHTAC model in conjunction with the individual patient data based ABHI model to inform decision making in this appraisal. And that furthermore, careful attention is paid by SHTAC and the committee to the drivers of any differences between the model results. This can only be done comprehensively once the fundamental flaws in the SHTAC analyses are addressed.

Finally, the ICD implant rates quoted in the Assessment Group report originate from TA11 published in 2000 and the subsequent update in TA95 (2006). An implant number of 100 per million has inappropriately been used as a 'national target implant rate' since 2006. This figure is from a NICE costing template¹ designed to estimate budget impact, rather than any published NICE guidance. This ceiling has led to rationing of devices through commissioning policies, contributing to the low penetration rates for device therapy in the UK. We are concerned that the continued reference to the 100 per million implant rate as 'a target' (SHTAC report p37) will reinforce this error with commissioning bodies and providers alike. We request that future Guidance issued by NICE in this therapy area should acknowledge that any reference to implants rates as used in costing templates or the appraisal process are in the context of budget impact estimation and therefore should not be used as justification by commissioning bodies or providers for rationing cost effective technologies as has been previously evident. The criteria for implant should be defined by NICE guidance rather than target implant rates.

¹ <http://www.nice.org.uk/nicemedia/live/11566/33173/33173.xls>

Part 1 – Subgroup definition

Throughout their systematic review and economic evaluation SHTAC have viewed these as three distinct and mutually exclusive populations (highlighted by the fact that separate cost-effectiveness results are generated for each of the three groups).

Clinical trials appear to have been allocated to each of these subgroups on an *ad-hoc* basis rather than by using formally defined criteria. SHTAC state “LVSD was defined as reduced LVEF using the cut-off provided by the publications (an arbitrary cut-off was not imposed by this review). Similarly, cardiac dyssynchrony was as defined by the publications; usually a prolonged QRS interval. Trials clearly stating that participants had reduced LVEF, cardiac dyssynchrony and an indication for an ICD were considered as having both conditions.” (Assessment Group report p43). We are concerned that the lack of clear definitions for Populations 1-3 mean that it will be very difficult to create clinically meaningful guidance based on the results of the SHTAC analysis.

Although SHTAC state “there is considerable overlap between the groups, such that people with HF due to LVSD are at risk of SCD from ventricular arrhythmia” (Assessment Group report p24), the extent of this overlap does not seem to have been fully understood and has not been reflected in the SHTAC modelling. This can be shown by looking at causes of death in SCD-HeFT (considered by SHTAC a “Population 1” trial) and Companion and CARE-HF (considered by SHTAC to be “Population 2” trials).

- In SCD-HeFT, 207 patients experienced sudden cardiac death, but an almost equivalent number (205) experienced heart failure deaths².
- In CARE-HF, 102 heart failure deaths and 86 sudden cardiac deaths occurred³ and in Companion 139 heart failure and 83 sudden cardiac deaths occurred⁴.

It is troubling that Companion, a trial which randomised patients to CRT-D, is included in the population of patients identified to be not at risk of sudden cardiac death (Population 2) and that CRT-D is included as a comparator in this population. Such allocation is fundamentally flawed and distorts the nature of the study populations and clinical conclusions.

SCD-HeFT, COMPANION and CARE-HF enrolled during overlapping periods (Sept 1997-July 2001; Jan 2000-Nov 2002 and Jan 2001-March 2003 respectively). The concurrent nature of the pivotal trials resulted in highly overlapping patient populations (e.g. all trials included significant numbers of patients with QRS \geq 120ms and NYHA III).

If the trials had not been run concurrently, it would have had important implications for their design, SCD-HeFT would have excluded patients with wide QRS due to the clear benefit of resynchronisation therapy in these patients and CARE-HF would have had to offer CRT-D to patients in NYHA III due to the clear benefit of defibrillation therapy observed in the other trials.

These changes were seen in later trials, for example a protocol amendment was applied to RAFT in 2006 to stop randomisation of NYHA III patients to ICD rather than CRT-D. This was driven by the clear benefit of resynchronisation therapy for NYHA III patients observed in CARE-HF.

² Packer 2009 <http://www.ncbi.nlm.nih.gov/pubmed/19917887>.

³ Cleland 2006 <http://www.ncbi.nlm.nih.gov/pubmed/16782715>.

⁴ Carson 2005 <http://www.ncbi.nlm.nih.gov/pubmed/16360067>.

This overlapping nature of the patient populations drove the ABHI group decision to develop an individual patient data analysis. This approach allowed the ABHI analysis to look both within and across the available trial evidence, and to identify where the devices could deliver most value.

The artificial separation of the evidence into three groups means that none of the SHTAC analyses incorporate all relevant available evidence. There are many instances where studies of direct relevance to more than one population (e.g. RAFT, MADIT-CRT; CARE-HF; COMPANION, SCD-HeFT) being used in one population but not the other.

Rather than trying to artificially allocate individual trials to individual subgroups, the ABHI analysis included a synthesis of trials to identify the characteristics that define the subgroups described in the scope. The utility of this approach is recognised by one of the clinical specialists consulted by SHTAC who stated that “what the manufacturers seem to be doing is providing a more rational basis for resource allocation” (Subgroups in the ABHI submission: clinical opinion. Southampton Health Technology Assessments Centre (SHTAC), March 2013 p1). This limited and artificial allocation of trials to only one population in the scope not only weakens the analysis, but is most likely to lead to distorted non-evidence based conclusions that do not reflect the totality of the data from the randomised trials.

A final point is that SHTAC use individual trials to estimate the prognosis in each of the populations and meta-analyses of multiple trials to estimate population-specific treatment effects. This ignores within-group heterogeneity in key prognostic factors (e.g. NYHA) and treatment effect modifiers (e.g. QRS, LBBB) which could be (and according to our analysis are) important predictors of the cost-effectiveness of the different devices.

Part 2 – Inclusion of device cross-over in treatment pathways

SHTAC have included ‘device crossover’ in the design of the economic model. This includes patient crossover from no device (OPT) to a device and the possibility of patients switching from one device to another.

As the key decision facing the committee is whether a given device should be made available or not, the analysis should compare costs and outcomes in ‘worlds’ where ICDs and/or CRTs are available with those where they not. The comparators as defined in the scope are entirely aligned with this principle and explicitly exclude the option of individuals switching to device based therapy from OPT. By considering cost-effectiveness related to “treatment pathways” (Assessment Group report p298) the SHTAC analyses are incompatible with the current appraisal.

In the previous CRT appraisal (TA120), patients on OPT were allowed to switch to an ICD device. This was within the scope of that appraisal since ICD was not a comparator technology and hence was viewed as a component of standard care. This is a different situation to the current appraisal where ICD is a comparator technology and hence citing NICE’s acceptance of the modelling within TA120 does not justify the current approach.

The Appraisal Committee should be aware that crossover is not a rare event in the SHTAC model. The crossover rates in each of the three patient groups are shown in Table 2 below.

Table 2: Crossover rates arising from SHTAC models (all values rounded to the nearest integer, all values obtained from “DetailedResults” sheets of models)

Population	Initial treatment	Switch to ICD	Switch to CRT-P	Switch to CRT-D
1	OPT	45%	N/A	N/A
	ICD	100%	N/A	N/A
2	OPT	<1%	1%	<1%
	CRT-P	6%	<1% ^b	16%
	CRT-D	16%	0%	0%
3	OPT	16%	<1%	81%
	ICD	1%	0%	5%
	CRT-P	17% ^d	0%	86%
	CRT-D	20%	0%	1% ^b

On Monday 11th March 2013 NICE supplied a revised analysis, the description of this provided is provided below:

“Scenario analysis was performed to estimate the impact of an alternative comparator arm with patients being managed with OPT only (i.e. no upgrades to a device) on the cost-effectiveness results for the three populations.”

Based on a comparison of the “Base case” and “OPT only scenario” results provided and the description provided by SHTAC of the modifications made to the model, it is clear that only cross-over from OPT has been removed from the model. The cross-over between all other devices documented in Table 2 does not appear to have been removed (though there are slight differences in the total costs for CRT-P and CRT-D in Population 2). This therefore represents only a partial removal of the extensive switching documented in Table 2.



We believe that the modelling of treatment sequences is the key driver in a number of the counter intuitive issues raised later in this response (see Appendix 2).

Part 3 - Clarification of points arising from the SHTAC review of the ABHI model

On a number of occasions SHTAC state that the ABHI analysis is not in line with the final scope issued in September 2011. This criticism is based on the way we have chosen to start from individual patient data from the published clinical trials to develop a model of clinical and cost effectiveness and the way we have used this model to define which patients would fall in to Populations 1, 2 and 3. As documented in Part 1 of this response, we believe that the evidence base cannot be segregated in the way employed in the SHTAC analysis to form a basis for specific guidance development.

The ABHI analysis addresses all patients with $LVEF \leq 35\%$ ⁵ but without ICD secondary prevention indications and, within these patients, seeks to identify clinical risk factors which predict better/worse response to each therapy. This includes clinical factors that identify patients at a higher risk of either sudden cardiac or heart failure mortality and also clinical risk factors that predict the magnitude of therapeutic effect on each of these causes of death. The ABHI results are presented for patient groups defined in terms of commonly measured clinical variables (NYHA class, aetiology (ischemic/non-ischemic), QRS duration and left bundle branch block (LBBB) conduction abnormality). The results of the analysis are presented with each device (and a no device option) included as individual comparators.

We believe this approach clearly addresses the decision problem as defined in the scope and are unsure why the ERG conclude that this approach is “challenging in terms of developing guidance” (Assessment Group report p256). On the contrary, the ABHI analysis provides clear definition of which patients comprise populations 1, 2 and 3 in terms of NYHA class, aetiology, QRS and LBBB and the cost-effectiveness of each device within these groups. These clinical features are routinely assessed in usual cardiological practice in the NHS. Despite examination of 48 subgroups defined by these characteristics in the ABHI analysis, the recommendations are relatively clear and simple. These recommendations are presented as Table 3.

Table 3: Treatment recommendations resulting from ABHI IPD-based cost-effectiveness model (replicates Table 1, all patients with severe left ventricular systolic impairment, $LVEF \leq 35\%$)

LBBB	NYHA	QRS (ms)	Treatment recommendation
No	I/II	<150	ICD
		≥150	CRT-D
	III	<120	ICD
		≥120	CRT-D
IV	≥120	CRT-P	
Yes	I-III	≥120	CRT-D
	IV	≥120	CRT-P

SHTAC do acknowledge that the approach of using individual patient data to develop a network meta-analysis meta-regression is justified. SHTAC also identifies no errors in the ABHI analysis and acknowledges that the results of the analysis make intuitive sense and that the conclusions seem valid.

⁵ The systematic review included studies including patients with $LVEF \leq 40\%$. However, as the database included only a very small number of patients with $LVEF > 35\%$ (see ABHI submission p112) we consider the analysis to be representative of a group with $LVEF \leq 35\%$.

However, throughout their review of the ABHI submission SHTAC have been unfairly critical. Principally, they have incorrectly grouped together the results from the IPD network meta-analysis as well as the IPD based analyses of hospitalisations and HRQoL into one entity ‘the NMA’ and used concerns about one aspect (the HRQoL analysis) to cast doubt on all aspects – in particular the estimates of treatment effect modifiers.

SHTAC emphasise the uncertainty in the treatment effect estimates from the adjusted network meta-analysis. However their critique seems to ignore that this analysis represents the systematic analysis of individual patient data from over 12,000 patients (95% of the randomised controlled trial evidence base) and the trade-off between improving precision of the treatment effects and retaining statistical significance within specific subgroups.

The ABHI group believes that the network meta-analysis of the overall trial evidence (unadjusted for subgroup effects) provides clear evidence that each device is highly effective in reducing all cause-mortality. The results of this analysis are shown in Table 4 below. We would also argue that our analysis adjusting for covariables serves to refine the point estimates to better reflect risk reduction in specific subgroups.

Table 4: Results of unadjusted network meta-analysis (taken from ABHI submission p123)

Comparison	Hazard ratio, all-cause mortality (mean, 95% CI)
CRT-P vs. OPT	
ICD vs. OPT	
CRT-D vs. OPT	

The Assessment Group correctly cites the fact that Figure 19 in the ABHI submission indicates that 14/52 treatment effect estimates were statistically significant (Assessment Group report p250). However, following submission of this report we have identified an error in the coding for this plot. Although the code for the analysis that entered the model (including variance parameters) was reviewed line-by-line by a second analyst, this was not the case for the associated plot code. Effectively uncertainty is overestimated in these plots due to incomplete accounting for the covariance between the model parameters. Appendix 3 of this document contains the original and revised results. These indicate that when the covariance is appropriately accounted for the treatment effect estimates are statistically significant in 28/52 subgroups.

In addition, we feel that the following aspects of the methodology were not clearly reflected in the SHTAC critique:

- 1) The use of conservative assumptions regarding treatment effect durations. All-cause mortality treatment effects were not assumed to be permanent; instead outside the follow-up period of the available trials (7.5 years) we assume that the hazard ratio converges to 1.0 over a 20 year period. Evidence that this assumption may be conservative is presented in Section 3.9 of the ABHI submission. Any HRQoL benefit associated with each device is also assumed to diminish over time with any benefit set to diminish after five years. Both of these assumptions are in contrast to those used in the academic models created during TA95 and TA120 which both assumed constant treatment effects. Our sensitivity analyses showed that both of these assumptions in the ABHI submission do indeed bias against treatments that provide clinical benefit (ABHI submission p194-199).

- 2) SHTAC also state that we did not provide cost and QALY breakdowns for all interventions in the 48 subgroups. This is incorrect on two counts. Firstly, we provided cost-effectiveness planes for all of the groups in an appendix to our dossier from which the information could have been derived. Secondly, we also provided SHTAC with a fully working model containing a separate worksheet from which they could directly examine the relevant information should they have wanted to.
- 3) SHTAC state that we did not included adverse events into our model. This statement is incorrect. While not explicitly modelled as health states (as in the SHTAC model), device related complications are included in the calculation of all implant costs (original and upgrade) as detailed in our submission dossier (ABHI submission p167).
- 4) The utility values used in the model are criticised by SHTAC on the basis of some counterintuitive device effects which were not used in the cost-effectiveness model. The critique provided does not acknowledge the strength of the utility analysis. The analysis incorporates all available EQ-5D data from the trials of interest, was corroborated by analyses of a large database of Minnesota Living with Heart Failure quality of life data and is therefore the most reliable data available for estimating quality of life adjustments in device eligible patients.
- 5) Finally, there was a concern raised by SHTAC that no evidence was provided to demonstrate whether or not the model had been validated. The model underwent two rounds of external cell-by-cell validation undertaken by an experienced health economist. We are happy to provide the validation reports to SHTAC or the committee if requested.

Appendix 1: Results of ABHI analysis

Table A1: Summary of cost-effectiveness results for all patients with LVEF ≤35% (Replicated from Assessment report Table 91)

Heart failure severity	QRS duration	Results summary
NYHA class I/II	QRS duration <120ms	The ICERs for ICD vs. OPT are below £25,200 per QALY gained.
	QRS duration 120-149ms	ICD is a cost-effective treatment option ^a (ICER < £17,000 / QALY) patients with no LBBB. For CRT-D all ICERs are below £25,000 per QALY gained in LBBB patients (£20,608 to £24,343)
	QRS duration ≥150ms	CRT-D is cost effective treatment with an ICER of less than £28,000 per QALY for all options.
NYHA class III	QRS duration <120ms	ICD vs. OPT generates ICERs below £30,000 per QALY
	QRS duration 120-149ms	CRT-P is cost-effective ^a . CRT-D generates ICERs between £23,900 and £27,400 per QALY gained relative to CRT-P.
	QRS duration ≥150ms	CRT-P is cost-effective vs. OPT (ICER < £20,000 per QALY). Compared with CRT-P, CRT-D generates ICERs below £30,000 per QALY gained. ICD is either dominated or extended dominated.
NYHA class IV	QRS duration <120ms	No comparative analysis was possible in this patient group, as no patients were identified for this combination.
	QRS duration ≥120ms	For CRT-P compared with OPT, all ICERs are close to or below £20,000 per QALY gained. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

^a According to willingness to pay threshold of £20,000 - £30,000 per QALY gained.

These conclusions can be summarised as follows:

Table A2: Treatment recommendations resulting from ABHI IPD-based cost-effectiveness model. All patients have severe left ventricular systolic impairment

LBBB	NYHA	QRS (ms)	Treatment recommendation
No	I/II	<150	ICD
		≥150	CRT-D
	III	<120	ICD
		≥120	CRT-D
IV	≥120	CRT-P	
Yes	I-III	≥120	CRT-D
	IV	≥120	CRT-P

Table A3: Deterministic base case results for ABHI analysis (patients without LBBB), replicated from ABHI submission

NYHA Class	Etiology	QRS Duration	N	C-E Sequence				ICERs			
				1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	66	OPT	ICD	N/A	N/A	Referent	£24,304	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	11	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,619	N/A
I	Non-Ischemic	>=150ms	8	OPT	ICD	CRTD	N/A	Referent	£18,074	£1,080,057	N/A
I	Ischemic	<120ms	272	OPT	ICD	N/A	N/A	Referent	£24,016	N/A	N/A
I	Ischemic	>=120, <150 ms	216	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,234	N/A
I	Ischemic	>=150ms	106	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,086	N/A
II	Non-Ischemic	<120ms	710	OPT	ICD	N/A	N/A	Referent	£25,110	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	232	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,016	N/A
II	Non-Ischemic	>=150ms	141	OPT	ICD	CRTD	N/A	Referent	£20,312	£27,175	N/A
II	Ischemic	<120ms	788	OPT	ICD	N/A	N/A	Referent	£23,884	N/A	N/A
II	Ischemic	>=120, <150 ms	756	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,749	N/A
II	Ischemic	>=150ms	470	OPT	ICD	CRTD	N/A	Referent	£20,697	£22,777	N/A
III	Non-Ischemic	<120ms	255	OPT	ICD	N/A	N/A	Referent	£29,402	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	150	OPT	CRTD	ICD	CRTD	Referent	Ext Dominated	£19,760	£27,336
III	Non-Ischemic	>=150ms	109	OPT	ICD	CRTD	CRTD	Referent	Dominated	£13,227	£24,350
III	Ischemic	<120ms	438	OPT	ICD	N/A	N/A	Referent	£26,923	N/A	N/A
III	Ischemic	>=120, <150 ms	426	OPT	CRTD	ICD	CRTD	Referent	£19,670	Ext Dominated	£24,796
III	Ischemic	>=150ms	192	OPT	ICD	CRTD	CRTD	Referent	Dominated	£14,392	£25,734
IV	Non-Ischemic	<120ms	5	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	12	OPT	CRTD	CRTD	N/A	Referent	£17,324	£30,624	N/A
IV	Non-Ischemic	>=150ms	9	OPT	CRTD	CRTD	N/A	Referent	£16,304	£33,901	N/A
IV	Ischemic	<120ms	42	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	52	OPT	CRTD	CRTD	N/A	Referent	£24,366	£43,500	N/A
IV	Ischemic	>=150ms	10	OPT	CRTD	CRTD	N/A	Referent	£18,065	£37,802	N/A

Table A4: Deterministic base case results for ABHI analysis (patients with LBBB), replicated from ABHI submission

NYHA Class	Etiology	QRS Duration	N	C-E Sequence				ICERs			
				1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	21	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,021	N/A
I	Non-Ischemic	>=150ms	33	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,118	N/A
I	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	76	OPT	ICD	CRTD	N/A	Referent	£19,989	£24,343	N/A
I	Ischemic	>=150ms	165	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,335	N/A
II	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	385	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,608	N/A
II	Non-Ischemic	>=150ms	1,308	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,794	N/A
II	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	477	OPT	ICD	CRTD	N/A	Referent	£20,640	£21,277	N/A
II	Ischemic	>=150ms	982	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,479	N/A
III	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	189	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,550	£23,831
III	Non-Ischemic	>=150ms	775	OPT	ICD	CRTD	CRTD	Referent	Dominated	£9,798	£27,592
III	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	355	OPT	ICD	CRTD	CRTD	Referent	Dominated	£15,449	£25,540
III	Ischemic	>=150ms	773	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,408	£29,912
IV	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	22	OPT	CRTD	CRTD	N/A	Referent	£14,715	£31,920	N/A
IV	Non-Ischemic	>=150ms	81	OPT	CRTD	CRTD	N/A	Referent	£12,076	£35,660	N/A
IV	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	38	OPT	CRTD	CRTD	N/A	Referent	£22,340	£41,695	N/A
IV	Ischemic	>=150ms	97	OPT	CRTD	CRTD	N/A	Referent	£17,722	£46,445	N/A

Appendix 2: Technical critique of Assessment Group model

We were given the opportunity to review the three Excel models developed by SHTAC. Each model is complex and has a relatively large number of health states. It was therefore not possible to review all aspects of the models within the time period available.

Two fundamental concerns regarding the definition of the decision problem have been described in detail in Part 1 and Part 2 of this document. The following additional methodological concerns and technical errors were also identified:

Derivation of treatment effects

The Assessment Group have effectively conducted a set of indirect comparisons to inform the cost-effectiveness analysis.

The adjusted indirect comparison in Population 2 is conducted on heart failure death and sudden cardiac death separately. Our fundamental concern with this comparison is with respect to the heart failure analysis. This comparison uses data from COMPANION and CARE-HF to inform the CRT-P vs. OPT treatment effect and from COMPANION only for the CRT-D vs. OPT treatment effect. Patients in CARE-HF were much more likely to have wide QRS (■ QRS<150ms in CARE-HF; ■ in COMPANION) (ABHI submission p125) and LBBB (89-90% in CARE-HF, 69-73% in COMPANION). Individual trial subgroup analysis (Assessment Group report p244), previous meta-analyses⁶ and the ABHI submission analysis identify QRS and LBBB as predictors of enhanced CRT efficacy. This indirect comparison is therefore likely to bias the treatment effect of CRT-P vs. CRT-D in favour of CRT-P. The treatment effect for CRT-P is also unlikely to reflect a clear patient population (as defined in terms of QRS and LBBB).

The indirect comparison in Population 3 is conducted on all-cause mortality. The CRT-D vs. ICD treatment effect is informed by eight trials (MADIT-CRT, MIRACLE-ICD II, RAFT, Pinter 2009, Contak-CD, Rhythm-ICD, MIRACLE ICD, RethinQ). The CRT-D vs. OPT treatment effect is taken directly from COMPANION. For CRT-P vs. CRT-D the Assessment Group have assumed equivalence. This appears to be illogical on the following grounds: (1) the direct evidence available from COMPANION (a group who may be *less* likely to receive additional benefit of CRT-D over CRT-P than the patients included in the CRT-D vs. ICD comparison due to Companion patients being more likely to die from heart failure causes) supports a stronger treatment effect for CRT-D than CRT-P; and (2) if ICD and CRT-P are effective it is illogical to assume that CRT-D is less effective than the two individual devices as a CRT-D device combines the treatment modalities of ICD and CRT-P.

For Population 1 pairwise analyses are presented. Patients with and without remote-MI are separated, without clear evidence of differential treatment effects from either individual trial subgroup analyses or the ABHI submission analysis (see ABHI submission Appendices p38). Neither analysis can therefore be thought to represent the full evidence base for these patients.

Derivation of survival curves

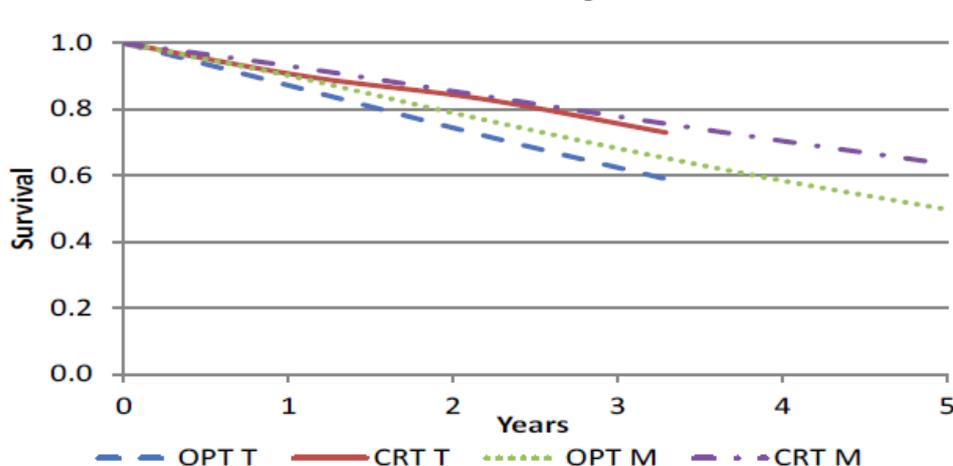
The SHTAC analysis applies relative risks as if they are hazard ratios in a number of instances. This is a violation of statistical principles and undermines the credibility of the analyses.

⁶ Sipahi 2012 <http://www.ncbi.nlm.nih.gov/pubmed/22305845>

In addition, the proportion of patients alive at any given time point in the models does not reflect the data on which the models were largely parameterised. This is particularly apparent for the ‘competing risk’ approach used by SHTAC to model Population 2. To aid the Appraisal Committee we have reproduced the plot prepared by SHTAC comparing the output from their model with the all-cause mortality data from the CARE-HF study below. Assuming that T refers to trial and M to model, the fit to the OPT arm is extremely poor and leads to an inflation in survival. This in turn will lead to a decrease in incremental benefit for CRT-P and a corresponding inflation in the ICER. We believe this is one reason why the ICER for CRT-P vs. OPT is a lot higher than in previous evaluations (another being the presence of device crossover mentioned earlier).

Figure A1: Comparison of SHTAC model output and CARE-HF clinical data (Assessment Group report appendices, appendix 17, p231)

Figure Overall survival curves for CRT and OPT compared to the CARE-HF RCT data



We have concerns about other curves and would have liked to have seen validation plots with longer follow up than five years in order to make an informed review. This is especially the case as an age specific scaling factor is applied to “all-cause mortality” data to reflect increasing risk of death in Population 1 and Population 3. Gamma values used in all survival analyses are greater than one, meaning that the rate of death is naturally increasing. Application of the scaling factor has therefore accelerated this rate of death, potentially “double counting” some mortality and biasing against treatments with a better survival profile. No validation of this approach is provided.

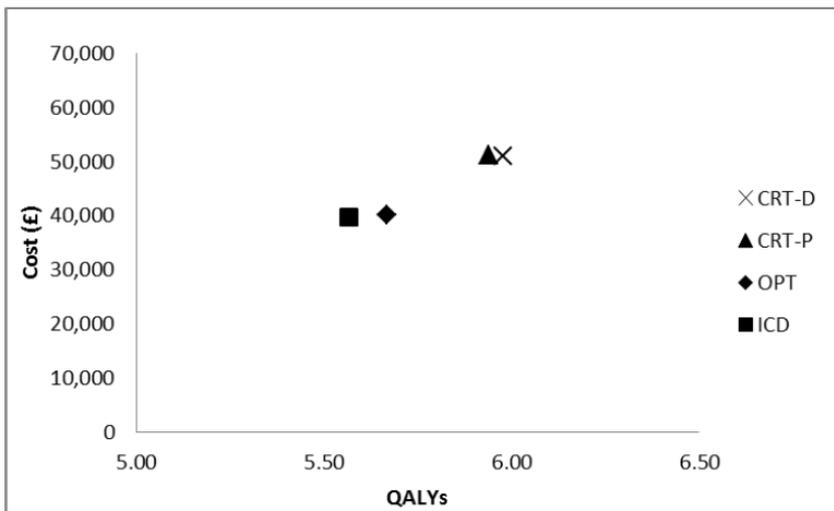
Use of RAFT mortality data in Population 3

Device-specific mortality in Population 3 is modelled by applying treatment effects for each treatment (vs. CRT-D) to the CRT-D mortality rates in RAFT. Although RAFT is a large trial with long follow-up, it cannot alone be viewed as representative of Population 3. Patients in RAFT were predominantly NYHA II (80%), whereas the patient population considered for CRT-D includes both patients with more severe heart failure (NYHA III/IV) and those with NYHA class I.

Lack of face validity of results for Population 3

One of the key tests of any cost-effectiveness model is whether or not the results are clinically plausible. To demonstrate why we believe the results for SHTACs Population 3 fail this simple test, we have reproduced the cost-effectiveness plane from the main report below.

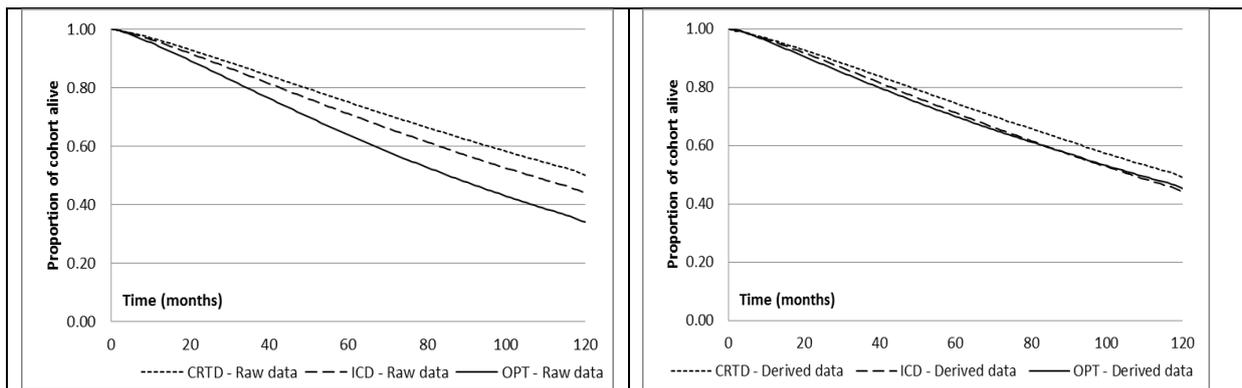
Figure A2: SHTAC base case results for Population 3 (Assessment Group report, p358)



By definition, this patient group are at an increased risk of sudden cardiac death but yet the use of ICD therapy (which includes OPT) results in the generation of fewer lifetime QALYs than were patients treated with OPT alone. This result is clinically implausible and undermines the validity of the results for this group.

We have not been able to undertake a full review of the model but we believe that this anomaly may have occurred due to the very high levels of device crossover. To demonstrate this point, consider the two plots below. The one to the left documents the treatment specific survival (as noted on the ‘mortality’ worksheet) and the one to the right the proportion of patients alive as derived from information on the relevant Markov traces. The extra benefit for the OPT arm is likely to be driven by the very high rate of cross-over to CRT-D.

Figure A3: Comparison of SHTAC mortality inputs (left panel) and outputs (right panel) in Population 3



Lack of face validity of results for Population 3 compared to Population 2

The fact that CRT-D is associated with poorer cost-effectiveness in Population 3 compared to Population 2 lacks face validity. CRT-D is the treatment arm providing both defibrillation and resynchronisation – the modalities from which a population with an increased risk of sudden death and heart failure despite OPT (Population 3 as defined in the scope) would be expected to benefit

most. This is likely to be again driven by the high level of cross-over in the OPT arm for Population 3 compared to Population 2 (see Table 2).

No quality of life benefit of CRT-P in Population 3

SHTAC state that no benefit is assumed based on the fact that “For Population 3, robust evidence of the effect of devices on heart failure progression was not found”. However, the failure to model a quality of life benefit with CRT-devices in this population appears to contradict SHTAC’s own systematic review findings. SHTAC state that “An improvement in QoL score was seen with CRT-D when the trials were pooled (MD -6.9, 95% CI -10.4 to -3.4, p=0.0001)” (Assessment Group report p224).

Transplant mortality

20% of transplant patients are still alive after 34 years (i.e. at age 100 in Population 3)

Utility data

NYHA class specific utility data were taken from a study which recruited only patients who had survived an acute MI (not an average device population). The relevance of this study to the current appraisal is debatable.

Systematic inflation of costs in the device arm

Focussing on the model used to generate results for SHTAC population 3, the higher cost of CRT-P when compared to CRT-D also appears implausible. This has occurred for two reasons: i) the very high rates of crossover to CRT-D and ii) incorrect modelling of device related infections and lead displacement.

Reason 1: very high rates of crossover to CRT-D

To explore the impact of device crossover, we have set the probability of hospitalisation due to non-fatal arrhythmia to zero. The impact on treatment specific costs is presented in Table A5. Device specific lifetime costs are lowered by approximately 20-30% for ICD and CRT-D and by approximately 70% for CRT-P. This is driven by the cross-over associated with non-fatal arrhythmia in the model.

Table A5: Impact of non-fatal arrhythmia on lifetime device related costs

Treatment pathway	Original cost	Cost if parameter iHA_CRT set to zero	Difference
ICD + OPT	£40,006	£28,046	£11,960
CRT-P + OPT	£51,202	£16,868	£34,334
CRT-D + OPT	£50,911	£40,369	£10,543

Of note is the fact that the device specific probabilities of a non-fatal arrhythmia requiring hospitalisation for individuals in Population 3 is very different to those in Populations 1 and 2. The values used in the model are replicated in Table A6. The large discrepancy between the values for Population 3 and for populations one and two (with the former being approximately, 400% higher than the latter) is supportive of the argument that device costs are inflated.

Table A6: Device specific four week probabilities of non-fatal arrhythmia requiring hospitalisation

	Population 1 ^a	Population 2 ^b	Population 3 ^c
ICD + OPT	0.0075	0.007	0.032
CRT-P + OPT	N/A	0.007	0.029
CRT-D + OPT	N/A	0.007	0.029

N/A: not applicable; **a)** reproduced from SHTAC report Table 96; **b)** reproduced from SHTAC report Table 100; **c)** CRT-D value reproduced from SHTAC report table 103, ICD and CRT-P values derived from information in SHTAC report table 103.

The model includes defibrillation upgrades following non-fatal arrhythmic hospitalisations (CRT-P to CRT-D; OPT to ICD or CRT-D). However, when non-fatal arrhythmic hospitalisations are set to zero (iHA_CRTD=0, reflecting a situation where nobody is at risk of the event) the number of patients being upgraded from ICD to CRT-D reduces from 48 to 8. It is unclear why the number of arrhythmic events is impacting on the number of switches to resynchronisation therapy. However, a brief review of the model suggests that this may be due to the joint modelling of arrhythmic and heart failure hospitalisations as one health state.

Reason 2: Incorrect modelling of device related infections and lead displacement

Lead displacements are predicted to occur in approximately 43% of CRT-P and CRT-D patients in Population 3 (cells D20 and E20, worksheet 'DetailedResults'). The corresponding values in population 2 for both devices are approximately 30% (cells AR24 and AS24, worksheet 'DetailedResults'). These figures are much higher than published long-term rates and appears to reflect the fact that SHTAC have applied the same event probability every month. Clinically, patients are at an increased risk of such a displacement for a short period of time after implant, after which, the risk is much lower. By comparison, the weighted average of reported rates in the studies from which the data was derived (and arguably more reflective of the actual lifetime risk) is approximately 6% (data sources as per SHTAC report p313).

Similarly, once the device is in place and the wound healed, the risk of device related infection is much lower than in the peri-operative period. Again, SHTAC have applied a common probability in all cycles a patient is alive resulting in implausibly high probabilities of infection. The event occurs in approximately 7.5% of CRT patients in Population 3 and approximately 5% of CRT patients in Population 2. The weighted average event rate in the studies used to inform the model parameter (again, arguably more reflective of lifetime risk) is approximately 1.5% (data sources as per SHTAC report p313).

Surgical failures are assumed to occur in approximately 8% of patients implanted with CRT-P or CRT-D every four week cycle. Again failure is more likely in the peri-operative period thus the approach exaggerates device failure. In addition to this, on failure of a CRT-D, the additional total cost of an ICD implant is incurred (£15,248, value taken from worksheet 'Inputs'). This is unrealistic. The vast majority of CRT-D system failures relate to pacing or sensing problems requiring the reposition or replacement of a lead, not a new defibrillation device. This clearly carries a much lower cost.

It is also illuminating to compare the predicted device specific event rates in the SHTAC model to those generated by the model developed during TA120. In this previous model, the lifetime likelihood of lead displacement for CRT-P and CRT-D was 10.3% and 11.6% respectively. The current SHTAC models therefore differ from those in this model by a factor of at least three.

Quantifying the impact of this error on lifetime costs is challenging since it is not possible to include time dependant values into the model structure for both parameters. What is clear, however, is that the SHTAC models are predicting far too many events when compared to either the clinical data or the model developed during TA120, resulting in an increase in lifetime costs for all devices.

Device longevity data

Despite being provided with device specific longevity data for approximately 40,000 implants sourced from the UK National Health service, SHTAC largely disregarded these data on two counts:

- i) By assuming each device lasts for a fixed period of time, after which all will fail immediately. The ABHI model included device replacement as a time dependant function and the parameters used are listed in the SHTAC dossier (p327). These data show the rate of failure is not constant. The approach used is therefore inconsistent with what is observed in clinical practice.
- ii) By performing a sensitivity analysis based on mean device specific survival times from the previous CRT appraisal. The justification for this was 'clinical advice'. We cannot understand how seven year old crude estimates of device longevity were thought to more accurately reflect current UK practice than up-to-date NHS data and would request the committee disregard these sensitivity analyses.

Promoting better understanding, diagnosis, treatment and quality of life for individuals suffering with cardiac arrhythmia

NICE assessment report: Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)

Comments from Arrhythmia Alliance

Arrhythmia Alliance (A-A) welcomes the recent publication of the assessment report produced by the Southampton Health Technology Assessment Centre ahead of the NICE review of TA95 and TA120. We are a coalition of charities, patient groups, patients, carers, medical groups and allied professionals, working together to promote the timely diagnosis and effective management of arrhythmias. By raising awareness and campaigning for the improved detection and care of heart rhythm disorders, A-A aims to extend and improve the lives of the millions around the world affected by these conditions.

We believe NICE's review of TA95 and TA120 comes at a crucial time and we hope the revised guidance reflects accurately the need for life-saving devices for those patients most at risk of sudden cardiac arrest and where drug therapy is failing. The recent publication of the Government's Cardiovascular Disease Outcomes Strategy is welcome; however, we believe it has not gone far enough in tackling deaths from sudden cardiac arrest. Many of those that die would have been saved by a simple implantable cardioverter defibrillator (ICD) but the UK currently lags third from the bottom in a table of Western European ICD use with the UK implanting 70 life saving devices per million people, while Germany implants 200 per million. There is also a wide variation in ICD use across the UK, with patients in North London twice as likely to receive an implant (113 per million) than those in Lancashire and Cumbria (42 per million). We welcome the fact this variation is addressed in page 37 of the assessment report.

The evidence contained within the assessment report clearly highlights the cost effectiveness of the addition of an ICD to optimal pharmaceutical therapy (OPT) and as such, we hope that further evidence given throughout this appraisal process will support our call for an increase in the rates of ICD implants across the UK. A-A consistently campaigns for improved patient access to appropriate therapies resulting in improved patient outcomes. If drug therapy fails to provide optimal treatment or is unable to address the needs of the patient, we advocate the value of introducing a device that is appropriate for the needs of the individual. Some anti-arrhythmic drugs produce negative side-effects, including skin reactions and problems affecting function of the thyroid gland, lungs and liver. Some patients also require regular monitoring for certain types of drug therapy which can have a significant impact upon a patient's quality of life and their ability to conduct day-to-day activities.

In these instances, where a device replaces anti-arrhythmic medication, side-effects can be avoided or minimised. Appropriately fitting a patient with a device should result in symptoms and complications relating to tachyarrhythmia and/or heart failure being reduced. As such, heart failure hospitalisations can be reduced and the NYHA class and changes in left ventricular ejection can be improved.

The most appropriate form of primary prevention must be provided for those at risk of sudden cardiac death, whether this is a device and/or drug therapy. We would emphasise that the most appropriate form of prevention

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Promoting better understanding, diagnosis, treatment and quality of life for individuals suffering with cardiac arrhythmia

and treatment is dependent upon an individual and their own medical circumstances. In addition to the data set out in the assessment report, the benefits of ICD implantation outlined above demonstrate the cost effectiveness of devices and the case must continue to be made for ICD implantation rates to be increased in order to save lives and improve outcomes for those at risk of sudden cardiac arrest.

President: Prof A. John Camm, QHP, MD, FRCP, FACC. **Trustees:** Mr Mark Bullock, Professor Richard Schilling, MB, BS, FRCP, MD, Mr Nigel Farrell, LLB (Hons), Dr Adam P Fitzpatrick, MD, FRCP, FACC, Mrs Trudie Lobban MBE.
Patrons: W B Beaumont, OBE, Rt. Hon Tony Blair, Prof Silvia G Priori, Prof Hein JJ Wellens

Registered Charity Number - 1107496

Dear Jeremy

Many thanks for providing Action Heart with the opportunity to consider the technical content of the above appraisal.

I am writing on behalf of Action Heart to confirm it has no comment to add at this point but looks forward to following the course of this appraisal during its development.

Yours sincerely



Head of Administration

Response to: Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)

1. The general standard of writing in the document is not high. For example, the word “parameter” is used frequently, and incorrectly. Little things, such as switching back and forth between UK and US spellings (“ischemic” and “ischaemic”) are just irritating.

There is frequent use of the construction “... with both conditions” – which is unhelpful. There’s a section entitled “People with both conditions” in the executive summary, but there is no effort to define what these conditions might be. The definition appears later in the main text, but is a very unhelpful and ambiguous separation of patients. Sliding between “people with both conditions” and “population 3”, for example, reads poorly. Subsequently throughout the text the phrase “patients with both conditions” appears – and given that the division of patients into these conditions is wholly artificial and with limited clinical relevance, confusing every time it appears.

Sentences such as “No significant difference was found in QoL” appear very frequently, but are very ambiguous – no difference between groups? Or between baseline and treatment? Similarly “Up to 30% of the ICDs groups” reported adverse effects: well, is that 30% of the groups had at least one patient with an adverse effect, or 30% of the patients randomised to ICD?

These are just some sentences picked out more or less at random, but such imprecision is rife throughout the document, and lessens one’s confidence in it. Some of the prose is simply impenetrable.

I have no doubt that the economic analysis has been conducted thoroughly and rigorously, but the overall document reads as if there has been minimal input from actual clinicians.

2. The figures did not survive to reach my desk, so I am unable to comment further about any of them.
3. One of the premises in the executive summary is incorrect: “[...] ICDs in addition to optimal pharmacological therapy (OPT) for the treatment of people who are at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT” – around half of sudden death is due to bradycardia. ICDs have a pacing function and thus prevent death from bradycardia, too.
4. Surely one of the objectives should have been to attempt to assess the clinical- and cost- effectiveness of CRT-D versus CRT-P using the

existing data.

5. One of the reasons I think there must have been little clinical input into the writing of the document is the categorisation of the patient populations. The division of patients into different populations is not especially helpful, and the definitions of the different populations suggest that there is a deal of misunderstanding in thinking about the patients.
 - a. The first population, those at risk of sudden death: either this should consider all people at risk of sudden death (including congenital heart disease, hypertrophic cardiomyopathy, chanelopathies and so forth); or should acknowledge that the defining feature of the group actually being considered in the manuscript is those with left ventricular systolic dysfunction. It's important, too, to recognise that sudden cardiac death can be due to bradycardias, not just ventricular tachyarrhythmias.
 - b. For the second population, statements suggesting that the trials examined were conducted in patients "at risk of heart failure due to LVSD and cardiac dyssynchrony" are profoundly incorrect and suggest a fundamental misunderstanding of the patient group studied. In the key studies of CRT, the patients were recruited on the basis of having left bundle branch block, and absolutely NOT on the basis of any measure of "dyssynchrony".

The only exception was CARE-HF in which a small sub-set of patients were included on the basis of left bundle branch block, a QRS duration between 120 and 150 ms, and some echocardiographic evidence of dyssynchrony.

Sections headed "*People with heart failure as a result of LVSD and cardiac dyssynchrony*" are just simply wrong from the outset. (The phrasing in fact suggests that the "cardiac dyssynchrony", whatever that is, is the cause of the heart failure.) I suspect what the authors actually mean is "People with heart failure caused by left ventricular systolic dysfunction who have left bundle branch block".

The call for a trial in patients with "non-ischaemic cardiomyopathy in the absence of dyssynchrony" is similarly flawed. Perhaps the authors mean "People with heart failure caused by left ventricular systolic dysfunction in the presence of normal coronary arteries who do not have left bundle branch block".

6. Although some mention is made of men v women in the CRT section, none seems to be made in the ICD section. Meta-analysis suggests that there is no benefit from ICDs in women (*Arch Intern Med* 2009;**169**:1500)

7. The section on heart failure physiology reads like an undergraduate text from 20 years and is wrong in several regards. The section on medical therapy is similarly poor.
8. Definitions of cardioversion v defibrillation are wrong.
9. The section defining what CRT does is simply woeful.
10. “modern ICDs provide the functionality of a standard pacemaker” – no: are there any ICDs that do not?
11. There appears to have been no effort at all made to address important issues in trying to determine clinical- and cost- effectiveness of these devices. Concerns include, for example:
 - a. For CRT
 - i. Whether there is any virtue in offering CRT to people with atrial fibrillation
 - ii. Whether there is any virtue at all in measuring “dyssynchrony”
 - iii. Whether there is any virtue in offering CRT to people without left bundle branch block
 - iv. Whether clinical “response” relates to survival benefits or not.
 - b. For ICDs
 - i. What features should help guide selection of patients for ICD?
 - ii. what are the consequences of using published risk scores to guide selection in terms of clinical- and cost-effectiveness?

Heart Rhythm UK

The SHTAC assessment report addresses both clinical and cost-effectiveness of ICD and CRT therapy in the groups of patients identified in the NICE scope – (i) people at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment (OPT), (ii) people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment (OPT) and (iii) people with both conditions. The Heart Rhythm UK submission dealt primarily with clinical effectiveness.

The conclusions of the SHTAC document are closely aligned with those of Heart Rhythm UK, as would be expected with both drawing on the same published clinical trial data, although there are some areas where interpretations differ.

- 1) *The addition of ICD to OPT was cost-effective at a WTP threshold of £30,000 for all of the scenarios modelled: previous ventricular arrhythmias/cardiac arrest, myocardial infarction more than 3 weeks previously, non-ischaemic cardiomyopathy, and ischaemic or non-ischaemic congestive heart failure and LVEF 35% or less; and in some cases at a WTP threshold of £20,000.*

This is consistent with our conclusions that ICD therapy is appropriate for secondary prevention of life-threatening ventricular arrhythmias, and those with severe left ventricular impairment (LVEF $\leq 35\%$ on echocardiography) regardless of aetiology.

- 2) *Both CRT-P and CRT-D presented an ICER below £30,000 per QALY gained compared with OPT, as did the comparison of CRT-D with CRT-P in people with heart failure as a result of LVSD and cardiac dyssynchrony.*

This is consistent with our conclusions that patients with severe left ventricular impairment (LVEF $\leq 35\%$), evidence of dyssynchrony on ECG (QRS $\geq 120\text{ms}$) and heart failure symptoms despite optimal pharmacological therapy benefit from CRT with improved symptoms, reduced hospitalisation and reduced all-cause mortality.

- 3) *In people with both conditions, the ICER for the comparison of CRT-D + OPT with ICD + OPT was below £30,000 per QALY (unless no difference in all-cause mortality was assumed) but not for the comparison with initial management with OPT alone. The costs and QALYs for CRT-D and CRT-P were similar.*

The SHTAC analysis is consistent with the Heart Rhythm UK assessment that CRT-D is clinically effective in this group. However, the SHTAC conclusion on cost-effectiveness appears to be counter-intuitive. The clinical event rate for the end-points of arrhythmias and heart failure events is higher in those with both increased risk of sudden cardiac death and heart failure due to left ventricular systolic dysfunction, than in those without an increased risk of sudden cardiac death. If CRT-D is cost-effective compared to OPT in group 2, it is difficult to envisage a scenario where it would not be cost-effective in group 3. We would suggest a re-examination of the assumptions behind these calculations.

We are concerned that the groups described in the scope have not been defined by clinical criteria in the SHTAC analysis. This makes it difficult to determine which clinical trial data should be considered for each group and to derive clinical selection criteria for the therapies being considered. We believe that the approach taken in the Heart Rhythm UK submission is more appropriate – describing patient characteristics which not only identify those with increased risk of sudden cardiac death and/or heart failure due to dyssynchrony but also identify patients who have been shown to benefit from ICD (group 1), CRT pacing (group 2) or both treatments (CRT-D, group 3).

We do not understand the proposed strategy of “initial management with OPT alone followed by device implantation and upgrades as necessary” (p374). It is part of routine clinical practice, international guidelines and the entry requirement for clinical trials that medical therapy is optimised before consideration of device therapy. Once this has been done, a decision on device therapy is required. The event indicating the necessity for implantation or upgrade is not defined in the text and this strategy has not been tested in a clinical trial. As a high proportion of clinical events in these groups of patients are fatal, we would be very concerned that many patients would not have the opportunity to benefit from device therapy.

We were very surprised by the decision to disregard the “UK device longevity estimates derived from NHS data of the Central Cardiac Audit Database (CCAD) on all implants with verified life status from 2000 to 2011 (~40,000 implants)” because of “clinical advice that these estimates seem to be overestimated”.

- **page 285, paragraph 4**

“The methodology used by the manufacturers to estimate devices’ longevity is commonly used; however, clinical advice indicated that these estimates seem to be overestimated.”

Clearly this could have had a very significant effect on cost-effectiveness calculations, device hardware costs being the largest part of total NHS costs. We think the authors should have used the device longevity data provided by CCAD on contemporary NHS patients or provide robust evidence that this is incorrect.

The SHTAC analyses do not separately consider people with rare conditions resulting in heart failure or increased risk of sudden cardiac death. We support the approach taken in the Heart Rhythm UK submission of using the best available risk stratification for these groups. SHTAC did not consider the use of CRT for patients in atrial fibrillation. We support the conclusions in the Heart Rhythm UK submission that patients in atrial fibrillation show similar benefit from CRT to those in sinus rhythm providing a high proportion of biventricular stimulation is achieved by pharmacological or ablation therapy.

There appear to be some factual errors in the descriptions of the technologies and their clinical context which are important to clarify in order to prevent any misunderstanding.

- **page 15, paragraph 2**

“One trial reporting hospitalisations found higher rates per 1000 months follow-up among people with ICDs (11.3 vs 9.4, $p=0.09$), with higher heart failure hospitalisations (19.9% vs 14.9%).” This appears to refer to the DAVID trial which demonstrated that specific dual chamber ICD programming, increasing right ventricular pacing, was associated with increased heart failure events. It did not show any effect of anti-tachycardia (ICD) therapy on heart failure. The results of this trial have altered routine clinical practice to avoid this effect.

- **page 14, paragraph 4**

“People scheduled for CABG surgery: One RCT found no difference in all-cause mortality (RR 1.08, 95% CI, 0.85 to 1.38; $p=0.53$), total cardiac deaths (HR 0.97, 95% CI, 0.71 to 1.33, $p=0.84$), non-arrhythmic (HR 1.24, 95% CI, 0.84 to 1.84; $p=0.28$), non-cardiac death (RR 1.50, 95% CI, 0.82 to 2.73; $p=0.19$). Rates of SCD 16 were lower with ICD, but this did not reach statistical significance (HR 0.55, 95% CI, 0.29 to 1.03; $p=0.06$).” This appears to refer to the CABG-patch trial published in 1997. This used selection criteria (signal averaged ECG) which have not been shown to be appropriate and are no longer part of clinical practice and the surgical implantation of epicardial patches for defibrillation which carried a high intra-operative mortality which have not been used in clinical practice for 20 years. This trial documents the history of ICD development but is not relevant to current ICD treatment in the UK. Its results should not be used to infer the clinical effectiveness or risk associated with current practice.

- **page 28, section 1.2**

Cardiac rhythm devices do not function to prevent ventricular arrhythmias – they treat arrhythmias once they have occurred with low-voltage (up to 10V) rapid pacing (anti-tachycardia pacing, ATP) or high voltage (750V) defibrillation. Cardioversion is a term usually reserved for the restoration of sinus rhythm in a patient with an atrial arrhythmia and remains part of the nomenclature of ICDs for largely historical reasons.

- **page 29, paragraph 4**

It is not clear to what the term “resynchronisation shocks” refers. In this context, resynchronisation refers to low-voltage pacing of the atria, left and right ventricles to improve cardiac efficiency. It is delivered to the chambers in a coordinated sequence to maximise synchronisation. It is designed to correct dyssynchrony, not arrhythmias. Ventricular arrhythmias

are treated by anti-tachycardia pacing or high voltage defibrillation shocks (as above). These affect the entire heart and cannot be confined to a specific chamber.

- **page 31, paragraph 3**

There appears to have been a typographical error suggesting that an ICD (ventricular only, VVIR, or dual chamber, DDDR) is more expensive at £18,303, than a CRT-defibrillator (triple chamber, biventricular pacing) at £17,184. This is not the case – CRT-D devices are more complex and are always more expensive than dual or single chamber ICDs. We would be grateful if the authors check that these figures have not been used in error in their calculations.

- **page 32, paragraph 3**

Blood samples are never routinely taken from within the heart to identify sudden cardiac death risk.

- **page 33, paragraph 4**

Amiodarone and other rhythm modifying drugs are not used routinely as part of pharmacological therapy in patients at risk of SCD. They are reserved for specific indications as it is recognised that there is no evidence that they reduce mortality.

- **page 40, paragraph 2**

There is a typographical error: “ICD, CRT-P and CRT-P” should read “ICD, CRT-P and CRT-D”.

- **page 40, paragraph 5**

The 3 groups defined in the scope – people at risk of sudden cardiac death (without heart failure and dyssynchrony), those with heart failure (without an increased risk of sudden cardiac death) and those with both conditions do not overlap by definition. We think a better description is that most affected people are in the 3rd group, with both problems.

- **page 62, paragraph 3**

The manuscript states that “All participants in CASH⁸³ and DEBUT,⁹¹ 90% in CIDS⁸⁶ and 60% in AVID⁷³ had congestive heart failure. The majority (approximately 87%) of people in CASH⁸³ had NYHA Class I or Class II heart failure, whereas about half those in AVID⁷³ and CIDS⁸⁶ fell into these categories. Almost 40% of participants in CIDS⁸⁶ had moderate to severe heart failure (NYHA Class III and IV), compared with 10% of people in AVID⁷³ and 16% (all NYHA Class III) of people in CASH.⁸³ Mean LVEF was higher in CASH⁸³ (46%) than in AVID⁷³ (32%) or CIDS⁸⁶ (34%), suggesting there may have been disproportionate representation of relatively healthy participants in CASH.⁸³”. However, these secondary prevention trials did not include only patients with heart failure. No patients in DEBUT had heart failure, 11% in CIDS were in NYHA III/IV heart failure, about 25% in CASH were asymptomatic (NYHA I) and the mean LVEF was 46% in ICD group and 47% in AAD group. We would suggest rechecking to ensure that this misconception has not resulted in the analysis of trial data against the incorrect group.



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From The Registrar

MD FRCP

Meindert Boysen
Programme Director
Centre for Health Technology Evaluation
NICE

By email to:
TACommB@nice.org.uk

20 March 2013

Dear Dr Boysen

Re: Multiple Technology Appraisal (MTA) - Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120) [ID481] – Assessment Report

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 28,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to respond to the above Assessment Report. We are concerned that relevant experts (in particular from the British Society for Heart Failure) feel that the assessment does not accurately reflect important clinical and technical issues.

Yours sincerely

Registrar

Dear NICE

Thank you for the opportunity to comment on the technical content of the assessment report for the above multiple technology appraisal.

I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.

Many thanks and best wishes



NICE Sponsor Team
Department of Health

Dear Jeremy

Many thanks for these and for the original documents.

The findings of the analysis are accurate. The document is good and well balanced.

I was sincerely hoping that the document would come more clearly on the side of stricter recommendations with regards to the duration of the QRS complex as a marker of potential response to the CRT devices which would strengthen the cost-effective argument for restricting the use of CRT devices to those more likely to benefit.

The summary and the presentation are excellent. I do hope that the final recommendations are articulated to the wider health community in a clear fashion as it will result in some change to the current practices in some centres. It is important to realise that certain devices can reduce sudden cardiac death without affecting the total mortality. This is effectively changing the mode of death (and may be the time to death).

I welcome the research recommendation of an RCT to compare CRTP and CRTD in patients with HF and LVSD.

The meta-analysis findings of the greater benefit for women in subgroup analysis than in men is interesting epidemiologically, and exciting scientifically to recommend further research into why this difference in response exists.

Best Regards,



Consultant Cardiologist

Sheffield Teaching Hospitals NHS Foundation Trust

Past clinical advisor to the GDG on CHF guidelines 2010 (CG 108)

Dear Jeremy

Here are comments on : Multiple Technology Appraisal (MTA)
Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac
resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120) [ID481]

We would have welcomed stronger recommendations with regards the duration of the QRS complex as a marker of potential response to the CRT devices which would strengthen the cost-effective argument for restricting the use of CRT devices to those more likely to benefit. This is more a criticism of the available data than a criticism of the appraisal itself.

We note and welcome the research recommendation of an RCT to compare CRTP and CRTD in patients with HF and LVSD.

The meta-analysis findings of the greater benefit for women in subgroup analysis than in men is both interesting epidemiologically (increasing the chances of more female dominance than is present in the population), and exciting scientifically to recommend further research into why this difference in response exists.

We would welcome clear recommendations especially where the devices reduce sudden death but not all cause mortality, asking the clinicians to communicate that fact honestly to the patient may be needed although very hard to do.

Regards

■

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SHTAC response to comments from consultees

11th April 2013

General response

Patient populations

Comments were received from Heart Rhythm UK, BSH and ABHI regarding the three patient populations included in the assessment report.

The three populations were defined by the NICE scope, which the assessment report must adhere to. The report acknowledges that these are not distinct groupings.

As ABHI state, there are no accepted a priori criteria which could be used to categorise trials. Clinical experts were consulted in order to allocate trials to the population groups. NICE were informed of the difficulties encountered in allocating trials and of the decisions made to ensure that the assessment report adhered to the finalised scope. Pragmatic decisions were taken to allocate trials and to ensure all relevant RCT evidence comparing eligible interventions and comparators was included.

Where trials used different criteria to define their target population, this was noted and highlighted in the assessment report. The baseline characteristics of the trials allocated to each population were described in detail. Only those trials whose populations were considered similar enough were combined in a meta-analysis. Scenario analyses were presented in the economic evaluation to account for the different target populations.

Population 1:

- The clinical effectiveness section summarises all eligible trials comparing ICD vs OPT (or medical therapy). The target populations of the trials differed (e.g. previous cardiac arrest, myocardial infarction or cardiomyopathy). Results were therefore presented separately within the clinical effectiveness chapter for the different target populations and scenario analyses were conducted in the economic analyses.

Population 2:

- The clinical effectiveness section summarises all trials comparing CRT vs OPT. All trials included in TA120 are included here, no additional trials were identified. The COMPANION trial randomised participants to 3 groups (CRT-P, CRT-D and OPT).
- ABHI questioned whether the COMPANION trial belonged in population 2. This trial excluded people *meeting the general indications for an ICD*; therefore a pragmatic decision was taken to allocate the trial to population 2 (all trials in population 3 included people with an ICD indication). COMPANION was the only trial that randomised people to CRT-P and CRT-D (or to compare CRT-D vs OPT), therefore these comparisons were not combined in any meta-analyses with other trials; the results stand alone. COMPANION was used in the economic model to provide evidence on the comparison of CRT-P and CRT-D for both population 2 and population 3, as it was the best available evidence. Allocating this trial to population 3 in the clinical effectiveness chapter would not impact the results.

Population 3:

- The clinical effectiveness section summarises all trials comparing CRT-D vs ICD. All trials in this section included participants with an ICD indication and cardiac dyssynchrony. The NYHA class differed between the trials therefore data were presented by NYHA class in the forest plots. About half the trials included people with NYHA class II and therefore had less severe heart failure than those in the population 2 trials. Inevitably the severity of heart failure in these patients may have impacted on the outcomes. This was examined in the economic evaluation in the assessment report through sensitivity analyses.

The SHTAC assessment report relied on the use of aggregate trial data, which limits the approach that can be taken, especially with regards to subgroups. The focus of the assessment report was an evaluation of the effectiveness of the devices for specific patient groups identified by the NICE scope. In contrast, the ABHI submission accessed individual patient data (IPD) to produce a network meta-analysis (NMA) to inform their model. This allowed the identification of specific subgroups of patients that the different devices appeared to benefit.

Although the approach and focus of the SHTAC assessment report and ABHI submission differed, both approaches are reasonable.

Inclusion of device cross-over in treatment pathways

The ABHI and Heart Rhythm UK criticise the approach in the SHTAC analysis with regard to 'device crossover' in which patients start on a given therapy and may subsequently cross-over to a different device.

The model structure was developed to reflect the management of patients under current clinical practice, consisting of a simplistic approximation of the clinically plausible care pathways. Therefore, the model allows patients initially managed with OPT or CRT-P to have a device implanted or upgrade to a different device according to disease progression.

The model output obtained with this approach is intended to capture the impact of all treatments received by the patient over lifetime, instead of only those of the treatment initially allocated, providing a more realistic estimation of the consequences of the adoption of a particular technology as initial treatment.

This approach has been devised in consultation with our clinical experts as the most clinically plausible. This approach is consistent with the approach developed by TA95 and TA120.

The assumptions for device upgrade are described comprehensively in the assessment report (section 5.4.3.4) Patients in population 1 who are assigned to OPT, can be upgraded to ICD implantation as a result of hospitalisation for major arrhythmia. Likewise patients initially assigned to CRT-P for population 2 and 3 can be upgraded to CRT-D if they experience serious arrhythmia. Furthermore, for population 2, patients receiving ICD initially can be upgraded to CRT-D after hospitalisation for heart failure.

We have modelled an 'OPT only' scenario, i.e. no upgrades (circulated to as a supplementary analysis). We considered modelling no upgrades in the other arms, however the number of device crossovers in all other arms is small (and so changes to these arms would have minimal effect on the model results) except for CRT-P in P3 model.

The CRT-P arm was included as comparator in P3 model to address the scope of the current appraisal. However, no clinical evidence was found for P3 patients with CRT-P and clinical advice

suggested CRT-P would not be appropriate in this group. Therefore, several assumptions on effect were required to include CRT-P in the P3 analysis (e.g. CRT-P assumed to have same risk of all-cause mortality and hospitalisation for severe arrhythmia as CRT-D), and results for the CRT-P arm should be regarded with caution. A scenario analysis assuming no upgrades in the CRT-P arm would also require several additional assumptions on what would happen to patients with CRT-P experiencing severe arrhythmia, and hence would not decrease uncertainty in this analysis.

Univariate sensitivity analyses were conducted for the effect of varying assumptions of treatment effect for CRT-P vs. CRT-D. For instance, when a relative risk of 1.2 for all-cause mortality was assumed for CRT-P vs. CRT-D, an ICER of £3,890/QALY was estimated for CRT-D vs. CRT-P. For a RR of 0.8, the ICER was £14,883/QALY for CRT-D vs. CRT-P (these results were not reported in the assessment report due to small impact in results, however can be found in the P3 model 'Sensitivity Analysis' spreadsheet).

Specific responses

Comments from ABHI: Technical critique of AG model

Derivation of treatment effects

ABHI criticise the use of trial data in population 2 for COMPANION and CARE-HF to inform CRT-P vs OPT but only COMPANION for the use of CRT-D vs OPT for the treatment effect for heart failure. ABHI state that patients in CARE-HF were much more likely to have wide QRS interval and LBBB than patients in COMPANION and identifies these as predictors of enhanced CRT efficacy. They state that this is likely to bias the treatment effect of CRT-P vs. CRT-D in favour of CRT-P.

However, we are unable to comment on the proportion of participants in CARE-HF and COMPANION with QRS >150 ms, or the proportion in CARE-HF with LBBB, as ABHI derived these from IPD. The reported median baseline QRS interval (160 msec) was the same in both trials, and distribution of NYHA class was similar. Therefore we took a pragmatic approach to include all the available evidence.

In view of the IPD data from ABHI, we acknowledge that the treatment effect from the COMPANION trial may be smaller than that expected if CARE-HF patients had received CRT-D.

This potential underestimation was explored in SA (Tables 127 to 129 of our report) by assuming a higher relative effect from CRT-D, i.e. a lower RR of HF death for CRT-D. For example, taking the case where the RR of HF death was at the 95% CI lower limit of RR HF death for CRT-D=0.47 (compared to RR = 0.73 baseline), the ICER for CRT-D vs OPT is £20,671/QALY compared to baseline of £27,899/QALY.

ABHI criticise the evidence used for population 3, in particular the assumptions regarding the relative treatment effect of CRT-P vs. CRT-D. For CRT-P vs CRT-D equivalence was assumed. This approach was taken due to the absence of evidence comparing CRT-D with OPT or CRT-P in population 3. As mentioned above, the CRT-P arm was included as comparator in P3 model to address the scope of the current appraisal. However, no clinical evidence was found for P3 patients with CRT-P and clinical advice suggested CRT-P would not be appropriate in this group. Therefore, several assumptions on effect were required to include CRT-P in the P3 analysis (e.g. CRT-P assumed to have same risk of all-cause mortality and hospitalisation for severe arrhythmia as CRT-D), and results for the CRT-P arm should be regarded with caution. As noted above, univariate sensitivity

analyses showing the effect of varying assumptions of treatment effect for CRT-P vs. CRT-D were conducted.

ABHI criticises the analyses conducted for population 1, on the basis that the evidence chosen does not represent the full evidence base for population 1 patients. The aim for population 1 was not for either trial to represent the full evidence base, but to present representative scenarios for the different target populations.

Derivation of survival curves

ABHI criticise the SHTAC analysis as it applies relative risk as if they are hazard ratio in a number of instances in the model. We acknowledge that we have assumed that the hazard ratio is representative of the relative risk and have applied this in some instances in the model. We consider that the hazard ratio provides a good approximation of the relative risk and using this approach does not have a material effect on the model results.

The ABHI state that the proportions alive at any given point in the SHTAC models do not reflect the data on which the models were largely parameterised. They raise concerns on the fit to OPT arm in population 2 and consider that this lead to an inflation in survival. In the validation appendices we acknowledge that the fit of the model to the trial data underestimates the benefit of CRT compared to OPT and therefore may be a conservative fit (this would reduce the ICER to less than the current base case of £27,900 vs. OPT).

ABHI criticise the age specific scaling factor applied to all-cause mortality data to reflect increasing risk of death in population 1 and population 3. They consider that including this scaling factor has accelerated the rate of death, potentially double counting some mortality and biasing against treatments with a better survival profile.

We note that we have included this scaling factor to be consistent with approach taken in TA120. Sensitivity analysis to the age-specific relative risks of all-cause mortality showed the results robustness to these parameters (removing the scaling factor gives slightly more favourable ICERs £1-2000 less for population 2 and 3 and almost no difference for population 1).

Use of RAFT mortality data in population 3

ABHI comment that they do not consider the RAFT trial to be representative of population 3 patients.

The proportions of participants in each NYHA class varied between the trials in population 3, however as can be seen in Table 53 of the assessment report, only a minority were in class I or IV. RAFT was the only trial demonstrating a statistically significant benefit of CRT-D vs. ICD and strongly influenced the results of the meta-analyses.

The mortality data from RAFT were used in the base case; RAFT included participants with NYHA class II (80%) and NYHA class III (20%). We considered that the RAFT trial was the best trial evidence available for this population. We conducted scenario analysis using mortality data from MADIT-CRT, which included participants with NYHA class I (15%) and class II (85%).

We also undertook sensitivity analyses using the upper and lower confidence limits of baseline mortality data from the RAFT trial. There was little impact on the results with cost effectiveness of CRT-D vs. OPT varying between £35,257 - £35,655 / QALY (these results were not reported in the assessment report due to small impact in results, however can be found in the P3 model 'Sensitivity Analysis' spreadsheet).

Lack of face validity of results for population 3

ABHI and Heart Rhythm UK criticise the face validity of population 3 results and contend that population 3 would be expected to benefit more from CRT-D than population 2, and therefore CRT-D should be more cost effective in population 3.

The reason for differences between the ICERs in these groups is that we have used different populations with different heart failure severity and life expectancies in population 2 and population 3, which makes it difficult to compare results between populations in this way. Due to the limited evidence base, the RAFT trial provided the best evidence for population 3, and as described above the majority of participants had NYHA class II. The P2 and P3 cost-effectiveness results for CRT-D vs OPT are £27,899/QALY for P2 and £35,193/QALY for P3.

To explore the effect of using a higher baseline risk for population 3, we undertook sensitivity analyses using the confidence limits of baseline mortality data from the RAFT trial. There was little impact on the results with cost effectiveness of CRT-D vs. OPT of £35,655 / QALY for a higher baseline mortality risk (these results were not reported in the assessment report due to small impact in results, however can be found in the P3 model 'Sensitivity analysis' spreadsheet).

ABHI criticised the face validity for population 3 because the use of ICD therapy results in the generation of fewer lifetime QALYs than with patients treated with OPT alone.

A significant proportion of P3 patients initially managed with OPT alone are estimated to be referred to CRT-D over their lifetime. These patients will therefore benefit from lower risk of death and of hospitalisation for HF than patients with ICD + OPT. We have also conducted a 'OPT only' scenario with no allowable device upgrades or cross overs for OPT patients (see SHTAC Additional scenario analysis).

No quality of life benefit of CRT-P in population 3

ABHI state that the failure to model a QoL benefit with CRT-devices in population 3 appears to contradict SHTAC's own systematic review findings.

We acknowledge that there was an improvement in QoL score for CRT-D, although this was for MLWHF, and it is uncertain whether there would also be an improvement in EQ-5D QoL, which is used in the economic model.

Data were not available from the RAFT trial (used to model the base case) that showed the progression of heart failure. However, we have investigated the effect of a beneficial effect of CRT devices on patients' HF progression and consequently on HRQoL (Table 145). The ICERs obtained with this scenario are similar to those of the base case analysis.

Transplant mortality

ABHI state that 20% of transplant patients are still alive after 34 years.

We are unclear how the ABHI has calculated that 20% of transplant patients are still alive at age 100 years. However, the numbers of patients who have transplant is very small < 0.1%, and so changes to the mortality rate for this group of patients have no effect on the model results.

Utility data

ABHI questioned the relevance of the study used for NYHA class specific utility data as they were not from an average device population.

The NYHA class specific utility data were taken from a study identified by our systematic review as being of the best quality for those with heart failure.

We have explored the use of different utility estimates with scenario analysis and these results are similar to those of the base case analysis.

Systematic inflation of costs in the device arm

ABHI criticised the results generated for population 3, and that the higher cost of CRT-P when compared to CRT-D appear implausible.

Very high rates of crossover to CRT-D

As noted by ABHI, there are high rates of crossover to CRT-D for patients originally allocated to CRT-P. Patients originally allocated to CRT-P crossover to CRT-D if they experience hospitalisation for arrhythmia. They criticise the hospitalisation rate for non-fatal arrhythmias which is much higher for population 3 than population 1 and 2.

The probability of hospitalisation for arrhythmia, as per our report, for population 3 of 0.029 (0.015-0.042) was derived from population 3 trials. For population 2, the estimate from the MIRACLE RCT participants of 0.0075 was used. The lack of estimates for population 1 led us to taking the conservative assumption of the same estimate as for P2 (the lowest risk estimate). A scenario was conducted for population 1 using population 3 estimates (Assessment report p. 344) that lead to a minimal change to the results (ICER ICD vs OPT of £18,185/QALY).

As noted above, CRT-P has been included within the P3 model to be consistent with the NICE scope and clinical advice suggested CRT-P wouldn't be appropriate in this group. Therefore in this population there is no clinical evidence available for CRT-P in P3 and this required several assumptions on effect. We consider that the results for CRT-P arm should be regarded with caution.

ABHI question the modelling approach with regard to the modelling of arrhythmic and heart failure hospitalisations.

We acknowledge that the hospitalisation health state combines patients hospitalised due to heart failure and non-fatal severe arrhythmia and this may be leading to an overestimation of the upgrades to CRT-D. As the probabilities of upgrade for hospitalised patients receiving ICD, CRT-P or OPT to CRT-D are very small, this is unlikely to have a relevant impact on results.

When the baseline probability of non-fatal arrhythmia is set to zero, CRT-D upgrades in the ICD arm still occur for patients with ICD or being managed with OPT (due to unsuccessful ICD implants) who experience hospitalisation due to heart failure and are subsequently referred to CRT-D. The number of CRT-D upgrades increases when the probability of arrhythmia-related hospitalisation is input because patients managed with OPT can then be referred directly to CRT-D and because those with an ICD who are hospitalised (irrespective of the cause) can be upgraded according to the probability derived from Essebag and colleagues (0.0068). This estimate has been subject to sensitivity analysis (95% CI 0.0006, 0.0129) and the cost-effectiveness results were very similar to the base case (and therefore not reported in the AG report).

The AG conducted an additional scenario setting the probability of upgrade of hospitalised patients receiving any treatment to CRT-D to zero and the results are also very similar to the base case (ICER for CRT-D vs. OPT £35,157 / QALY compared to the base case of £35,193 / QALY) as these probabilities are very small.

Incorrect modelling of device related infections and lead displacement

ABHI state that the proportions of displacement are much higher than expected (43% of CRT-P and CRT-D patients in population 3, compared to 10.3% in TA120) according to the detailed results sheet. In addition, ABHI criticise the assumption used in the model whereby the complication event probability is constant each month. They consider this unrealistic as patients are at an event risk of such a displacement for a short period of time after implant, after which, the risk is much lower.

SHTAC used the same approach as in TA120 but whilst estimates in TA120 were based upon expert opinion, those used in the SHTAC model were based upon trial estimates. SHTAC acknowledge that the event rates are higher for the numbers of lead displacements than in TA120.

SHTAC acknowledge the limitation of the approach which assumes constant probabilities for events and has conducted a new sensitivity analysis to show the effect of a lower event rate (similar to that used in TA120) on the model results (not previously reported in the AG report).

Scenario analysis using same probability per cycle for lead displacement with CRT (0.0015) as previous model for TA120 are shown in Table 1, and show marginal changes to the results (slight improvement in ICER of about £1000).

Table 1. Lead displacement scenario analysis results for Population 2

Strategy	Cost (£)	Life-years	QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY gained)
vs next best option^a						
OPT	7,605	4.86	3.48	-	-	-
CRT-P + OPT	25,645	5.52	4.18	18,040	0.69	25,994
CRT-D + OPT	37,050	7.23	4.59	11,405	0.41	27,504
vs OPT						
CRT-D + OPT	37,050	7.23	4.59	29,445	1.11	26,559

Discounted costs and benefits; QALY, Quality-adjusted life year. ICER, Incremental cost-effectiveness ratio

^a Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated

We also note that the rates of infection (0.0006) and surgical failure (0.084 and 0.087 for CRT-P and CRT-D, respectively) used in the SHTAC model are lower than in the TA120 AR (0.0022 for infection and 0.0938 for surgical failure, for both devices).

ABHI states surgical failure is assumed to occur every cycle in the AG model and therefore the AG approach exaggerates device failure. We restate that surgical failure is modelled only in patients that undergo surgery (due to initial implantation, device replacement or infection) in the cycle that follows a surgical intervention (assumption listed in AG report p.304) so limiting the effect upon the ICER.

ABHI also criticise the cost for surgical failures. They consider that the vast majority of CRT-D system failures relate to pacing or sensing problems requiring the reposition or replacement of a lead, not a new defibrillation device (total cost of ICD implant is £15,248).

Following clinical experts advice (as reported on AG report pages 301 and 302), the model assumes that patients experiencing CRT-P surgical failure (i.e. unsuccessful CRT-P implantation) or ICD surgical failure are assumed to return to being managed with OPT alone. Those with unsuccessful CRT-P who

go back to OPT management and experience severe arrhythmia are assumed to have an ICD implant and patients who survive an unsuccessful CRT-D implantation are assumed to undergo ICD implantation. We acknowledge that an overestimation of the cost associated to CRT-D surgical failure in population 3 model due to the ICD implantation cost is possible and have therefore conducted a new scenario where this cost is null (not previously reported in the AG report, see results in Table 2 below). Results for this scenario show that the costs associated with this assumption are relatively small and that it has a minimal impact on the relative cost-effectiveness of the different strategies.

Table 2. Scenario without CRT-D failure-related costs results for Population 3

Strategy	Cost (£)	Life-years	QALYs	Incremental			ICER (£/QALY gained)
				Cost (£)	Life-years	QALYs	
Base case^a							
<i>vs next best option^b</i>							
ICD + OPT	39,719	7.45	5.57	-	-	-	-
OPT	40,006	7.59	5.67	287	0.14	0.10	2,824
CRT-P + OPT	51,202	7.96	5.94	11,196	0.37	0.27	Extendedly dominated
CRT-D + OPT	50,911	8.01	5.98	10,906	0.42	0.31	35,193
No CRT-D surgical failure-related costs							
<i>vs next best option^b</i>							
ICD + OPT	39,620	7.45	5.57	-	-	-	-
OPT	38,034	7.59	5.67	-1,586	0.14	0.10	Dominant
CRT-P + OPT	49,134	7.96	5.94	11,099	0.37	0.27	Extendedly dominated
CRT-D + OPT	48,372	8.01	5.98	10,338	0.42	0.31	33,361

^a replicated from report Table 141, ^b Treatments compared with the preceding best option, i.e. the preceding treatment, which is neither dominated or extendedly dominated; Discounted costs and benefits; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Device longevity data

- i) ABHI criticised the SHTAC analysis for using a fixed period of time for device longevity. They claim the rate of failure is not consistent.

SHTAC adopted a pragmatic approach to deal with device longevity, consistent with the approach taken in the TA120 analysis. We have tested the effect of different device lifetimes in sensitivity analyses.

- ii) ABHI criticised the use of mean device survival time from the previous CRT appraisal.

For the base case analysis, SHTAC used mean device longevity estimates derived from data reported in the ABHI submission. However, SHTAC's clinical advice questioned the device longevity estimates, presented in the ABHI submission. Therefore we considered it appropriate to show the effect of the estimates used in the previous appraisal in sensitivity analyses (Table 131, Table 144).

Specific responses to Heart Rhythm UK

Heart device longevity

Heart Rhythm UK commented that they were surprised that SHTAC had disregarded the UK device longevity estimates from the ABHI submission.

In fact we have used UK device longevity estimates from the ABHI (Table 107), and tested these in sensitivity analyses (Table 131).

page 15, paragraph 2

Heart Rhythm UK quote from the Executive Summary “One trial reporting hospitalisations found higher rates per 1000 months follow-up among people with ICDs (11.3 vs 9.4, $p=0.09$), with higher heart failure hospitalisations (19.9% vs 14.9%)” and suggests it refers to the DAVID trial.

However, this sentence is in the section ‘People with a remote MI’ in the Executive Summary and refers to the MADIT II trial.

page 14, paragraph 4

Heart Rhythm UK refer to the CABG Patch trial and state that it is not relevant to current ICD treatment in the UK and that its results should not be used to infer the clinical effectiveness or risk associated with current practice.

This comment refers to the Executive Summary. The CABG Patch trial met the inclusion criteria for the systematic review. Details of the trial are described in section 4.2.1.1 ‘characteristics of included studies’.

page 62, paragraph 3

Heart Rhythm UK suggest checking baseline characteristics relating to NYHA class.

On checking an error was discovered in Table 11 and related text for the CIDS trial, which should read that around 50% had no congestive heart failure, 40% had NYHA class I or II and 11% had NYHA class III or IV . This does not affect the analysis or results.

ABHI clarification of points arising from the SHTAC review of the ABHI model: SHTAC's response

IPD and NMA

In reviewing the comments that SHTAC made concerning the IPD and NMA presented in the ABHI's submission, it does not appear that SHTAC has been unfairly critical. First, section 4.1 of the MS (page 100), which outlines the basis for the IPD analysis of the three outcomes of all-cause mortality, all-cause hospitalisation and health related quality of life conducted in section 4, states that this is the first network meta-analysis of individual patient data in the field of CRT/ICD devices and does not specify that it only relates to all-cause mortality. Having mapped the network of evidence for the different outcomes, it is evident that those for all-cause hospitalisations and health related quality of life do not provide sufficient evidence for all the comparisons presented in figure 12 that are encompassed in the network meta-analysis for all-cause mortality. Although the evidence base and the comparisons possible are more limited for all-cause hospitalisations and health related quality of life, the basic methodology used in the analyses is similar (i.e. meta-regression). This is identified in the ABHI's submission on page 141. Importantly, it does not affect the outcomes of the analyses presented or the interpretation of the results. Second, SHTAC has not 'used concerns about one aspect (the HRQoL analysis) to cast doubt on all aspects – in particular the estimates of treatment effect modifiers'. SHTAC has looked at the analysis of each outcome separately, critically appraising the methodology used and trying to provide appropriate context for assessing the results presented. In specific instances SHTAC has provided an indication of where uncertainties are in the analysis due to a lack of presentation of information about the analyses undertaken in the ABHI submission (e.g. limited information on fitting of parametric distributions used for survival analysis) and in others SHTAC has highlighted limitations presented by the ABHI itself concerning interpretation of the findings (particularly those concerning the treatment effect modifiers). Importantly, it should be noted that SHTAC states that it considers that 'the steps taken seem appropriate and the results presented appear reasonable given the note of caution provided in the MS throughout all three analyses' (see page 249 Assessment Report). However, use of the results should recognise the uncertainties in the analyses and the potential difficulties in relating its findings to the original scope.

SHTAC would agree that the IPD NMA presented in the ABHI submission, like the meta-analyses in SHTAC's assessment report, provides evidence that the different devices appear clinically effective. However, given the different approaches taken, it is less clear which should form the basis for developing subsequent guidance.

ABHI corrected treatment effect presentation

The re-analysis of the predicted treatment effects for the different sub-groups, having corrected the error in the previous ABHI submission concerning the failure to take proper account of the covariance between the model parameters (identified by ABHI post-submission), resulted in a narrowing of the confidence intervals around the hazard ratios for the comparisons with OPT (see Table 3). As SHTAC does not have access to the IPD analyses, the error can't be verified. Although this increased the number of comparisons where there was a statistically significant benefit, the groups identified differed little from those that were shown to benefit significantly or that were on the margins of statistical significance in the previous SHTAC assessment. In the re-analysis ICDs were shown to provide a statistically significant benefit for all males irrespective of age, QRS or LBBB status and for women aged <60 years with a QRS ≥ 120 to <150 and no LBBB. CRT-D benefitted a wider group of patients. Benefits that were statistically significant or on the margins of statistical significance were reported for males and females of all ages with a QRS ≥ 120 with or without LBBB. In contrast, CRT-P only had a statistically significant effect for males and females aged ≥ 60 years with a QRS of ≥ 150 ms with LBBB.

Table 3 Updated hazard ratios (95% confidence intervals) for all-cause mortality from NMA with covariables for the comparisons between the different devices and OPT following revised analysis by ABHI

Non-LBBB					
QRS	Device	Sex and Age Groups			
		Male <60yrs	Male ≥60yrs	Female <60yrs	Female ≥60yrs
<120	ICD	██████████	██████████	██████████	██████████
≥120 to <150	ICD	██████████	██████████	██████████	██████████
	CRT-D	██████████	██████████	██████████	██████████
	CRT-P	██████████	██████████	██████████	██████████
≥150	ICD	██████████	██████████	██████████	██████████
	CRT-D	██████████	██████████	██████████	██████████
	CRT-P	██████████	██████████	██████████	██████████
<u>LBBB</u>					
QRS	Device	<u>Sex and Age Groups</u>			
		Male <60yrs	Male ≥60yrs	Female <60yrs	Female ≥60yrs
≥120 to <150	ICD	██████████	██████████	██████████	██████████
	CRT-D	██████████	██████████	██████████	██████████
	CRT-P	██████████	██████████	██████████	██████████
≥150	ICD	██████████	██████████	██████████	██████████
	CRT-D	██████████	██████████	██████████	██████████
	CRT-P	██████████	██████████	██████████	██████████

Association of British Healthcare Industries

**NATIONAL INSTITUTE FOR HEALTH AND
CLINICAL EXCELLENCE**

Multiple Technology Appraisal

**Implantable cardioverter defibrillators for the
treatment of arrhythmias and cardiac
resynchronisation therapy for the treatment of
heart failure (review of TA95 and TA120)**

Main submission document

6th July 2012

Executive summary

This is a unique, joint submission from all five major device manufacturers (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical) to the NICE clinical and economic appraisal of the use of implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT) for the treatment of cardiac arrhythmias and heart failure (HF) (review of TA95 and TA120). **This submission includes a network meta-analysis of individual patient data (IPD) from over 12,000 patients and 13 randomised clinical trials (RCT), representing the first analysis of its kind and magnitude.**

TA95 found ICD therapy to be both clinically effective and to provide good value for money in secondary prevention of sudden cardiac death. Given the lack of new studies published for this indication and the real term price reduction of an ICD device we have not re-considered this indication in the submission. Hence, we have focused solely on the use of ICD in a primary prevention setting in patients with HF. We have also excluded, for reasons of data paucity, primary prevention ICD use in patients with familial cardiac conditions (long QT syndrome, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome etc.).

HF encompasses a very heterogeneous patient population, requiring extensive exploration of different subgroups. Although we have endeavored to be concise, the submission is of necessity an extensive document. Additional material is contained in the appendices which are intended to be used in conjunction with the main submission document.

Overall findings suggest benefit for device treated HF patients (and subgroups) in all-cause mortality, Health Related Quality of Life (Utility), and cost effectiveness as compared to optimal medical treatment.

We believe this analysis reconfirms the clinical and economic value of ICD, CRT-P, CRT-D in NYHA Class I-IV HF patients.

Background

Heart failure is a major cause of mortality and morbidity, and is responsible for approximately 1 million inpatient bed days annually (2% of all NHS inpatient days), and 5% of medical emergency hospital admissions. Heart failure-related death occurs via two principal mechanisms: sudden cardiac death (usually caused by fatal arrhythmia, and most common in NYHA classes I to III) or progressive HF (most common in NYHA class IV).

Prognosis is poor despite optimal medical therapy. Patients suffer increasing breathlessness and fatigue on exercise and eventually at rest, with consequent impairment of functional ability, health related quality of life, and need for hospitalisation. The goals of treatment are to relieve symptoms and signs, prevent hospital admission, and improve survival. Effective therapies also improve functional capacity and quality of life.

Implantable devices have an established role in the treatment of these patients in addition to optimal medical therapy, with a large body of high quality evidence supporting their safety and efficacy.

- Implantable cardioverter defibrillators (ICD) continuously monitor the heart for arrhythmia and maintain normal heart rate using small, painless electrical signals. They deliver high energy shock therapy (defibrillation) in the event of a potentially life-threatening arrhythmia.
- Cardiac resynchronisation therapy (CRT) uses electrical stimulation to resynchronise the contraction of the ventricles, thereby improving pumping efficiency. Devices that deliver CRT alone are known as CRT-P. While they improve HF symptoms, they do not offer direct protection against sudden cardiac death.
- CRT-D devices combine CRT with a defibrillation function, offering protection from sudden cardiac death in addition to the benefits of CRT.

New evidence has become available since current NICE guidance was published in 2006 (ICDs) and 2007 (CRT), and UK clinical practice has evolved. In addition, device costs have fallen in real terms and battery life has increased. It is therefore to be expected that both clinical recommendations and cost-effectiveness calculations will need to be re-examined at this appraisal.

Device implantation rates vary considerably between cardiac networks within England and Wales: the adjusted annual number of new ICD implants per million population varied from 34 to 131, and annual implantation rates per million for new and replacement CRT devices ranged from 68 to 182/million. The Network Device Survey Group has suggested a minimum annual target of 100 new implants/million population for ICD and 130 total (new + replacement)/million for CRT (CRT-P and CRT-D combined). Current overall rates in England are approximately 72/million and 114/million, respectively, suggesting continuing under-provision and poorer quality care for UK patients compared to other European countries.

Systematic review and network-meta-analysis of individual patient data

A comprehensive systematic review of RCT evidence for clinical effectiveness of OPT (optimal pharmacological therapy), ICD, CRT-P and CRT-D was carried out in accordance with NICE guidelines. 46 articles reporting the results of 22 trials met the criteria for inclusion in the qualitative summary. The review confirms that there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF. This is backed up by several previously published meta-analyses. Additional evidence from long-term follow-up of two studies shows a persistent mortality benefit from both ICD and CRT. No new evidence was identified relating to the use of ICD in a secondary prevention setting.

Individual patient data from over 12,000 patients in 13 clinical trials identified from the systematic review were made available by three Medical Device manufacturers to inform construction of an economic model for this appraisal. This unique collaborative effort resulted in a data set that covered 95% of the patients included in studies identified in the systematic review and followed patients for up to 7.5 years. The power of the IPD approach means the results contained in this document are the best and most robust information available on the impact of CRT and ICD in terms of mortality, health related quality of life and hospitalisations. In particular, the use of IPD has allowed unprecedented exploration of device effects in the widely heterogeneous patient subgroups within HF.

Summary of findings on clinical efficacy

i) Mortality

A baseline risk analysis was conducted in order to predict mortality risk over time for patients receiving OPT (3,477 patients, followed up for up to up to 6.1 years). This analysis found NYHA functional class, ischaemia, QRS duration and LVEF all to be highly significant predictors of survival, along with patient age and gender.

The risk equation developed was able to differentiate between the highly heterogeneous prognoses of patients included in the trials. For patients predicted to be in the upper 20% with respect to survival time, four year survival was [REDACTED]. For patients predicted to be in the lowest 20%, four year survival was [REDACTED].

Inclusion of age as a time-dependent covariable in the analysis appeared to produce realistic predictions of survival both within the database follow-up period and when extrapolated over patient lifetime.

A network meta-analysis was conducted including data from all studies identified by the systematic review (12,000+ patients followed up for up to 7.5 years). The analysis found CRT-D to have the strongest effect on all-cause mortality, with a hazard ratio of [REDACTED] for CRT-D vs. OPT. Treatment effects for the other individual devices were [REDACTED] for CRT-P vs. OPT and [REDACTED] for ICD vs. OPT (fixed effects analysis of all trials). These results are similar to those published previously, and support the strong effect of all devices on the all-cause mortality end point.

Given the high level of heterogeneity in the patient groups under consideration, a series of analyses were conducted exploring the impact of patient characteristics on the magnitude of benefit associated with the devices. These analyses identified patients' age, gender and QRS morphology (both QRS duration and the presence of left bundle branch block (LBBB)) to be independently predictive of the magnitude of benefit associated with the devices. Younger patients and male patients appear to benefit more from ICD; but less than other groups from CRT. This is likely to be due to the relatively higher rate of sudden cardiac death relative to other causes in younger and male patients. Patients with a QRS duration of ≥ 120 ms to < 150 ms benefit more from ICD therapy than those with

shorter or longer QRS durations. Both CRT-P and CRT-D have a stronger impact on mortality in patients with $QRS \geq 150\text{ms}$ and/or LBBB.

ii) Health Related Quality of Life

NYHA class, age, ischemic etiology status, gender and age were all significant ($P < 0.05$) predictors of baseline utility. CRT has a strong impact on health related quality of life (HRQoL): it was associated with changes in utility of █████ in NYHA I/II patients █████ in NYHA III/IV patients. There was also a small positive impact for ICD in patients with NYHA I/II █████, evidence of a quality of life benefit for ICD in NYHA III/IV is equivocal. Exploratory analysis of Minnesota Living with Heart Failure data showed that HRQoL benefits lasted for at least █████ years in all NYHA classes (contingent on being alive). A recently published paper arising from the CARE-HF study demonstrated significant CRT-P related HRQoL: benefits that were still apparent at study end (median follow up 2.5 years). In a more conservative approach than previous appraisals, we assumed that HRQoL benefits are maintained for five years and then taper off over time.

iii) All cause hospitalisation

A 'number of events per month' based approach was used. Amongst patients receiving OPT, NYHA class, ischemic aetiology status, QRS duration and age were all independent predictors of hospitalisations. Device therapy is associated with significant reductions in all cause monthly hospital admission rates across all NYHA classes. In NYHA class I to class III, ICD therapy reduced monthly admission rates by █████ and CRT by █████ The effect in NYHA class IV patients is even more pronounced, with CRT offering a █████ reduction in monthly admission rates.

Summary of findings from economic modelling

We used conservative assumptions throughout the economic modelling. In particular, in contrast to the models used in TA95 and TA120, we assumed that any treatment effects on mortality or HRQoL are not constant but diminish over time, with the 'tailing off' beginning after five years in our model. ICD and CRT device longevity is based on time to replacement data from approximately 40,000 UK implants provided by the Central Cardiac Audit Database (run by the NHS information Centre). Data were made available for approximately ten years of follow up. This is unique data on UK-only implants.

Implant costs were based on a combination of UK NHS specific average selling prices (aggregated across all manufacturers and device subtypes) and NHS tariff values. The aggregate data were supplied via the Association of British Healthcare Industries. The values used in the model for ICD, CRT-P and CRT-D implants (including hospital admission costs) are £15,248, £8,281 and £17,849 respectively.

Results of the base case deterministic cost-effectiveness analysis are presented fully incrementally for 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology. Data from 4,992 distinct patient profiles were aggregated to generate weighted lifetime costs and QALYs in these groups, with patient counts used to undertake all weightings. Thus, patient level heterogeneity has been fully incorporated into the economic evaluation. Ischemia did not significantly affect cost-effectiveness; the results presented below are therefore applicable to both ischemic and non-ischemic patients.

Base case results (all relate to patients with LVEF \leq 35%)

NYHA I/II

For patients with a QRS < 120ms, the ICERs are below £25,200 per QALY gained and cost-effective; ICD is likely to be an acceptable use of resources. For patients with a QRS duration between 120 and 149ms and no LBBB, ICD is cost-effective with ICERs all approximately £17,000 per QALY gained. In patients with LBBB all ICERs for CRT-D are below £24,500 per QALY gained, meaning CRT-D is likely to be cost-effective. For patients with QRS \geq 150ms, with or without LBBB: CRT-D is, overall, a cost-effective treatment (all ICERs less than £27,200 per QALY gained).

NYHA III

For patients with a QRS<120ms, the only intervention of interest is ICD and all ICERs are below £29,500 per QALY gained and cost-effective. For patients with QRS 120-149ms: CRT-P is cost-effective (all ICERs less than £19,700 in absence of LBBB and £15,500 in presence of LBBB). CRT-D generates ICERs between £23,000 and £27,400 per QALY gained relative to CRT-P, and provides significantly greater mortality reductions, so is cost-effective and an acceptable use of resources. For patients with QRS \geq 150ms: CRT-P is cost-effective (all ICERS below £14,400). Compared to CRT-P, CRT-D generates ICERs close to

£25,000 per QALY gained in absence of LBBB and close to £29,000 per QALY gained in the presence of LBBB, and is an acceptable use of resources.

With the exception of one small patient group, ICD is either dominated or extended dominated regardless of QRS duration.

Due to the high risk of sudden cardiac death in patients who are in NYHA class III, and hence the perceived clinical need for defibrillation based therapy, we ran a comparison of defibrillation based therapies to no device therapy (i.e. CRT-D/ICD to OPT). In all but one instance, ICD therapy was dominated/ extended dominated and the highest ICER generated for CRT-D vs. OPT was approximately £22,400 per QALY gained. Where ICD was not dominated, the ICER for ICD vs. OPT was approximately £19,700 per QALY gained and for CRT-D vs. ICD £27,400 per QALY gained. Hence, defibrillation based therapy is cost-effective in NYHA class III.

NYHA IV

For patients with a QRS < 120ms no comparative analysis was possible in this patient group. For all other patients, compared to OPT, CRT-P represents value for money in NYHA IV patients: all ICERs are close to or below £25,000 per QALY gained and cost-effective, with ICERs decreasing as QRS duration increases. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

Sensitivity analyses

When we assumed constant treatment effects for mortality and HRQoL, across all QRS and LBBB categories, in patients who are NYHA I-III the highest ICER generated is approximately £24,600 per QALY gained for the comparison of ICD to OPT in patients with ischemic, non-LBBB NYHA III heart failure. All other ICERs on the frontier, for all relevant comparisons are lower with the most cost-effective ICER being below £20,000 per QALY gained in ten of the seventeen distinct groups for which results were generated. The general picture in patients who are NYHA IV remains unchanged.

When we viewed NYHA as a mortality treatment effect modifier across all QRS and LBBB categories, the highest ICER generated in patients who are NYHA III is approximately £26,700 per QALY gained for the comparison of ICD to OPT in patients with ischemic, non-LBBB NYHA III heart failure. All other ICERs on the

frontier, for all relevant comparisons are lower, with nine of the seventeen most cost-effective ICERs being below £20,000 per QALY gained

Additional sensitivity analyses surrounding device longevity, procedure costs, and short term adverse event rates were performed to explore alternative modelling assumptions and potential changes in the NHS. Most generated ICERs lower than, or similar to, the base case values, confirming that the base case results are conservative.

Comparison of results to those deemed acceptable in previous appraisals

We found that for CRT, ICERs were nearly always lower than in the previous appraisal (except in NYHA IV). In particular, the ICERs for CRT-D vs. CRT-P in NYHA class III are 30% to 50% lower than the accepted 2007 value. For ICD, given that EP testing was not included as a covariate, it was not possible to generate ICERs assuming no EP testing in patients where ICD is recommended (NYHA class I/II, LVEF \leq 35% and QRS <150ms). In the nearest equivalent patient groups, the values generated in the current model are similar to those generated previously when EP testing was stipulated.

In general, ICER improvements are likely to be due to lower real-terms total implant costs, increased device longevity, better estimates of the impact of treatment on mortality and HRQoL, and the explicit exploration of patient level heterogeneity.

Implications for clinical practice

We are advised that, while NYHA Class, LVEF and QRS duration remain integral to clinical decision making, other tests, in particular electrophysiology (EP) tests as specified in the guidance arising from TA95, no longer reflect best clinical practice. Other tests included in the TA95 and TA120 guidance (non-sustained VT on Holter monitoring and a requirement for mechanical dyssynchrony) do not have a firm basis in the RCT evidence, and are not required to demonstrate cost-effectiveness. These supplementary tests do not appear in recent European guidelines. Recent clinical guidelines have highlighted the importance of LBBB as a decision criterion.

The aim of this analysis was to generate simple decision rules to allow cardiologists to provide any given patient with the most beneficial intervention that falls within cost-effectiveness boundaries. On the basis of our findings, these can

be summarised as follows:

For patients with LVEF $\leq 35\%$ but without LBBB:

- NYHA class I/II:
 - QRS duration $< 150\text{ms}$: ICD should be used.
 - QRS duration $\geq 150\text{ms}$, the patient should be given CRT-D.
- NYHA class III:
 - QRS duration $< 120\text{ms}$ ICD should be offered.
 - QRS duration $\geq 120\text{ms}$, doctors should use either CRT-D or CRT-P, with CRT-D the preferred device because of the high incidence of SCD in this population (and hence clinical need for defibrillation therapy).
- NYHA class IV:
 - QRS durations $\geq 120\text{ms}$ CRT-P is the treatment of choice

For patients with LVEF $\leq 35\%$ and LBBB:

- NYHA class I, II or III: CRT-D is the treatment choice.
- NYHA class IV: CRT-P is the preferred treatment.

Guidance based on our findings would result in an increase in device implantation rates. **However, growth in implant rates should be viewed in the context that current rates are still below the minimum levels suggested under current guidance.** In addition, there remains unacceptable geographical variation in device implantation rates between different cardiac networks in England and Wales, suggesting many eligible HF patients are not being offered device therapy.

Most importantly, the devices under consideration prolong life and bring symptomatic and quality of life benefits to patients in the proposed widened indications, as well as reducing the burden on NHS services through reduced hospitalisation rates. We show that the cost of giving patients access to these benefits would not exceed willingness to pay thresholds given the substantive health outcome benefits observed.

Contents

Executive summary	2
Contents	11
Table of tables	14
Table of figures	19
Table of abbreviations	22
1 Background	25
1.1 Heart failure: disease overview.....	27
1.2 Epidemiology	31
1.3 Burden of illness	32
1.4 Description and current application of relevant technologies	33
1.5 Current UK guidance on implantable cardiac devices in heart failure	36
1.6 Current Service Provision	40
1.7 Price of technologies under appraisal	42
1.8 Equity and equality	43
2 Statement of the decision problem.....	44
2.1 Overview.....	44
2.2 End points of interest in assessing clinical efficacy	47
2.3 Presentation of cost-effectiveness results.....	48
3 Clinical effectiveness: systematic review of the literature.....	50
3.1 Identification and assessment of studies	51
3.2 Studies identified by the review	54
3.3 Baseline patient characteristics	55
3.4 Results from mortality end points.....	73
3.5 Heart failure related hospitalisations	81
3.6 Other clinical end points	83

3.7	Health related quality of life	90
3.8	Device- and procedure-related adverse events	94
3.9	Long-term follow-up data on mortality.....	96
4	Analysis of individual patient level data.....	98
4.1	Introduction.....	100
4.2	Mortality.....	101
4.3	Overview of methods.....	102
4.4	Description of analyses.....	112
4.5	Results	117
4.6	Discussion of results.....	135
4.7	All cause hospitalisation	138
4.8	Health related quality of life	147
5	Assessment of cost-effectiveness.....	162
5.1	Description of modelling approach.....	162
5.2	Mortality.....	163
5.3	Event probabilities	163
5.4	Resource use	168
5.5	Costs	169
5.6	Health related quality of life	175
5.7	Other parameters	176
6	Results from the cost-effectiveness analysis.....	177
6.1	Base case deterministic analysis	180
6.2	Deterministic sensitivity analyses	194
6.3	Results presented by LVEF category	203
6.4	Probabilistic sensitivity analysis	203
6.5	Discussion of cost-effectiveness results	204
7	Financial implications to the NHS and other parties	212

7.1	Introduction.....	213
7.2	Implant rates arising from previous appraisals.....	214
7.3	Input values for current budget impact assessment.....	214
7.4	Results	220
7.5	Implications to other interested stakeholders	222

Table of tables

Table 1: The NYHA HF classification	28
Table 2 The ACC/AHA classification	29
Table 3: Major actions by device type.	36
Table 4: European and US guidelines on CRT-P and CRT-D in heart failure.....	39
Table 5 European and US guidelines on ICD in heart failure	40
Table 6: Rationale for excluding interventions from some subgroups	45
<i>Table 7: Summary of treatments and randomisation in each trial.....</i>	<i>57</i>
Table 8: Summary of patient crossover in all included studies	60
<i>Table 9: Baseline patient characteristics by NYHA class and LVEF.....</i>	<i>64</i>
<i>Table 10: Baseline patient characteristics: demography and QRS Morphology .</i>	<i>67</i>
Table 11: Characteristics by cardiac history (n (%))	70
<i>Table 12: Effect of interventions on all-cause mortality*</i>	<i>75</i>
<i>Table 13: Effect of interventions on sudden cardiac death*.....</i>	<i>78</i>
<i>Table 14: Effect of intervention on death due to heart failure*.....</i>	<i>80</i>
<i>Table 15: Effect of intervention on incidence of hospitalisation*.....</i>	<i>82</i>
Table 16: NYHA class, mean (SD) value at 90 days	84
Table 17: NYHA at baseline and six months (mean, SD)	84
Table 18: Change in NYHA class, number of pts (%) at 6 months (CRT-P and OMT only)	84
Table 19: Change in NYHA class , number of pts. (%) (CRT-D and ICD only) ...	84
Table 20: Change in NYHA class, number of pts. (CRT-D and ICD only)	84
Table 21: Improvement at 6 months in NYHA class symptoms (%)	84
Table 22: Change in NYHA class - baseline and 6 months (median, 95% CI) ...	85
Table 23: Change in NYHA class - baseline and 6 months (mean, SD).....	85

Table 24: Percentage of patients that worsened/improved NYHA at 12 months	85
Table 25: NYHA class distribution after one year of treatment (number of pts) ..	85
Table 26: <i>Effect of intervention on change in LVEF</i>	87
Table 27: <i>Effect of intervention on incidence of VT/VF (n/N)</i>	89
Table 28: <i>Health related quality of life: EQ-5D instrument (mean (95% CI))</i>	90
Table 29: <i>Absolute MLWHF scores by study</i>	92
Table 30: <i>Effect of intervention on change in MLWHF scores*</i>	92
Table 31: <i>Effect of intervention: change in MLWHF dimension scores (mean (SD))</i>	93
Table 32: <i>Trials included in network meta-analysis - IPD availability</i>	105
Table 33: <i>Cross-over during follow-up provided for IPD Trials</i>	106
Table 34: <i>Follow-up period used in analysis of IPD Trials dataset</i>	107
Table 35: <i>Covariable data for IPD Trials dataset</i>	110
Table 36: <i>UK Summary data (reproduced from Cunningham et al., 2010)</i>	111
Table 37: <i>Preferred baseline risk model</i>	121
Table 38: <i>Results of univariate analysis and multivariate automated stepwise analyses used to inform interaction effect selection</i>	129
Table 39: <i>Preferred model for IPD network meta-analysis</i>	132
Table 40: <i>NBRM results used to predict all cause hospitalisation in OPT arm (baseline risk)</i>	139
Table 41: <i>Monthly probability of hospitalisation by covariate pattern (OPT)</i>	140
Table 42: <i>Negative binomial model used to predict the impact of treatment on all cause hospitalisations per month</i>	142
Table 43: <i>Derived all cause hospitalisation treatment effects</i>	142
Table 44: <i>All cause hospitalisation treatment effects used in the model (events per month)</i>	143
Table 45: <i>Monthly all cause hospitalisation transition probabilities (ICD, events per month)</i>	144

<i>Table 46: Monthly all cause hospitalisation transition probabilities (CRT-P, events per month).....</i>	144
<i>Table 47: Monthly all cause hospitalisation transition probabilities (CRT-D, events per month).....</i>	145
<i>Table 48: Overview HRQoL modelling approaches used in previous economic models</i>	148
<i>Table 49: Age and gender specific UK EQ-5D population norms (mean, SD.) reproduced from Kind et al. ¹³⁴</i>	150
<i>Table 50: Regression coefficients used to model age specific population utility</i>	150
<i>Table 51: Distribution of baseline EQ-5D observation counts by NYHA class..</i>	151
<i>Table 52: NBRM Coefficients used to predict baseline utility decrement.....</i>	152
<i>Table 53: Comparison of indicative individuals with population equivalents (non-ischaemic aetiology).....</i>	153
<i>Table 54: Comparison of indicative individuals with population equivalents (ischaemic aetiology)</i>	153
<i>Table 55: Summary EQ-5D statistics from the three clinical trials in which data was collected</i>	154
<i>Table 56: Mean changes from baseline in EQ-5D at six months by device and NYHA group (mean, s.e.).....</i>	155
<i>Table 57: Mean changes from baseline in MLWHF at six months by device and NYHA group (mean, s.e.).....</i>	156
<i>Table 58: Treatment specific utility increments used in the economic model ...</i>	157
<i>Table 59: CARE-HF based long term EQ-5D gains (mean, 95% CI) reproduced from Cleland et al. ⁵⁶</i>	158
<i>Table 60: Parameters used to derive time to second and subsequent device replacement estimates</i>	167
<i>Table 61: Distribution of reasons for hospitalisations by intervention</i>	168
<i>Table 62: Background medication by NYHA class</i>	169
<i>Table 63: Recommended doses</i>	170
<i>Table 64: Purchase costs.....</i>	171

Table 65: Total cost of treatment per 1 month model cycle	172
Table 66: Hospitalisation event costs	173
Table 67: ICD and CRT system costs	174
Table 68: Device costs used in the model.....	175
Table 69: Remaining model parameters	176
Table 70: Deterministic base case results (patients without LBBB).....	181
Table 71: Deterministic base case results (patients with LBBB).....	182
Table 72: Deterministic base case results (NYHA III, CRT-D vs. OPT).....	182
Table 73: Deterministic base case results (NYHA III, CRT-D vs. ICD vs. OPT)	184
Table 74: Deterministic sensitivity analysis – constant mortality treatment effect (no LBBB)	195
Table 75: Deterministic sensitivity analysis – constant mortality treatment effect (with LBBB)	195
Table 76: Deterministic sensitivity analysis – constant HRQoL treatment effect (no LBBB)	197
Table 77: Deterministic sensitivity analysis – constant HRQoL treatment effect (with LBBB)	197
Table 78: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (no LBBB).....	198
Table 79: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (with LBBB)	199
Table 80: Deterministic sensitivity analysis –alternative all-cause mortality treatment effects (no LBBB)	200
Table 81: Deterministic sensitivity analysis – alternative all-cause mortality treatment effects (with LBBB).....	201
Table 82: Deterministic sensitivity analysis – 10% increase in device longevity (no LBBB).....	202
Table 83: Deterministic sensitivity analysis – 10% increase in device longevity (with LBBB)	202

Table 84: Summary of most cost-effective ICERs across all analyses (ischaemic individuals without LBBB).....	206
Table 85: Summary of most cost-effective ICERs across all analyses (ischaemic individuals with LBBB).....	207
Table 86: Summary of cost-effectiveness recommendations arising from our analysis*.....	208
Table 87: England and Wales population estimates (in millions) 2012-2016....	215
Table 88: Projected ICD implant rates (per million) and procedure counts.....	216
Table 89: New implant counts (CRT-P and CRT-P) reproduced from the HES database	217
Table 90: Projected CRT implant rates (per million) and procedure counts.....	217
Table 91: Implant rates (per million) used in all alternative scenarios	218
Table 92: Annual cost of treatment estimates used in the financial impact assessment.....	219
Table 93: Survival estimates used in the financial impact assessment	220
Table 94: Budget impact analysis: Scenario one.....	220
Table 95: Budget impact analysis: Scenario two	220
Table 96: Budget impact analysis: Scenario three	221
Table 97: Budget impact analysis: Scenario four	221

Table of figures

Figure 1 Changing proportions of deaths from progressive HF and SCD by NYHA Class. SCD is the commonest cause of death in both NYHA II and NYHA III, while progressive HF is most important in NYHA IV. Data from MERIT-HF	31
Figure 2 Location of ICD and leads	34
Figure 3: Function and lead positioning of a dual chamber ICD	34
Figure 4: Lead positioning in a CRT device	35
Figure 5: New ICD implant rate by cardiac network, compared with the national target. Source: Cunningham et al. 2010. ²¹	41
Figure 6: New CRT (CRT-P and CRT-D combined) implant rate by cardiac network, compared with the national target. Source: Cunningham et al. 2010. ²¹	41
Figure 7: Observed ASPs for CRT-P and expected inflation-adjusted price (data on file, ABHI)	42
Figure 8: Observed ASPs for CRT-D and expected inflation-adjusted price (data on file, ABHI)	43
Figure 9: Observed ASPs for ICD and expected inflation-adjusted price (data on file, ABHI)	43
Figure 10: Example cost-effectiveness plane	48
Figure 11: Illustration of dominance and extended dominance	49
<i>Figure 12: Network of randomised controlled trials</i>	<i>103</i>
<i>Figure 13: Comparison of Kaplan Meier and parametric curves for patients in different risk quintiles (risk quintiles defined by the parametric model)</i>	<i>119</i>
<i>Figure 14: Predictions over 50 year time horizon (by risk quintiles)</i>	<i>120</i>
<i>Figure 15: Example predictions, with and without age as time-dependent covariable: low risk patient (male, age 51 in NYHA class I/II, non-Ischaemic aetiology, QRS duration <120ms and LVEF between 25% and 30%)</i>	<i>122</i>
<i>Figure 16: Example predictions, with and without age as time-dependent</i>	

<i>covariable: high risk patient (male, age 71 in NYHA class III, ischaemic aetiology, QRS duration >120ms and LVEF ≤20%)</i>	122
Figure 17: Comparison of network meta-analysis results using IPD Trials and All Trials, and fixed and random effects models	124
Figure 18: Comparison of Fixed Effects IPD Trials analysis to individual trial results	125
Figure 19: Forest plot of results of analysis adjusting for covariables (LBBB) ..	133
<i>Figure 20: Comparison of observed vs. fitted baseline hospitalisation rates (events per month)</i>	140
<i>Figure 21: Histogram of baseline EQ-5D data across all three clinical trials</i>	151
<i>Figure 22: Histogram of baseline EQ-5D data across all three clinical trials expressed as proportional change from unity</i>	151
<i>Figure 23: difference in difference (device-OPT) long term change in MLWHF (NYHA I/II)</i>	159
<i>Figure 24: difference in difference (device-OPT) long term change in MLWHF (NYHA III)</i>	159
Figure 25: UK device longevity data (Jan 2000 to April 2011, time unit: days) .	164
Figure 26: Parametric function fitted to UK CRT-P implant data.....	165
Figure 27: Parametric function fitted to UK ICD implant data	165
Figure 28: Parametric function fitted to UK CRT-D implant data	166
Figure 29: Extrapolation of parametric functions: CRT-D data only	166
Figure 30: CE frontier (NYHA II, ischaemic aetiology, no LBBB).....	186
Figure 31: CE frontier (NYHA II, ischaemic aetiology, LBBB).....	187
Figure 32: CE frontier (NYHA II, ischaemic aetiology, LBBB).....	188
Figure 33: CE frontier (NYHA III, ischaemic aetiology, non-LBBB).....	189
Figure 34: Cost-effectiveness frontier (NYHA III, ischaemic aetiology, with LBBB)	189
Figure 35: CE frontier (NYHA IV, ischaemic aetiology, LBBB, QRS>150ms) ...	192
Figure 36: England and Wales annual ICD implant rates (Data taken from	

Cunningham et al.).....	215
Figure 37: England and Wales annual CRT implant rates (Data taken from Cunningham et al.).....	216

Table of abbreviations

Abbreviation	Full description
2LL	Two times log-likelihood score
ABHI	Association of British Healthcare Industries
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AHA	American Heart Association
AIC	Akaike's Information Criterion
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ARVD	Arrhythmogenic Right Ventricular Dysplasia
ASP	Average selling prices
AT/AF	Atrial tachyarrhythmia
BGR	Brooks Gelman-Rubin
BIC	Bayesian Information Criteria
BNF	British National Formulary
BNP	B-type natriuretic peptide
CCAD	Central Cardiac Audit Database
CENTRAL	Cochrane Central Register of Controlled Trials
CMT	Conventional medical therapy
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy defibrillator
CRT-P	Cardiac resynchronisation therapy pacemaker
DIC	Deviance information criteria

ECG	Electrocardiography
EF	Ejection fraction
EP	Electrophysiology
ESC	European Society of Cardiology
HES	Health Episode Statistics
HF	Heart failure
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health related quality of life
HRUK	Heart rhythm UK
ICD	Implantable cardioverter defibrillators
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention-to-treat
LBBB	Left bundle branch block
LOS	Length of stay
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MLWHF	Minnesota Living with Heart Failure Questionnaire
ms	millisecond
NBRM	Negative binomial regression
NYHA	New York Heart Association
OMT	Optimal medical therapy
OPT	Optimal pharmacological therapy

OS	Overall survival
PASA	Purchase and Supplies Agency
PbR	Payment by results
PRM	Poisson regression
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SE	Standard error
SAE	Serious adverse event
SCD	Sudden cardiac death
SD	Standard deviation
SRC	Schedule of Reference Costs
Std. Dev	Standard deviation
VT/VF	Ventricular tachycardia/ ventricular fibrillation
ZINB	Zero Inflated Negative Binomial

1 Background

- Heart Failure (HF) is a clinical syndrome characterised by breathlessness, fatigue and fluid retention. It is classified using New York Heart Association (NYHA) functional class, ranging from Class I (no limitation of physical activity) to Class IV (symptomatic at rest and discomfort from any physical activity).
- Age-adjusted prevalence of diagnosed HF in the UK is approximately 0.9% (men) and 0.7% (women).
- Heart failure is a major cause of mortality and morbidity. It accounts for approximately 1 million inpatient bed days annually (2% of all NHS inpatient days), and 5% of medical emergency hospital admissions.
- Prognosis is poor despite optimal pharmacological therapy. Implantable devices have an established role in these treatment of patients.
- HF-related mortality results from sudden cardiac death due to ventricular arrhythmias (most common in NYHA I to III) or progressive HF (most common in NYHA IV).
- Patients with structural heart disease which does not result in heart failure as well as patients with primary conditions are also at risk of sudden cardiac death.
- The implantable cardioverter defibrillator (ICD) continuously monitors the heart for arrhythmia and maintains normal heart rate using painless electrical stimulation. In the event of a potentially life-threatening arrhythmia it can deliver rapid stimulation or an electrical shock (defibrillation).
- Cardiac resynchronisation therapy (CRT) is a form of pacing that uses electrical stimulation to resynchronise the contraction of the ventricles, thereby improving pumping efficiency.

- Devices that deliver CRT alone are known as CRT-P. Devices which combine CRT with a defibrillation function, offering protection from sudden cardiac death in addition to the benefits of CRT are known as CRT defibrillators (CRT-D)
- New evidence has become available and UK clinical practice has evolved since current UK guidance on ICDs and CRT was published in 2006/2007. In addition, device costs have fallen in real terms. Further, as with many similar technologies there has been a reduction in procedural invasiveness and procedural efficiency. Thus, both clinical recommendations and cost-effectiveness calculations will need to be re-examined in the light of current data.
- While NYHA Class, LVEF and QRS duration remain integral to decision making for ICD and/or CRT therapy, other tests for example electrophysiology (EP) tests included in TA95 guidance have been shown to have limited sensitivity and specificity and no longer reflect best clinical practice.
- Device implantation rates vary considerably between cardiac networks within England and Wales: The adjusted annual number of new ICD implants per million population varied from 34 to 131, and implantation rates for new and replacement CRT devices ranged from 68 to 182/million.
- The Network Device Survey Group and Heart Rhythm UK have suggested a minimum annual target of 100 new ICD implants/million population and 130 total (new + replacement)/million for CRT (CRT-P and CRT-D combined). Current rates in England are approximately 72/million and 114/million, respectively, suggesting continuing under-provision.
- Device prices paid by the NHS have either remained constant or declined over the five years from 2006-2010. In real terms, after adjustment for inflation, average prices have fallen by 17% for CRT-P, 10% for CRT-D and 8% for ICD.

1.1 Heart failure: disease overview

1.1.1 Definition

Heart failure (HF) can be defined as 'A complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood'.^{1:2} Because not all patients have volume overload, the older term 'congestive heart failure' is no longer preferred.

The most common cause of HF is myocardial dysfunction, commonly left ventricular systolic dysfunction, which reduces mechanical efficiency and can also lead to dysynchronised pumping. Myocardial dysfunction is most often caused by damage to heart muscle. In western countries, coronary artery disease is the initiating cause in about 70% of cases of HF. A further 10% of cases arise from valve dysfunction and 20% from non-ischaemic cardiomyopathies, with perhaps half of those being 'idiopathic' [no known cause].³

Whatever the precipitating event, a complex and wide-ranging set of adaptive mechanisms comes in to play to compensate for the underlying dysfunction. Although these initially enable adequate cardiac function to be maintained, over time they contribute to a vicious cycle in which pathological remodelling of the heart leads to further deterioration in cardiac function. As well as affecting mechanical function, these changes can also lead to electrical instability.⁴

HF is a clinical diagnosis based on physical examination and patient history; there is no specific diagnostic test. Additional evaluation may include exercise testing, echocardiography or cardiac catheterisation and blood testing. The most recent NICE guidance recommends that a patient with suspected heart failure (due to symptoms, signs, and history) should have a BNP blood test and be fully assessed by a specialist within two to six weeks.⁵

1.1.2 Symptoms

Symptoms are caused by an inability of the heart's pumping capacity to support metabolic demands. Thus early-stage HF may produce symptoms only under conditions of high demand, principally exercise, whereas severe HF is symptomatic even at rest.

The characteristic symptoms of HF are breathlessness (dyspnoea), fatigue, and

fluid retention (oedema). The relative importance of breathlessness and fluid retention varies between patients. Other symptoms can include orthopnoea (breathlessness when lying down that is relieved by moving to a more upright position); paroxysmal nocturnal dyspnoea (breathless attacks at night); palpitations; nocturia; anorexia, nausea and weight loss; abdominal bloating and discomfort; confusion, light-headedness, and impaired memory.

1.1.3 Classification

The most widely used classification system for HF is the New York Heart Association (NYHA) classification, which is based on functional classes (see Table 1).

Table 1: The NYHA HF classification

NYHA Class	Definition
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnoea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

NYHA class can fluctuate over time. It is also prone to considerable inter-observer variability, and may not reflect important changes in exercise capacity.² Another limitation of the NYHA classification is that the severity of symptoms does not necessarily correlate with the severity of the underlying damage to the heart. Patients with severe damage can have relatively mild symptoms, and vice versa. Nevertheless, NYHA class has been shown in multiple clinical trials and observational studies to be an excellent predictor of morbidity and mortality in heart failure.

To complement the NYHA Classification, a staging system based on structural abnormality was developed by the American College of Cardiology and American Heart Association (the ACC/AHA classification; see Table 2). Stages A and B cover patients at high risk of developing HF, while patients with symptomatic HF are classed as stage C or D.

Table 2 The ACC/AHA classification

ACC/AHA Stage	Definition
A	Risk factors for HF (hypertension, diabetes) but otherwise no structural damage or symptoms.
B	Structural damage present (myocardial infarction, valvular disease, low ejection fraction) but no symptoms present
C	Structural heart disease with HF symptoms
D	Refractory, end-stage disease. Marked symptoms at rest despite maximal medical therapy

In practice, the terms mild, moderate, and severe are often used to describe NYHA Classes II, III, and IV, respectively.

1.1.4 Management

The goals of treatment in patients with established HF are to relieve symptoms and signs, prevent hospital admission, and improve survival.⁴ Reductions in mortality and hospital admission rates reflect the ability of effective treatments to slow or prevent progressive worsening of HF. This is often accompanied by reversal of harmful cardiac remodelling. Effective therapies also improve functional capacity and quality of life.⁴

The cornerstones of medical therapy are diuretics, ACE inhibitors and beta-blockers, with the addition of a mineralocorticoid receptor antagonist and/or digoxin if this triad is not sufficiently effective.⁴ Implantable devices are used in the treatment of patients who remain symptomatic despite optimal medical therapy (see 1.4). Ventricular assist devices and transplantation are options for selected patients in end-stage HF.⁴

1.1.5 Prognosis

Even with the use of optimal pharmacological therapy, the prognosis for HF is poor. UK studies show one-year mortality from diagnosis for all-class HF is just under 40%.^{6,7} About half of patients will die within 4 years.³ There are two mechanisms of HF-related death: progressive HF (failure of the heart's ability to pump), and sudden cardiac death (SCD; see section 1.1.6), most commonly defined as death from a cardiovascular cause within one hour of the onset of symptoms. SCD is the most common cause of HF-related death in mild to moderate HF, while progressive HF failure is more common in severe HF (Figure

1).

Role of left bundle branch block

Patients with HF often have electrical dysfunction of the heart resulting in delayed activation and contraction of areas of the myocardium, leading to cardiac dyssynchrony.⁸ The most common conduction abnormality is left bundle branch block (LBBB) which delays conduction to the left ventricle and affects approximately one-third of patients with chronic stable HF.⁹ An additional 11% will develop new-onset LBBB within one year of follow-up.

LBBB in the presence of HF has an adverse effect on haemodynamics and has been shown to be an independent predictor of decreased survival in an Italian study of patients with all forms of chronic heart failure published in 2002.¹⁰ However, caution needs to be taken when interpreting the results from this study since, while multivariate, the authors did not control for QRS duration. Hence, the direct applicability of the results to the population being assessed in this appraisal is debatable. There is evidence that HF patients with LBBB (particularly those with mildly symptomatic disease) may derive an increased survival benefit from cardiac resynchronisation therapy,^{11;12} which acts to reduce dyssynchrony. Hence, CRT may be a treatment effect modifier in patients with LBBB.

Role of atrial fibrillation

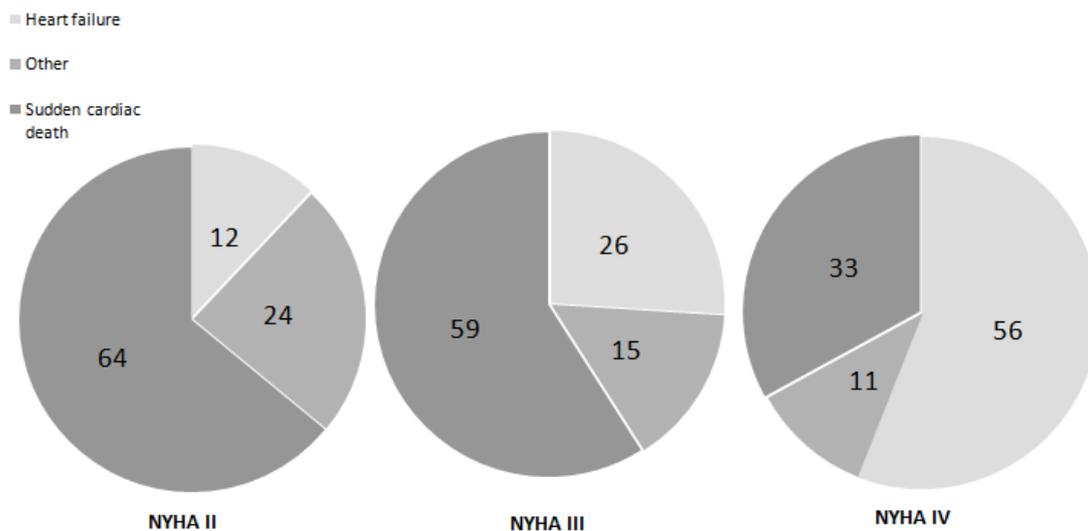
Most of the randomised controlled trials of CRT have excluded patients with persistent atrial fibrillation (AF), although those with paroxysmal AF were often included. AF can reduce the effect of CRT by reducing the proportion of biventricular pacing, and this has been associated with poorer outcomes.¹³ However, when at least 95% biventricular pacing is achieved by increasing atrio-ventricular block with medical or ablation therapy, similar beneficial effects are seen in patients in AF and sinus rhythm. AF is not considered a contraindication to CRT in clinical practice. The European Society of Cardiology (ESC) estimates that 20% of CRT implantations in HF are in patients with AF³ and both ESC and American guidelines endorse the use of CRT in patients with AF (see Section 1.5), provided adequate rate control can be achieved by either drugs or atrioventricular node ablation.

1.1.6 Sudden cardiac death in HF

Sudden cardiac death (SCD) is generally defined as a natural death resulting from cardiac causes in a person with or without pre-existing heart disease, within 1 hour of onset of acute symptoms.¹⁴ In 75% of SCDs the underlying disease is coronary artery disease^{15;16}, and the risk factors with the highest predictive value for SCD are reduced left ventricular ejection fraction and clinical HF.^{17;18}

SCD is the most common cause of death for HF patients in NYHA classes I, II, and III, accounting for 64% and 59% of on-study deaths, respectively, in the MERIT-HF study (Figure 1).¹⁹ In severe HF, the largest proportion of deaths (56% in MERIT-HF) are from progressive HF, although SCD still accounts for approximately one-third.

Figure 1 Changing proportions of deaths from progressive HF and SCD by NYHA Class. SCD is the commonest cause of death in both NYHA II and NYHA III, while progressive HF is most important in NYHA IV. Data from MERIT-HF



1.2 Epidemiology

1.2.1 Incidence and prevalence

The age-standardised incidence of HF in England (2009) is approximately 37.5/100,000 for men and 23/100,000 for women.²⁰ The incidence rises steadily with age, increasing in men from 19.2/100,000 at age 45-54 to 72.3 at age 55-64, 179.3 at age 65-74 and 326.0 at age 75+. In women, the equivalent incidence

rates are 9.1, 31.7, 102.9 and 256.2, respectively. In the UK, the mean ages of ICD, CRT-D and CRT-P implant are 63.1, 67.1 and 71.7 years respectively.²¹ these values are in line with patients recruited into major clinical trials (see section three) meaning that they were conducted in patients of comparable age to the UK HF population. A commonly quoted study of UK heart failure patients reported an incidence of approximately 1:1000 per annum which would result in approximately 65,000 new cases of HF in the UK each year.²²

Age-adjusted prevalence of diagnosed HF in England in 2009 was 0.9% for men and 0.7% for women.²⁰ Prevalence is highest in people aged 75 or over, at 13.7% in men and 12.5% in women. Prevalence of HF in an English population-based study was found to be approximately 1 in 35 people aged 65–74 years, rising to approximately 1 in 15 at age 75–84, and more than 1 in 7 at age 85 and older.²³ In the UK Heart of England study, 31% of definite HF patients were found to have class NYHA III and IV symptoms.²³

The incidence and prevalence of HF are likely to increase, due to ageing of the population and therapeutic advances in the management of acute myocardial infarction and other cardiovascular conditions.²³ Increasing numbers of people are surviving acute myocardial infarction but are left with permanent left ventricular dysfunction, and are consequently at high risk of developing HF.²⁴

1.3 Burden of illness

1.3.1 Economic cost

Heart failure is a major cause of mortality and morbidity in the UK and is responsible for about 2% of total NHS spending.²⁵ It accounts for approximately one million inpatient bed days annually (2% of all NHS inpatient days), and 5% of medical emergency hospital admissions.²⁶ One patient in four is readmitted within three months of HF hospitalisation.²⁷ It is projected that admissions due to HF will increase by 50% in the 25 years from 2010.²⁶

Hospitalisation accounts for 60-70% of the healthcare cost of HF. The costs extend beyond direct healthcare costs associated with the initial admission. Stewart et al. estimated that secondary HF admissions and long term nursing care consumed an additional 2% of UK healthcare expenditure.²⁸ A recent study has generated similar findings.²⁹

1.3.2 Humanistic burden

Quality of life is affected both by the physical limitations resulting from HF and by the consequent limitations on social activity. This in turn can affect psychological and emotional wellbeing. In people with severe HF, functional ability is severely limited and depression is common.³⁰

HF has been shown to have an important impact on all aspects of quality of life, in particular patients' mobility and usual activities.³¹ For example, patients with HF in the CARE-HF study were found to have significant HRQoL reductions (as measured using the EQ-5D instrument) compared with a representative sample of the UK population. The authors concluded that the impact of HF varies amongst patients, but the overall burden of disease appears to be comparable to other chronic conditions such as motor-neuron disease or Parkinson's disease.

1.4 Description and current application of relevant technologies

A range of devices is available from different manufacturers. These differ in their specifications and features: Manufacturers' literature should be consulted for product-specific information. The principal characteristics of the three technology classes under assessment are described below.

1.4.1 Implantable cardioverter defibrillator (ICD)

An implantable cardioverter defibrillator (henceforth "ICD") is a small, battery powered device that is implanted under the skin (often sited below the collar bone; Figure 2). It continuously monitors the heart for arrhythmia (ventricular tachyarrhythmia/ventricular fibrillation) and, depending on its programming, acts to restore normal heart rate using small, painless electrical signals. If necessary the device delivers a stronger shock (defibrillation) that is triggered when it senses a potentially life-threatening arrhythmia.

An ICD system typically includes three parts: the ICD itself, leads and a programmer. The leads are implanted as shown in Figure 3, and carry signals between the ICD and the heart. Dual chamber (atrial and ventricular sensing and pacing) and single chamber (ventricular sensing and pacing only) devices are available. The programmer is in an external computer located in a doctor's office or clinic. Many ICD systems now include remote monitoring: A device installed in the patient's home transmits data from the ICD to a secure website where it can

be viewed by the clinical team. This alerts the team to any significant events and minimises the need for patients to travel to hospital for device review. The ICD can be programmed in order to optimise the detection and treatment of arrhythmias and provide diagnostic information important to patient management.

Figure 2 Location of ICD and leads

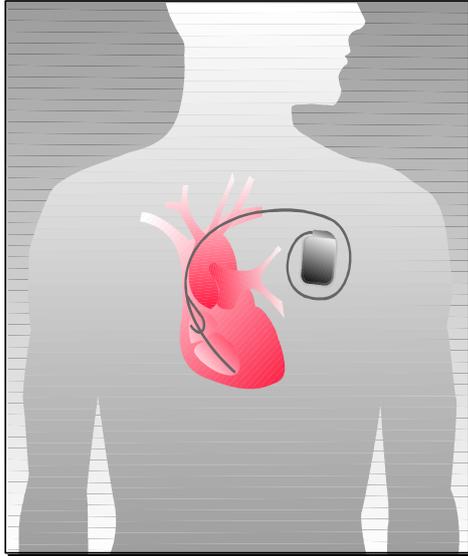
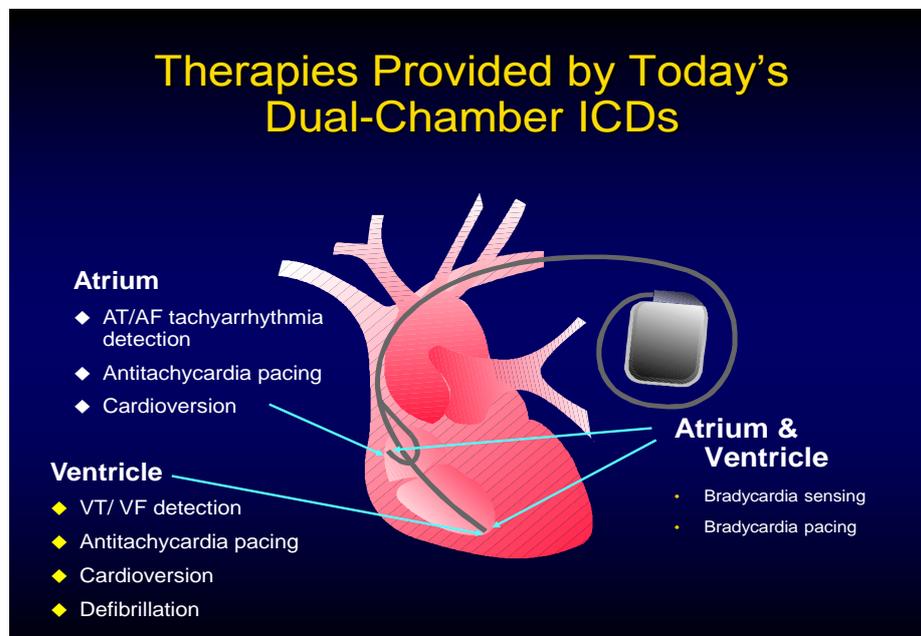


Figure 3: Function and lead positioning of a dual chamber ICD



1.4.2 Cardiac resynchronisation therapy (CRT)

CRT-P

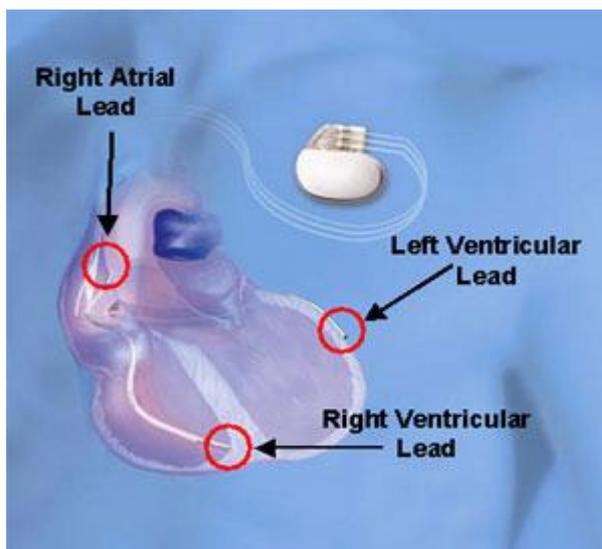
Cardiac resynchronisation therapy (CRT), also known as biventricular pacing, uses an implantable device to deliver pacing via biventricular or left ventricular electrical stimulation. For HF patients with impaired electrical conduction in the heart, CRT is intended to resynchronise the contraction of the ventricles, thereby improving pumping efficiency and increasing blood flow to the body. This may reduce HF symptoms, improve quality of life and increase patients' ability to perform the tasks of daily living. CRT is intended to complement standard drug therapy, dietary and lifestyle modifications.

CRT involves implantation of a pulse generator in the upper chest of the pulse generator, from which three leads descend via veins into the heart. Leads are placed in the right atrium and the right ventricle, with a third lead (the left ventricular lead) usually being placed in the coronary sinus (Figure 4).

Implantation success rates in clinical trials have been high. For example, the success rate in the CARE-HF study was 96%.³²

CRT with pacing function only, as described above, is henceforth referred to as "CRT-P".

Figure 4: Lead positioning in a CRT device



CRT-D

HF patients are also at risk of sudden cardiac death and may benefit from an implantable cardioverter defibrillator, or a combination CRT/defibrillator

(henceforth “CRT-D”). CRT-D is designed to combine the distinct but complementary benefits of CRT and ICD devices.

1.4.3 Summary of device actions

A summary of the major actions of each device type is presented in Table 3 below. Of note, CRT-P does not offer defibrillation in the event of potentially fatal arrhythmia, so does not directly protect against SCD.

Table 3: Major actions by device type.

Action	ICD	CRT-P	CRT-D
Heart rate (bradycardia) pacing	✓	✓	✓
Cardiac resynchronisation (improves pumping efficiency)	X	✓	✓
Arrhythmia detection and correction (anti-tachycardia pacing, cardioversion and defibrillation to prevent SCD)	✓	X	✓

✓ - Performs function; x - does not perform function

1.5 Current UK guidance on implantable cardiac devices in heart failure

Implantable cardiac devices in HF are addressed by NICE Technology Appraisals 95 (ICD, henceforth ‘TA95’)³³ and 120 (CRT-P and CRT-D, henceforth ‘TA120’)³⁴. The NICE Guideline on Heart Failure (CG 108, 2010)⁵ refers to these two appraisals and does not provide new recommendations.

1.5.1 CRT-P and CRT-D

Under NICE guidance issued in 2007 (TA120³⁵), CRT-P is recommended as a treatment option for people with HF who fulfil all the following criteria:

- They are currently experiencing or have recently experienced NYHA class III–IV symptoms
- They are in sinus rhythm: **either** with a QRS duration of 150ms or longer estimated by standard ECG; **or** with a QRS duration of 120–149ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography
- They have a left ventricular ejection fraction of 35% or less

- They are receiving optimal pharmacological therapy.

CRT-D may be considered for people who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD device, as recommended in TA95 (see section 1.5.2 below).

1.5.2 ICD

NICE guidance issued in 2006 (TA95³⁶) recommends ICDs for the following categories of patient:

'Secondary prevention', that is, for patients who present, in the absence of a reversible cause, with one of the following:

- Having survived a cardiac arrest due to either VT or VF
- Spontaneous sustained VT causing syncope or significant hemodynamic compromise
- Sustained VT without syncope or cardiac arrest, and who have an associated reduction in EF (LVEF < 35%) (no worse than NYHA III)

'Primary prevention', that is, for patients who have:

- A history of previous (> 4 weeks) myocardial infarction (MI) and: either LV dysfunction with LVEF <35% (no worse than NYHA III), **and** non-sustained VT on Holter (24-hour ECG) monitoring, **and** inducible VT on EP testing;

or

LV dysfunction with an LVEF <30% (no worse than NYHA III) **and** QRS duration of equal to or more than 120ms.

- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, ARVD, or have undergone surgical repair of congenital heart disease.

TA95 does not cover the use of implantable defibrillators for non-ischaemic dilated cardiomyopathy.

1.5.3 Discussion of current guidance

Current NICE guidance is based on the clinical evidence available up to its

publication in 2006/2007. Since then, the evidence base has expanded, and UK clinical practice has evolved. In addition, device costs have fallen by 9-17% in real terms (see Section 1.7). Thus, it is to be expected that both clinical recommendations and cost-effectiveness calculations will need to be re-examined in the light of current data.

Several major trials have been published since the previous guidance, notably

- SCD-HeFT
- MADIT-CRT
- RAFT
- REVERSE

SCD-HeFT examined the use of ICDs in NYHA II and III patients, the remaining trials focus primarily on the use of CRT-D versus ICD in patients who are mild to moderately symptomatic (NYHA I/II) and are discussed in detail in Section three of the dossier. In terms of UK clinical practice, we have sought expert opinion on changes since the last guidance. We are advised that, while NYHA Class, LVEF and QRS interval remain integral to decision making, other tests, in particular electrophysiology (EP) tests as specified in the guidance arising from TA95, no longer reflect best practice.

The most recently updated international guideline was issued by the European Society of Cardiology in May 2012. Its recommendations are summarised in Table 4 and Table 5, along with the most recent US guidelines dating from 2008. All recommendations apply to patients who are receiving optimal medical therapy and have expected survival with good functional status of more than one year.

Table 4: European and US guidelines on CRT-P and CRT-D in heart failure.

Patient population	Recommendation	Level
European Society of Cardiology (2012)⁴		
<u>NYHA Class II</u>		
<i>LBBB QRS morphology</i>		
LVEF ≤30%, QRS ≥130 ms, sinus rhythm	CRT, preferably CRT-D, is recommended to reduce risk of HF hospitalisation and risk of premature death	IA
<i>Non- LBBB QRS morphology</i>		
LVEF ≤30%, QRS ≥150 irrespective of morphology, sinus rhythm	CRT, preferably CRT-D, should be considered to reduce risk of HF hospitalisation and risk of premature death	IIaA
<u>NYHA Class III/IV</u>		
<i>LBBB QRS morphology</i>		
LVEF ≤35%, QRS ≥120 ms, sinus rhythm, ambulant	CRT-P/CRT-D is recommended to reduce risk of HF hospitalisation and risk of premature death	IA
<i>Non-LBBB QRS morphology</i>		
LVEF ≤35%, QRS ≥150 ms irrespective of morphology, sinus rhythm, ambulant	CRT-P/CRT-D should be considered to reduce risk of HF hospitalisation and risk of premature death	IIaA
<i>Permanent AF</i>		
LVEF ≤35%, QRS ≥120 ms, ambulant	CRT-P/CRT-D may be considered to reduce risk of HF worsening if: pt requires pacing for intrinsically slow ventricular rate; or is pacemaker-dependent resulting from AV nodal ablation; or has ventricular rate ≤ 60 bpm at rest and ≤ 90 bpm on exercise	IIbC
<u>American Heart Association/American College of Cardiology (2008)²</u>		
<u>NYHA Class III/IV</u>		
LVEF ≤35%, cardiac dyssynchrony (QRS ≥120 ms), sinus rhythm, ambulant	Should receive cardiac resynchronisation therapy, with or without ICD, unless contraindicated	IA
LVEF ≤35%, QRS ≥120 ms, atrial fibrillation, optimal medical therapy, ambulant	CRT with or without an ICD is reasonable	IIaB

Table 5 European and US guidelines on ICD in heart failure

Patient population	Recommendation	Level
European Society of Cardiology, 2012⁴		
NYHA Class II/III		
LVEF ≤ 35%, optimal medical therapy	ICD is recommended for primary prevention of sudden cardiac death	IA (ischaemic aetiology)
i) Ischaemic aetiology ≥ 40 days post-MI		IB (non-ischaemic aetiology)
ii) Non-ischaemic aetiology		
American Heart Association/American College of Cardiology²		
NYHA Class II/III		
As above, ischaemic or non-ischaemic aetiology	ICD is recommended for primary prevention of sudden cardiac death, to reduce total mortality	IA

1.6 Current Service Provision

There is significant local variation in ICD and CRT implantation rates within England and Wales. The 2010 UK National Clinical Audit on Cardiac Rhythm Management found that the adjusted annual number of new ICD implants per million population varied from 34 in the Cardiac Network with the lowest provision to 131 in the network with highest provision. Implantation rates for new and replacement CRT devices ranged from 68 to 182/million.²¹

The Network Device Survey Group, in its UK National Clinical Audit of Heart Rhythm Devices, states that, while targets remain open to investigation and debate, “realistic target implant rates, based on a consensus of the best epidemiological and international comparative data possible, serve as a vital stimulus for the planning and improvement of device services”.²¹ The audit group uses an annual target of 100 new implants/million population for ICD and 130 total (new + replacement)/million for CRT (CRT-P and CRT-D combined). Current rates in England are approximately 72/million and 114/million, respectively, suggesting considerable under-provision of this treatment.²¹ Figure 5 and Figure 6 show wide regional variation relative to these targets.

In addition, comparison of the ICD prevalence estimates presented in section 1.2 with the information in Figure 5 highlights the fact that the upper control limit on

current procedures is below the derives estimates for most network population sizes.

Figure 5: New ICD implant rate by cardiac network, compared with the national target.

Source: Cunningham et al. 2010.²¹

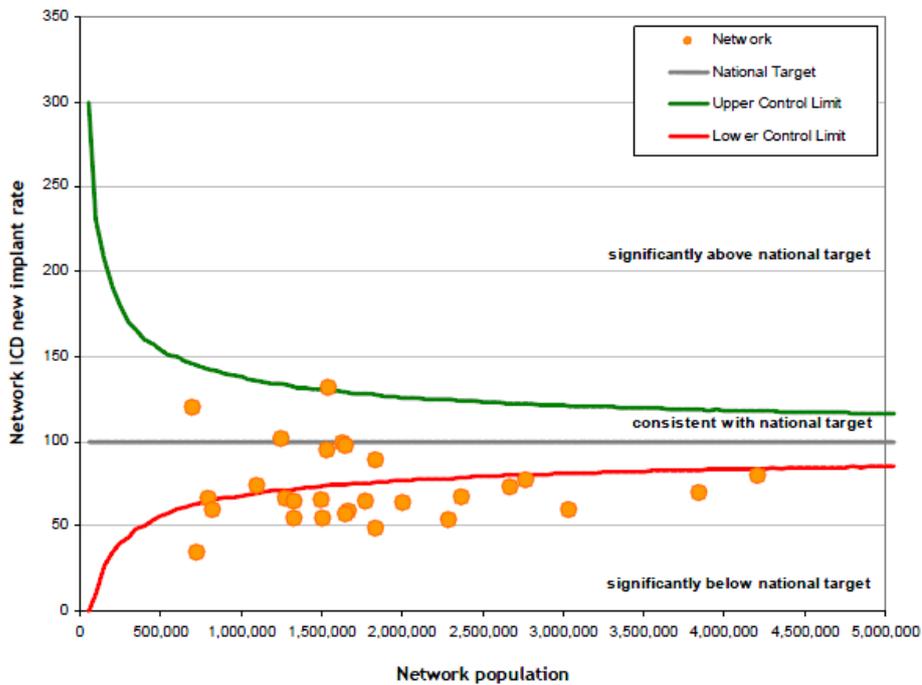
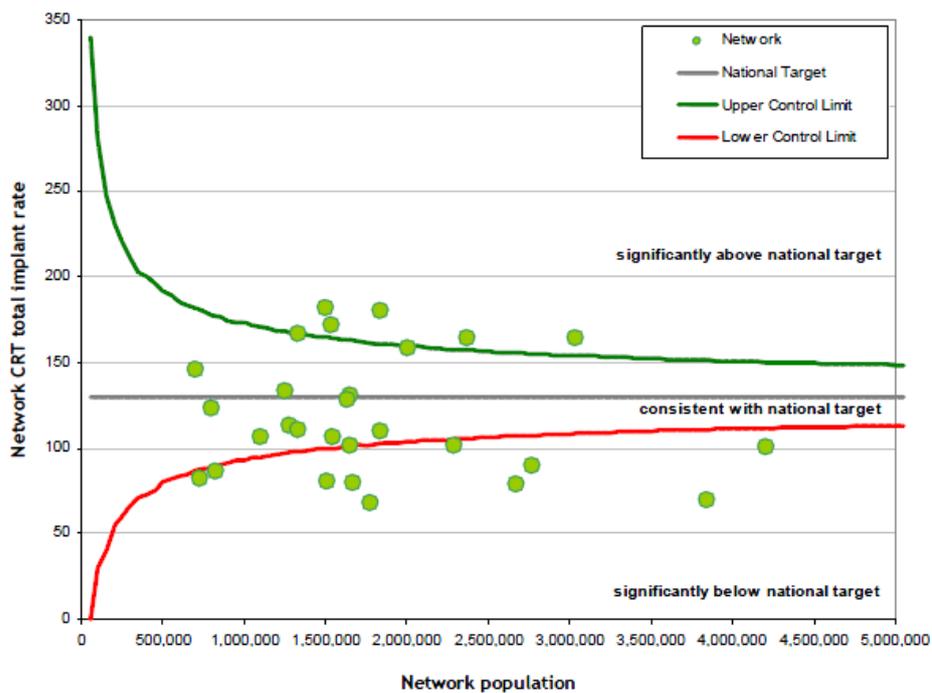


Figure 6: New CRT (CRT-P and CRT-D combined) implant rate by cardiac network, compared with the national target. Source: Cunningham et al. 2010.²¹



1.7 Price of technologies under appraisal

UK NHS specific average selling prices (ASP) for both whole systems (devices and leads) and just leads were provided by five device manufacturers (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical) for all ICD and CRT devices from 2006 to 2011 inclusive via the Association of British Healthcare Industries (ABHI). These prices represent the actual costs paid in the UK NHS for CRT and ICD based treatments. 2006 data were not available for ICD therapy.

In order to make a fair comparison across years, the 2006 (CRT) and 2007 (ICD) values were inflated to 2011 equivalents (the most recent date of data availability) using the Hospital & Community Health Services pay inflation index.³⁷ The observed values are presented graphically in Figure 7 to Figure 9, along with the values expected if prices had risen in line with inflation. For all three treatment options, actual prices have declined over the five year period. In real terms, prices have fallen by 17% for CRT-P, 10.4% for CRT-D and 8% for ICD. When interpreting these values, it is impossible to know the impact of future innovation etc. on future prices. Hence, any trend in real term prices have not been extrapolated beyond the observed period.

Figure 7: Observed ASPs for CRT-P and expected inflation-adjusted price (data on file, ABHI)

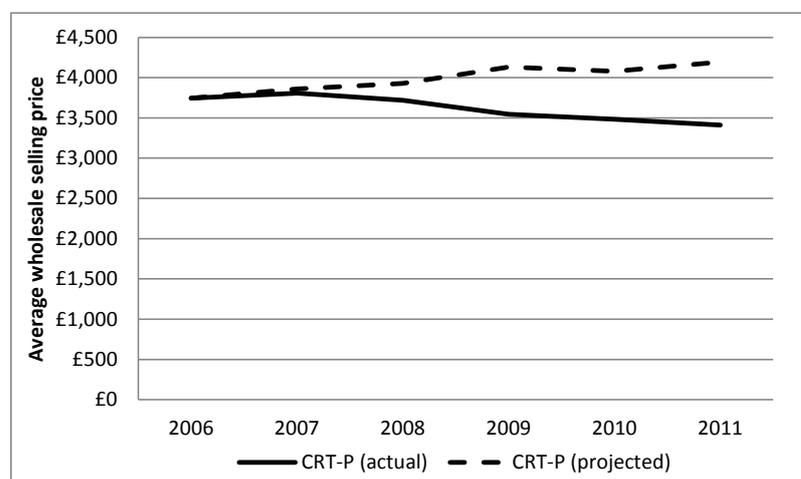


Figure 8: Observed ASPs for CRT-D and expected inflation-adjusted price (data on file, ABHI)

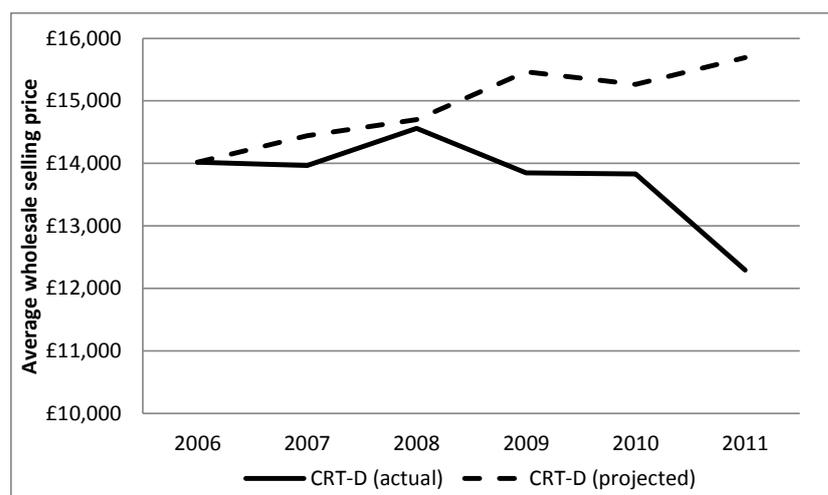
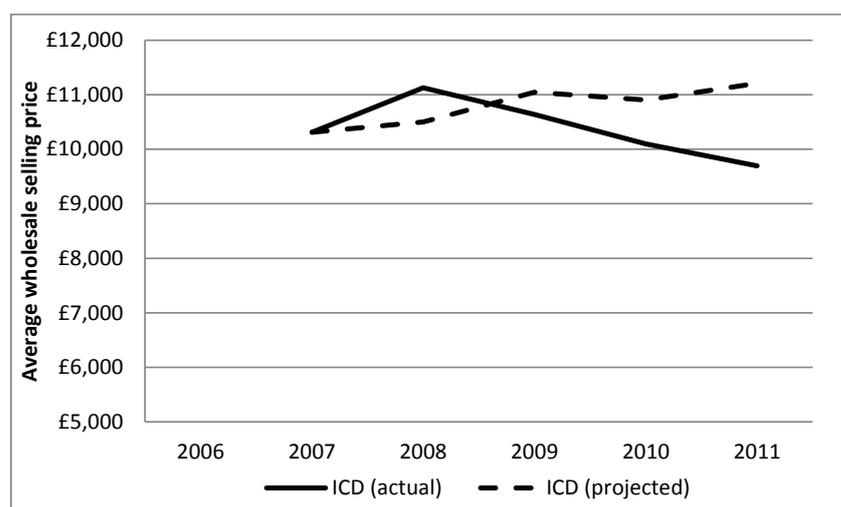


Figure 9: Observed ASPs for ICD and expected inflation-adjusted price (data on file, ABHI)



1.8 Equity and equality

1.8.1 Geographical

Device implantation rates vary widely between different regions of the UK (as defined by Cardiac Networks): see Section 1.6 for details. According to the National Director for Heart Disease, Roger Boyle, quoted in the 2010 HRUK Clinical Audit ²¹ this represents “a continuing and unyielding problem of geographical inequity of service provision” for ICD and CRT devices in the NHS. The report states that the causes of this inequity are not known.

2 Statement of the decision problem

2.1 Overview

2.1.1 Definition of the decision problem

The decision problems addressed in this submission are in line with the NICE scope, namely:

- Based on a range of commonly collected clinical parameters, who should receive an ICD device?
- Based on a range of commonly collected clinical parameters, who should receive a CRT-P device?
- Based on a range of commonly collected clinical parameters, who should receive a CRT-D device?

2.1.2 Patient population of interest

Adults with heart failure (NYHA I to IV) and LVEF \leq 35%, and/or at risk of sudden cardiac death.

2.1.3 Interventions included

The approach used in the submission is predicated on the definition of a large number of patient subgroups using clinically relevant variables. The appraisal protocol listed four interventions of interest (optimal pharmacological therapy - OPT, ICD, CRT-P, and CRT-D), but not all have been included as comparators in all the patient subgroups in this submission. The rationale behind the choice of interventions for each subgroup is presented in Table 6. In general, the justification for exclusion is based on either contraindication (e.g. CRT not being recommended for patients with a QRS duration <120 ms), or on a paucity of data, which has been used as a proxy for non-use in routine clinical practice.

Table 6: Rationale for excluding interventions from some subgroups

Treatment option	Subgroup from which excluded	Rationale/ justification
OPT	None	
ICD	NYHA IV	Minimal IPD data available from clinical trials (of 12,638 patients included in IPD database only [REDACTED] were NYHA IV and randomised to an ICD)
CRT-P	NYHA I/II	Minimal IPD data available from clinical trials (of 12,638 patients included in IPD database only [REDACTED] were NYHA I-II and randomised to a CRT-P)
	QRS <120ms	Prolonged QRS duration required for consideration of device insertion. No evidence of benefit from CRT in patients with normal QRS duration
CRT-D	QRS <120ms	Prolonged QRS duration required for consideration of device insertion. No evidence of benefit from CRT in patients with normal QRS duration

2.1.4 Role of left bundle branch block (LBBB) in decision problem definition

LBBB in the presence of HF has adverse haemodynamic effects and may be a treatment effect modifier for CRT therapy. There is evidence that HF patients with LBBB (particularly those with mildly symptomatic disease) may derive an increased survival benefit from CRT, which acts to reduce dyssynchrony (full discussion and references in section 1.1.5). For this reason, and in line with recently issued ESC guidelines,⁴ we have viewed LBBB as a potentially important decision variable (that is, one that could be used in final guidance to define who gets which treatment, if any). Thus, all cost-effectiveness analyses have been stratified into patient subpopulations with and without LBBB.

LBBB status was not used to restrict the systematic review of clinical efficacy.

2.1.5 The role of atrial fibrillation (AF) in decision problem definition

Although AF is not considered a contraindication to CRT in clinical practice, patients with persistent AF were excluded from most of the RCTs identified. The resulting paucity of data on patients with AF in the clinical trial database (on

which all patient level analyses were performed) meant it was not possible to include AF amongst the list of potential baseline risk or treatment effect modifiers. Hence, the analyses presented in this submission will not distinguish between patients with and without AF.

AF status was not used to restrict the review of clinical efficacy.

2.1.6 Role of electrophysiology (EP) testing

Electrophysiology (EP) testing has been proposed as a tool for identifying patients at increased risk of sudden cardiac death. It has been argued that patients who do not have inducible ventricular tachycardia or fibrillation on EP testing are at lower risk of SCD. However, evidence from the MADIT-II and SCD-HeFT trials, and the MUSTT trial and registry, suggests that this is not a clinically useful method of risk stratification as 'inducible' and 'non-inducible' patients have a similar risk of sudden cardiac death. These findings have been incorporated into the most recent European guidelines⁴, which do not include EP testing in their recommendations on device use.

EP testing is an invasive procedure involving the insertion of wires into the heart via leg veins. Rapid pacing is used to determine whether ventricular arrhythmias can be induced. This inevitably results in some inconvenience to the patient and is associated with a risk of complications. It carries the costs of the equipment, staff and procedure time and is available only at a limited number of centres in the UK. We are advised by clinical experts that EP tests, as specified in the guidance arising from TA95, no longer reflect best evidence-based practice. Therefore our analysis does not distinguish between patients on the basis of response to EP testing.

2.1.7 Other subgroups of interest

For the patient level data analyses we also considered NYHA class, ischaemic aetiology, LVEF, QRS duration, age and gender as potential subgroups of interest. However, in recognition that NICE would be unlikely to issue guidance contingent on age and gender in addition to LBBB status, we have defined subgroups on the basis of NYHA class (I/II/III/IV), QRS duration (less than 120ms, between 120ms and 149ms, at least 150ms) and ischaemic aetiology status.

2.1.8 Patient groups of interest in assessing ICD therapy

Individuals who meet the criteria laid out in TA95 for secondary prevention (in particular having survived a cardiac arrest) have a strong clinical indication for an ICD. Given the real term reduction in implant costs, as well as the absence of new studies in this patient group we believe that this patient group lies outside the scope of the current appraisal. Hence, we have focused solely on the use of ICD in a primary prevention setting.

Similarly, we have not included patients with a familial cardiac condition which results in a high risk of death in the analyses. These include, but are not restricted to, long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC). The rationale for this exclusion is that the available trials do not include data on these indications and thus information from smaller trials and registries represents the best available information on which to base these treatment decisions.

2.2 End points of interest in assessing clinical efficacy

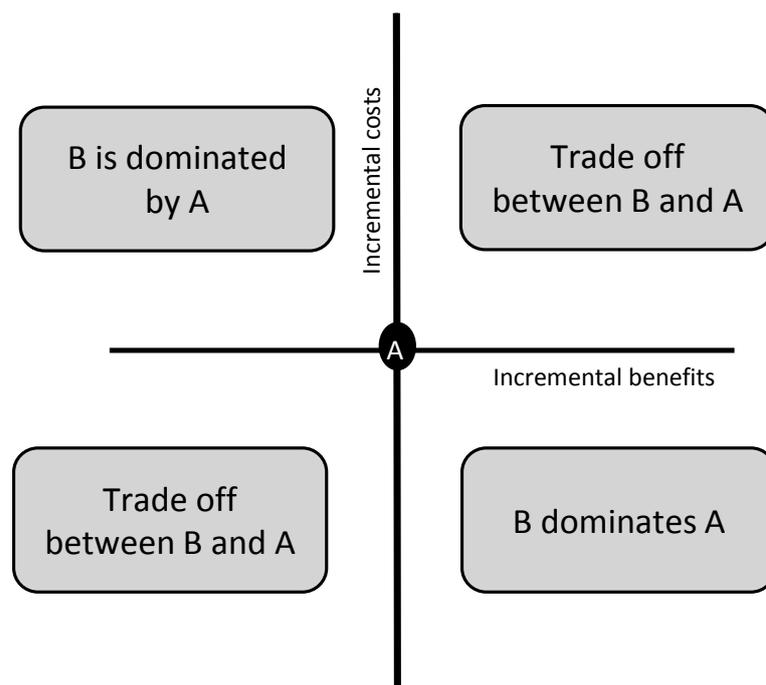
In line with the appraisal scope and with previous reports prepared by technology appraisal groups, we have focused on the following outcomes of interest:

- All-cause mortality
- Sudden cardiac death
- Death due to heart failure
- All cause hospitalisation
- Incidence of ventricular tachycardia/fibrillation
- Change from baseline in NYHA class
- Change from baseline in LVEF
- Treatment related serious adverse events
- Health Related Quality of Life (HRQoL) using Minnesota Living with Heart Failure Questionnaire (MLWHFQ)
- HRQoL using the EQ-5D questionnaire

2.3 Presentation of cost-effectiveness results

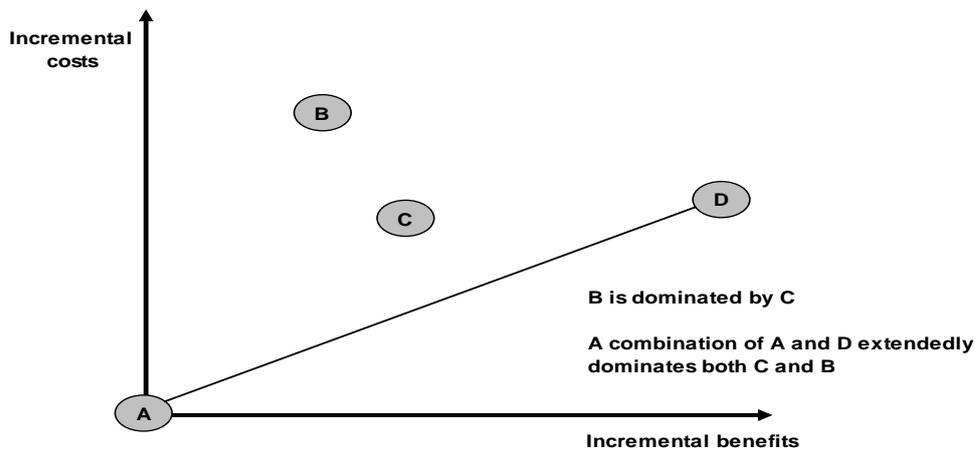
Deterministic results are presented in fully incremental format for all subgroups of interest. In order to interpret correctly the results presented in section six, it is important to be aware of a number of key concepts. In general, for a pairwise comparison of two interventions (B vs. A for simplicity), if the mean incremental results are in the bottom right quadrant of the cost effectiveness plane, corresponding to B being both cheaper and more beneficial than A, then intervention B “dominates” intervention A. Conversely, if the incremental results are in the top left quadrant of the cost-effectiveness plane, B is more expensive and less efficacious than A and is hence “dominated”. In either of the two other quadrants of the cost-effectiveness plane, the ratio of incremental costs to incremental benefits is compared to different threshold values. The process is shown graphically in Figure 10.

Figure 10: Example cost-effectiveness plane



However, in situations where there are more than two interventions being compared, the concept of dominance needs to be modified, with the costs and benefits of each intervention being compared both to the option at the origin (the least costly and least effective) and also all other interventions. Combinations of treatments are also used to make comparisons (“extended dominance”). The general principle is shown in Figure 11.

Figure 11: Illustration of dominance and extended dominance



Clinical trial evidence and expert advice indicate that patients who have NYHA class III symptoms are at high risk of sudden cardiac death and may require ICD therapy (see Figure 1). Thus, because of the most recent ESC guidelines⁴ and the large overlap in eligible patient populations in the current NICE CRT and ICD recommendations, patients who are in NYHA class III and meet the current NICE criteria for CRT are likely to have indications for CRT-D. The latest heart failure clinical guideline issued by NICE⁵ also notes that ICD usage is higher up the 'decision tree'.

Thus, in this patient group, there is need for a comparison of defibrillation based alternatives (CRT-D or ICD) to OPT and also to each other (CRT-D to ICD). We have therefore provided head to head ICERs for these comparisons in all relevant patient groups, as well as a three-intervention incremental analysis, to allow the appraisal committee to incorporate existing clinical practice into their decision making.

Cost-effectiveness planes for all subgroups are presented in appendices. Because multiple comparisons are available for many of the subgroups of interest, conventional one-way parameter uncertainty analyses were not performed. Instead, fully incremental analyses were undertaken for a range of alternative structural approaches and parameter values.

Due to the computation intensive approach used to fully assess the impact of patient level heterogeneity on cost-effectiveness, a full probabilistic sensitivity analysis was not performed.

3 Clinical effectiveness: systematic review of the literature

- A systematic review of RCT evidence for clinical effectiveness of all interventions in the scope was carried out in accordance with NICE guidelines. Full details of methodology can be found in Appendices 1-5.
- The results of a formal evidence synthesis are presented in a separate section of the dossier.
- Qualitative narrative summaries are provided of mortality, other clinical, hospitalisation and health-related quality of life end points, and of adverse events.
- 46 articles reporting the results of 22 trials met the criteria for inclusion in the qualitative summary.
- The review confirms that there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF. This is backed up by several previously published meta-analyses.
- Additional evidence from long-term follow-up of two studies shows a persistent mortality benefit from both ICD and CRT.
- No new evidence was identified relating to the use of ICD in a secondary prevention setting.

The clinical effectiveness of all interventions included in the project scope was assessed by a systematic review of published randomised controlled trial (RCT) based research. This systematic review was executed in line with the requirements of NICE as stated in their methods guideline.³⁸ The aim was to summarise the literature on the clinical efficacy of ICD, CRT-P and CRT-D in all published randomised controlled trials. The results from a formal evidence synthesis of studies identified are presented in a separate section of the dossier. Narrative summaries of the studies identified are provided in this section. We also discuss the findings of previous meta-analyses.

Four of the studies are collecting long-term follow-up data on mortality, some of which became available after both the data lock date for the Individual Patient Data meta-analysis and date of search strategy execution. These data are discussed separately in Section 3.9.

3.1 Identification and assessment of studies

3.1.1 Search strategy

The systematic review was undertaken using the timelines initially provided by NICE to all technology sponsors. Hence, to identify potential relevant articles, electronic searches were conducted on the 27th and 28th of June 2011 in the following databases:

- Medline and Medline in process 1950 to present (OVID SP)
- EMBASE 1980 – present (OVID SP)
- Cochrane Central Register of Controlled Trials (CENTRAL)

All searches were limited to English language and start publication date of 1990. Further details of the search strategies are contained in Appendix 1. To further ensure all relevant articles have been identified, we scanned the reference list of full text papers retrieved from the searches.

3.1.2 Inclusion and exclusion criteria

Studies were selected according to the following criteria:

Population

- Adults with LVEF $\leq 40\%$ or those who may not have (LVEF) $\leq 40\%$ but are considered to be secondary prevention patients according to TA95 criteria (see Section 1.5.2)
- Adults who have experienced prior myocardial infarction (MI) or coronary revascularisation; this must have occurred more than 45 days prior to enrolment.

Interventions

Studies comparing any two or more of the following treatments (including at least one device) were included:

- Implantable cardioverter defibrillator (ICD)
- Cardiac resynchronisation therapy with a pacing device (CRT-P)
- Cardiac resynchronisation therapy with a defibrillator device (CRT-D)
- Placebo
- Medical therapy
 - Optimal pharmacological therapy (OPT): For inclusion in the trial patients must be on a particular drug regimen with stable doses before randomisation. A common synonym used in the literature is optimal medical therapy (OPT). these two have both been used in this dossier and refer to the same treatment option.
 - Conventional medical therapy (CMT): Patients included in the trial are not required to be on a particular drug regimen before randomisation.

Study type

Full publications of randomised controlled trials (RCTs) from the start of 1990.

Exclusion criteria

The following criteria were used to exclude studies from the review:

- Patients with familial cardiac conditions with a high risk of SCD, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and following surgical repair of Tetralogy of Fallot
- Non English-language publications
- Conference abstracts and non-randomised controlled trials.
- Trials comparing different variant of the same device (e.g. comparisons of different pacing strategies).

3.1.3 Study selection

The selection of studies was undertaken by two reviewers. After de-duplication, articles were screened at title and abstract level. Those that met the eligibility criteria stated above were selected for full article review. Articles that did not meet the inclusion criteria from the full text review were excluded with reasons and

documented in the PRISMA flow diagram in Appendix 2.

3.1.4 Data extraction

Data were extracted for the following variables:

Study characteristics

Author, year, study duration, sample size

Baseline characteristics

- Age
- Gender
- QRS Duration
- NYHA class
- LVEF
- History of MI
- History of AF
- Aetiology status
- Incidence of LBBB
- History of prior pacing
- Normal sinus rhythm
- Randomisation

End points of interest

- All-cause mortality
- Sudden cardiac death
- Death due to heart failure
- All cause hospitalisation
- Incidence of ventricular tachycardia/fibrillation
- Change from baseline in NYHA class
- Change from baseline in LVEF
- Device related serious adverse events
- Quality of life using Minnesota Living With Health Failure questionnaire (MLWHFQ) and the EQ-5D (these were the most commonly used quality of life instruments in cardiovascular diseases).

A standardised data extraction form was designed and tailored to the review (n.b. this form can be made available to the academic review group on request). Data were not extracted for secondary prevention of SCD studies (survivors of sudden cardiac events or patients with recurrent unstable rhythms). The rationale for this is presented in section 2.1.8.

3.1.5 Assessment of risk of bias

Two independent reviewers critically appraised the quality of included studies according to the criteria specified by NICE which is based on the evaluation of all components of the trial that could affect the risk of bias³⁸ (see Appendix 3 for further details).

3.2 Studies identified by the review

A total of 7860 articles were retrieved: 7858 from the electronic databases, the summary of safety and effectiveness data from one trial (Rhythm ICD³⁹) were provided by the manufacturer and the summary of another study (VeCtoR⁴⁰) was identified from the reference list of retrieved papers. Of these, 46^{8;39-83} articles reporting results of 22 trials were included in the qualitative synthesis of the review of relative treatment effects. An additional 11⁸⁴⁻⁹⁴ articles reporting results of five trials on secondary prevention patients were identified. Data were not extracted for these six trials as explained above, and references are provided in appendix four for completeness. Further details on the study selection process can be found in the PRISMA flow diagram in Appendix 2.

The studies included in the qualitative synthesis are summarised in Table 7.

Note about the REVERSE trial

The REVERSE trial⁶³⁻⁶⁵ was an international multicentre, randomised, double-blind controlled trial conducted in United States, Canada and Europe. The trial enrolled patients with NYHA class I and II heart failure.

Patients underwent implantation of a CRT system with or without ICD capabilities. To receive an ICD the patient had to have a class I or II indication for an ICD according to US and Canadian guidelines. In Europe, the ICD implantation was left to physicians' judgement based on European guidelines. A CRT-ICD (CRT-D) was implanted in 83.4% and a CRT pacemaker (CRT-P) in 16.6% of patients and they were randomised to CRT-ON and CRT-OFF.

Therefore the trial included the following interventions:

- Patients with a CRT-D implanted (83.4%):
 - CRT-ON- delivered therapy: CRT-D

- CRT-OFF- delivered therapy: ICD
- Patients without an ICD (i.e. CRT-P implanted) (16.6%):
 - CRT-ON: delivered therapy: CRT-P
 - CRT-OFF: inactive pacing

Results were provided for the total group of patients randomised to CRT-OFF and CRT-ON. Data were not stratified for those patients that received an ICD and those without and ICD. As most of the patients in the trial received an ICD, in order to simplify the presentation in the tables, the interventions have been described as patients receiving CRT-D and randomised to CRT-ON and CRT-OFF. This information should be taken into account when reading the data extraction tables.

Note about medical therapy

As stated in the inclusion criteria, there were two types of medical therapy interventions according to whether patients were required to be on a particular drug regimen before randomisation (OPT) or there were no requirements for a particular drug regimen before randomisation (CMT).

A statement indicating that patients were required to be on OPT was present in the following studies: CARE-HF, COMPANION, CONTAK-CD, MADIT CRT, MIRACLE, MIRACLE-ICD, MIRACLE ICD II, MUSTIC, RAFT, RESPOND, RETHINQ, REVERSE, RHYTHM-ICD, Piccirillo *et al.*, Pinter *et al.*, SCD-HeFT and Vector.

No statement regarding requirements for a particular medical therapy before randomisation was present in the following studies: AMIOVIRT, DEFINITE, CAT, MADIT and MADIT II. These studies therefore have been categorised as patients receiving CMT.

In order to simplify the presentation in the tables, the interventions for medical therapy have been collectively described as OPT. This should be taken into account when reading the tables.

3.3 Baseline patient characteristics

A summary of treatments used in each study, as well as patient counts and the list of all relevant references is presented in Table 7. Details of patients that

crossed over from intervention to control arms are described in Table 8. The characteristics of patients at the baseline are summarised by LVEF and NYHA distribution in Table 9, by demography and QRS morphology in Table 10 and by cardiovascular history in Table 11.

Table 7: Summary of treatments and randomisation in each trial

Study	Randomised	Implanted	Randomisation	Delivered therapy	Max Follow up (months)	Number enrolled	Number randomised	Protocol mandated cross-over																																																																																																								
AMIOVIRT ^{79;82}	Before implantation	ICD	ICD	ICD	24 (15.6)[1.2-57.6] ^a	NR	103	No																																																																																																								
		None	OPT	OPT					CARE-HF ^{8;55-58}	Before implantation	CRT-P	CRT-P	CRT-P	37.6 (31.5-42.5) ^b	NR	813	No	None	OPT	OPT	CAT ^{341;42;47}	Before implantation	ICD	ICD	ICD	66 (26.4) ^d	104	104	No	None	OPT	OPT	COMPANION ^{46;51-53}	Before implantation	CRT-P	CRT-P	CRT-P	16.5 ^e	NR	1520	No	CRT-D	CRT-D	CRT-D	16 ^e	None	OPT	OPT	14.8 ^e	Contak-CD ^{60;76}	Before implantation	CRT-D	CRT-ON	CRT-D	6 ^f	581	490	Yes	CRT-D	CRT-OFF	Inactive pacing	DEFINITE ^{62;73}	Before implantation	ICD	ICD ^g	ICD	29.0 (14.4) ^g	NR	458	No	None	OPT	OPT	MADIT ^{68;69}	Before implantation	ICD	ICD	ICD	27 ^h	196 ⁱ	196	No	None	OPT	OPT	MADIT CRT ^{67;77;95}	Before implantation	CRT-D	CRT-D	CRT-D	28.8 ^h	NR	1820	No	ICD	ICD	ICD	MADIT II ^{70;71}	Before implantation	ICD	ICD	ICD	91.2 (42 to 108) ^j	1232	1232	No	None	OPT	OPT	MIRACLE ^{43;45;61}	After implantation	CRT-P
CARE-HF ^{8;55-58}	Before implantation	CRT-P	CRT-P	CRT-P	37.6 (31.5-42.5) ^b	NR	813	No																																																																																																								
		None	OPT	OPT					CAT ^{341;42;47}	Before implantation	ICD	ICD	ICD	66 (26.4) ^d	104	104	No	None	OPT	OPT	COMPANION ^{46;51-53}	Before implantation	CRT-P	CRT-P	CRT-P	16.5 ^e	NR	1520	No	CRT-D	CRT-D	CRT-D			16 ^e	None	OPT	OPT				14.8 ^e	Contak-CD ^{60;76}	Before implantation	CRT-D	CRT-ON	CRT-D	6 ^f	581	490	Yes	CRT-D	CRT-OFF	Inactive pacing	DEFINITE ^{62;73}	Before implantation	ICD	ICD ^g	ICD	29.0 (14.4) ^g	NR	458	No	None	OPT	OPT	MADIT ^{68;69}	Before implantation	ICD	ICD	ICD	27 ^h	196 ⁱ	196	No	None	OPT	OPT	MADIT CRT ^{67;77;95}	Before implantation	CRT-D	CRT-D	CRT-D	28.8 ^h	NR	1820	No	ICD	ICD	ICD	MADIT II ^{70;71}	Before implantation	ICD	ICD	ICD	91.2 (42 to 108) ^j	1232	1232	No	None	OPT	OPT	MIRACLE ^{43;45;61}	After implantation	CRT-P	ON	CRT-P	6	571	453 ^k	No	
CAT ^{341;42;47}	Before implantation	ICD	ICD	ICD	66 (26.4) ^d	104	104	No																																																																																																								
		None	OPT	OPT					COMPANION ^{46;51-53}	Before implantation	CRT-P	CRT-P	CRT-P	16.5 ^e	NR	1520	No	CRT-D	CRT-D	CRT-D			16 ^e	None	OPT	OPT				14.8 ^e	Contak-CD ^{60;76}	Before implantation	CRT-D	CRT-ON	CRT-D	6 ^f	581	490	Yes	CRT-D	CRT-OFF	Inactive pacing	DEFINITE ^{62;73}	Before implantation	ICD	ICD ^g	ICD	29.0 (14.4) ^g	NR	458	No	None	OPT	OPT	MADIT ^{68;69}	Before implantation	ICD	ICD	ICD	27 ^h	196 ⁱ	196	No	None	OPT	OPT	MADIT CRT ^{67;77;95}	Before implantation	CRT-D	CRT-D	CRT-D	28.8 ^h	NR	1820	No	ICD	ICD	ICD	MADIT II ^{70;71}	Before implantation	ICD	ICD	ICD	91.2 (42 to 108) ^j	1232	1232	No	None	OPT	OPT	MIRACLE ^{43;45;61}	After implantation	CRT-P	ON	CRT-P	6	571	453 ^k	No													
COMPANION ^{46;51-53}	Before implantation	CRT-P	CRT-P	CRT-P	16.5 ^e	NR	1520	No																																																																																																								
		CRT-D	CRT-D	CRT-D	16 ^e																																																																																																											
		None	OPT	OPT	14.8 ^e																																																																																																											
Contak-CD ^{60;76}	Before implantation	CRT-D	CRT-ON	CRT-D	6 ^f	581	490	Yes																																																																																																								
		CRT-D	CRT-OFF	Inactive pacing																																																																																																												
DEFINITE ^{62;73}	Before implantation	ICD	ICD ^g	ICD	29.0 (14.4) ^g	NR	458	No																																																																																																								
		None	OPT	OPT																																																																																																												
MADIT ^{68;69}	Before implantation	ICD	ICD	ICD	27 ^h	196 ⁱ	196	No																																																																																																								
		None	OPT	OPT																																																																																																												
MADIT CRT ^{67;77;95}	Before implantation	CRT-D	CRT-D	CRT-D	28.8 ^h	NR	1820	No																																																																																																								
		ICD	ICD	ICD																																																																																																												
MADIT II ^{70;71}	Before implantation	ICD	ICD	ICD	91.2 (42 to 108) ^j	1232	1232	No																																																																																																								
		None	OPT	OPT																																																																																																												
MIRACLE ^{43;45;61}	After implantation	CRT-P	ON	CRT-P	6	571	453 ^k	No																																																																																																								

Study	Randomised	Implanted	Randomisation	Delivered therapy	Max Follow up (months)	Number enrolled	Number randomised	Protocol mandated cross-over
		CRT-P	OFF	Inactive pacing				
MIRACLE-ICD ⁸³	After implantation	CRT-D	CRT-ON	CRT-D	6	639	369	No
		CRT-D	CRT-OFF	Inactive pacing				
MIRACLE-ICD II ⁴⁴	After implantation	CRT-D	CRT-ON	CRT-D	6	222	186	No
		CRT-D	CRT-OFF	Inactive pacing				
MUSTIC ⁵⁴	After implantation	CRT-P	ON	CRT-P	6	67	58	Yes
		CRT-P	OFF	Inactive pacing				
Piccirillo <i>et al</i> ⁷⁴	Before implantation	ICD	ICD	ICD	12	NR	31	No
		CRT-D	CRT-D	CRT-D				
Pinter <i>et al</i> ⁷⁵	After implantation	CRT-D	CRT-ON	CRT-D	6	90	72	No
		CRT-D	CRT-OFF	Inactive pacing				
RAFT ^{80;81}	Before implantation	CRT-D	CRT-D	CRT-D	40 (20) ⁹	179 ^h	179 ^h	No
		ICD	ICD	ICD				
RESPOND ⁵⁹	Before implantation	CRT-P	CRT-P	CRT-P	22.3 ^l	110	60	No
		None	OPT	OPT				
RETHINQ ^{49;50}	After implantation	CRT-D	CRT-ON	CRT-D	6	250	172	No
		CRT-D	CRT-OFF	Inactive pacing				
REVERSE ^{63-65;78}	After implantation	CRT-D	CRT-ON	CRT-D	12	684	610	No
		CRT-D	CRT-OFF	ICD				
Rhythm-ICD ³⁹	After implantation	CRT-D	CRT- ON	CRT-D	12.1 (3.4) ^g	205	178	No
		CRT-D	CRT- OFF	Inactive pacing				
SCD-HeFT ^{48;72}	Before implantation	ICD	ICD	ICD	45.5 ^e	NR	2521	No

Study	Randomised	Implanted	Randomisation	Delivered therapy	Max Follow up (months)	Number enrolled	Number randomised	Protocol mandated cross-over
		None	Amiodarone	OPT				
		None	OPT	OPT				
Vector ⁴⁰	Before implantation	CRT-P	ON	CRT-P	19.9 (8.9) ^g	144	106	No
		CRT-P	OFF	OPT				

a - Mean (SD) [range] reported in years, and converted into months; **b** - Data obtained from Cleland 2006. It represents median (IQR) for longer follow up for mortality. Mean FU for hospitalisation is 29.4 months as reported in main publication 2005; **c**- Presented result of a pilot study; **d**- maximum follow up in mean (SD) reported in years, then converted into months; **e**- Follow up reported as median months of follow up; **f**- Study treatment phase 6 months, length of long-term follow-up phase unknown; **g**- reported as mean follow up (standard deviation); **h**- Mean follow-up; **i**- the author reported that there may have been selection bias during enrolment because a consistent log of eligible who did not qualify on the basis of electrophysiology study was not kept; **j**- Median Follow up (interquartile range) reported in years and converted into months; **k**- 47 patients were not enrolled (device not successfully implanted n=43, patient required cardiac pacing n=2, patient's condition became clinically unstable n=2. 71 patients agreed to be enrolled in an initial pilot phase of the study which followed patients for only three months; **l**- Median FU, reported in days, converted into months; **NR** - not reported

Table 8: Summary of patient crossover in all included studies

Study	Details of crossovers	Details of data analyses as reported from the paper
AMIOVIRT	Amiodarone (n=52); ICD (n=51) 25 patients initially treated with amiodarone had the drug discontinued because of adverse side effects 17.8 +/- 13.3 months (range 1.2 to 43.8 months) after initiation of therapy. 8 patients initially treated with amiodarone were later implanted with an ICD while 11 patients in the ICD group received amiodarone	Cut off for analysis: Study enrolment was discontinued at the first scheduled interim analysis of the first 10 deaths (September 2000). Stopping rule: mortality difference at a significance level of < 0.025 or a significance level of > 0.025 (90% power). The mean duration of follow-up was 2.0 +/- 1.3 years (range 0.1 to 4.8). All analyses were based on the intention-to-treat principle. Information from Wijetunga and Strickberger 2003- AMIOVIRT was conducted from August 1996 to June 2001
CARE-HF	Data from the extension study (8 months extension): 19 out of 409 patients assigned to CRT-P did not receive the device and 95 of 404 in OPT group received a CRT device and had it activated during follow-up. (Cleland et al. ⁵⁷).	Prior to study closure, an extension phase lasting a further 8 months (allowing time for data analysis and presentation) was declared during which cross-over was discouraged. Data lock occurred in January 2005. Results were presented in March 2005. Although knowledge of the results would be expected to lead to an increase in cross-over from assigned therapy, the Steering Committee considered that this would have little effect on the results before May 2005, as investigators would probably not been able to act immediately on the findings. Median follow-up time was 37.6 months (range 26.1-52.6). All analyses were based on intention-to-treat principle.
CAT	Number of patients cross-over was not reported.	
COMPANION	26% of patients in OPT arm withdrew from the optimal medical therapy to receive commercially available implants due to arrhythmia or Heart Failure. Withdrawal rate for the CRT-P arm was 6% and for the CRT-D 7%.	To mitigate the withdrawal rate patients who withdrew were asked to consent to the collection of data on vital status and hospitalisations for the duration of the trial. Data on patients who withdrew before reaching an end point who were not known to have died and for whom complete post-withdrawal information on hospitalisation could not be obtained were censored at the time of elective hospitalisation for device implantation or on the day of last contact. For the mortality end point analysis, data on patients whose vital status was not known at the end of the study were censored on the date of the last known contact. All analyses were censored at the time

		of cardiac transplantation. Each of the devices used in the study became commercially available during the trial. Since this was an open-label study, the subsequent event was a disproportionately high rate of withdrawal from the OPT so that patients could receive cardiac-resynchronisation therapy with one of these devices. This change was particularly common in patients with ischaemic cardiomyopathy, for whom such treatment became an option with the publication of MADIT II. Authors addressed this disproportionate rate by excluding elective implantation of devices from analyses of the primary end point and other hospitalisation end points and obtaining consent of patients who withdrew to complete the ITT analyses. All analyses were conducted according to the intention-to-treat
CONTAK-CD	This was a cross-over study. Patients with an ICD were randomised to pacing (CRT-D) or no pacing (IDC) and crossed over at 3 months (Phase I) until end of study (6 months) at the end of these therapy phases, pacemaker programming was left to the discretion of the investigator. The study design was modified (Phase II) from cross-over to parallel design.	Patients in phase I contributed data from a three month treatment phase and patients in phase II contributed data from a six-month treatment phase.
DEFINITE	Patients who were randomised to OPT were allowed to receive an ICD if they had a cardiac arrest or an episode of unexplained syncope. 27 crossovers occurred: Of the 229 in the OPT arm 23 (10%) received an ICD and of the 229 patients in the ICD group 4 either did not undergo implantation of the ICD, had the device explanted or inactivated. All 4 patients were included in the ITT analysis.	This report presents the results of the final analysis at the time of the 68th death. The first patient underwent randomisation on July 9 1998, and the 458th patient underwent randomisation on June 6, 2002. The 68th death occurred on May 25, 2003.
MADIT	OPT (n=101), ICD (n=96). 16 patients crossed over, 11 in OPT and 5 in the ICD group	Data were analysed weekly beginning at the point at which 10 deaths had been reported. Because of the slow rate of enrolment and before the first patient enrolled had reached the 5th year of the study, it was decided in Nov 12, 1995 that data on patients will be censored for analytical purposes at five years. The efficacy boundary of the sequential designed was crossed when 51 deaths were reported, and the study was officially stopped at that time. All analyses were conducted according to the intention-to-treat principle.
MADIT CRT	A total of 173 crossovers occurred. 91 (12.4%) patients who were assigned to ICD only group received a CRT-D device, while 82 (7.5%) patients assigned to CRT-D group subsequently received an ICD only therapy. Devices were removed in 14 patients (1.3%) in the CRT-D arm and 5 patients (0.7%) in the	The trial was stopped on June 22, 2009, shortly after the 9th of 20 planned analyses since the monitoring statistics had reached the prespecified efficacy boundary. Study-group assignments were then unblinded, and all analyses were limited

	ICD arm. 44 patients in the CRT-D arm (4%) and 55 in the ICD arm (7.5%) declined to continue participating in the study, were withdrawn or lost-to-follow up.	to events occurring before trial termination.
MADIT II	There were 202 crossovers: Among the 742 patients in the ICD arm 22 did not receive an ICD after randomisation and 13 had the ICD extracted during the trial; among the 490 patients in the OPT group. 27 crossed over to the ICD arm during the trial, and 140 received an ICD within 4 months after trial closure.	The trial began on July 11, 1997 and stopped on November 20, 2001 shortly after analyses revealed the prespecified efficacy boundary was reached. The primary analysis was carried out including data on crossover between the treatment arms and the consistency of the results was further validated in an intention-to-treat analysis.
MIRACLE	Crossover from the control group to CRT-P group before the six months study period was prohibited, except for patients in whom a bradyarrhythmia requiring cardiac pacing developed. As a result, 10 patients in the control group had their device reprogrammed to the cardiac- resynchronisation mode.	Patients were recruited between November 1998 and December 2000. Study duration, six months. Patients randomised to the ON or OFF group who had their pulse generator turned OFF or ON before the 6months duration of the study had their safety data included in the statistical analysis; however their efficacy data was not pooled with that of the rest population. Analyses were performed according to the ITT principle.
MIRACLE-ICD	14 (8%) patients in the control group and 10 (5%) patients in the CRT-D crossed over before the end of randomisation phase	Study conducted from October 1, 1999 to August 31, 2001. Duration of the study, 6 months. The low incidence of crossovers had no effect on the results of analyses, which were performed on an ITT basis.
MIRACLE-ICD II	7 crossovers occurred before the end of the trial: 5 (5%) patients in the inactive-pacing group and 2 (2%) in the CRT-D group	Analyses were performed according to the ITT principle.
MUSTIC	This was a cross-over study. Patients were randomised to three months each of inactive pacing and active pacing. During inactive pacing, one patient had severe decompensation leading to premature switch to active pacing.	Analyses were performed according to the ITT principle. Efficacy end points were assessed only in patients with no missing data after the completion of both crossover phases.
PICCIRILLO <i>et al</i>	Number of patients cross-over was not reported.	
PINTER <i>et al</i>	CRT-D (n=36), ICD (n=36). Two patients crossed over. 1 patient in the CRT-D group and another in the ICD group.	Cross over patients were regarded as patients who did not complete the study. It appears data from these patients were not included in the analyses.
RAFT	53 patients (6.0%) in the CRT-D group did not receive CRT device. 36 patients (4.0%) in the ICD arm crossed over before the occurrence of the primary outcome and 60 (6.6%) after hospitalisation for heart failure. Mean follow up 40 months.	Patients were recruited from January 2003 through February 2009. Analyses were performed according to the ITT principle.
RESPOND	CRT-P (n=29), OPT (n=31). 1 patient crossed over from OPT to CRT after development of sustained ventricular tachycardia. Median follow-up 677,5 days.	Analyses were performed according to the ITT principle. No censoring was carried out at 6 months.

RETHINQ	ICD (n=85), CRT-D (n=87). 3 patients in the ICD arm crossed over to CRT-D. No patients in the CRT-D crossed over to ICD.	Analyses were performed according to the ITT principle. Data for all patients were censored at 196 days, the last day of the 6-month window for clinical visits.
REVERSE	ICD (n=191), CRT-D (n=419). Cross-over from the assigned treatment mode was prohibited before the 12-months assessment, except patients who experienced chronic worsening of heart failure. There were 20 permanent cross overs in 12 months: 6 patients in the CRT-D and 14 in the ICD group crossed over.	Analyses were performed according to the ITT principle.
RHYTHM-ICD	CRT-D (n=119), ICD (n=59). Cross-over from the control group was allowed after completing 6-months follow up visit. Two patients crossed over from the CRT OFF group to the CRT ON group before their 6-month follow-up visit. Mean follow-up 12.1 patient months.	Analyses were performed according to the ITT principle.
SCD-HeFT	Amiodarone (n=845), Placebo (n=847), ICD therapy (n=829). Of the 829 patients in the ICD group, 17 (2%) declined to undergo implantation and implantation was unsuccessful in one. An additional 32 patients (4%) had their ICD removed during follow-up. 188 patients (11%) in the drug groups crossed over to receive ICD therapy during follow up. Median time from randomisation to cross-over is 26.7 months. Median follow-up was 45.5 months.	Analyses were performed according to the ITT principle.
VECTOR	Cross-over into the CRT-P treatment group was at physician's discretion. However number of patients that crossed over was not reported.	

Table 9: Baseline patient characteristics by NYHA class and LVEF

Study	Arm	NYHA I n (%)	NYHA II n (%)	NYHA III n (%)	NYHA IV n (%)	LVEF- Mean (SD)
AMIOVIRT	ICD	10 (18)	33 (64)	8 (16)	0	0.22 (0.10)
	OPT	7(13)	33 (63)	12 (24)	0	0.23 (0.08)
CARE-HF	CRT-P	0	0	386 (94)	23 (6)	25 (21-29) ¹
	OPT	0	0	377 (93)	27 (7)	25 (22-29) ¹
CAT	ICD	0	33 (66.7)	17 (33.3)	0	24 (6)
	OPT	0	35 (64.1)	19 (35.8)	0	25 (8)
COMPANION	CRT-P	0	0	536 (87)	81 (13)	0.202
	CRT-D	0	0	511 (86)	84 (14)	0.222
	OPT	0	0	252 (82)	56 (18)	0.222
Contak-CD	CRT-D	0	78 (32)	147 (60)	20(8)	21 (7)
	ICD	0	81 (33)	140 (57)	25 (10)	22 (7)
DEFINITE	ICD	58 (25.3)	124 (54.2)	47 (20.5)	0	20.9 (7 - 35) ³
	OPT	41 (17.9)	139 (60.7)	49 (21.4)	0	21.8 (10 - 35) ³
MADIT	ICD	NR	636		0	0.27 (0.07)
	OPT	NR	677		0	0.25 (0.07)

Study	Arm	NYHA I n (%)	NYHA II n (%)	NYHA III n (%)	NYHA IV n (%)	LVEF- Mean (SD)
MADIT II	ICD	260 (35)	260 (35)	186 (25)	37(5)	23 (5)
	OPT	191 (39)	167(34)	113(23)	20 (4)	23 (6)
MADIT-CRT	CRT-D	152 (14.0)	937 (86)	0	0	0.24 (0.05)
	ICD	113 (15.5)	618 (84.5)	0	0	0.24 (0.05)
MIRACLE	CRT-P	0	0	205 (90)	23 (10)	21.8 (6.3)
	OPT	0	0	205 (91)	20 (9)	21.6 (6.2)
MIRACLE-ICD	CRT-D	0	0	165 (88.2)	22 (11.8)	24.2 (6.5)
	ICD	0	0	163 (89.6)	19 (10.4)	23.9 (6.0)
MIRACLE-ICD II	CRT-D	0	85 (100)	0	0	24.4 (6.6)
	ICD	0	101 (100)	0	0	24.6 (6.7)
MUSTIC	First study group (1-CRT-P active-2 CRT-P inactive)	0	0	29 (100)	0	
	Second study group (1-CRT-P inactive- 2 CRT-P active)	0	0	29 (100)	0	23 (7) ⁴
Piccirillo <i>et al</i>	ICD	0	0	5 (33)	10(67)	22 (8)
	CRT-D	0	0	5 (31)	11 (69)	23 (4)
Pinter <i>et al</i>	CRT-D	NR	NR	NR	NR	21.2 (7.9)
	ICD	NR	NR	NR	NR	24 (8.3)

Study	Arm	NYHA I n (%)	NYHA II n (%)	NYHA III n (%)	NYHA IV n (%)	LVEF- Mean (SD)
RAFT	CRT-D	0	708 (79.2)	186 (20.8)	0	22.6 (5.4)
	ICD	0	730 (80.8)	174 (19.2)	0	22.6 (5.1)
RESPOND	CRT-P	0	0	19(65.5)	10(34.5)	22.3 (8.42)
	OPT	0	0	26(83.9)	5(16.1)	22.1 (10.2)
RETHINQ	CRT-D	0	0	87 (100)	0	25 (5)
	ICD	0	0	84 (99)	0	26 (6)
REVERSE	CRT-D	75 (18)	344 (82)	0	0	26.8 (7.0)
	ICD	32 (17)	159 (83)	0	0	26.4 (7.1)
Rhythm-ICD	CRT-D	1 (0.8)	6 (5.0)	104 (87.4)	8 (6.7)	25.6 (8.3)
	ICD	2 (3.4)	4 (6.8)	50 (84.7)	3 (5.1)	23.3 (6.4)
SCD-HeFT	ICD	0	566 (68)	263 (32)	0	24 (19.0-30.0) ¹
	Amiodarone	0	594 (70)	253 (30)	0	25 (20.0-30.0) ¹
	Placebo	0	594 (70)	253 (30)	0	25 (20.0-30.0) ¹
Vector	CRT-P	0	NR ⁴	NR ⁴	NR ⁵	NR
	OPT	0	NR ⁴	NR ⁴	NR ⁵	NR

1. Median LVEF (IQR); 2- Median LVEF; 3-Mean LVEF (range); 4- Mean LVEF (SD) for all the patients at baseline; 5-NYHA was not reported by intervention group. 29%, of patients were NYHA class II, 65% were NYHA class III and 6% were NYHA class IV of 106 patients randomised and 38 who were not randomised; 6- 63% Of patients in the ICD groups had NYHA class II or III; 7- 67% of patients in the OMT group had NYHA class II or III. **NR**: not reported

Table 10: Baseline patient characteristics: demography and QRS Morphology

Study reference	Arm	Age- mean (SD)	Male- n (%)	QRS duration (ms)- Mean (SD)	LBBB-n (%)
AMIOVIRT	ICM	58 (11)	34 (67)	NR	21(42)
	OPT	60 (12)	38 (74)	NR	27 (53)
CARE-HF	CRT-P	67 (60-73) ¹	304 (74)	160 (152-180) ¹	NR
	OPT	66 (59-72) ¹	293 (73)	160 (152-180) ¹	NR
CAT	ICD	52(12)	43 (86)	102(29)	42 (84.6)
	OPT	52(10)	40(74)	114(29)	44 (81.8)
COMPANION	CRT-P	67 ²	413 (67)	160 ²	425 (69)
	CRT-D	66 ²	398 (67)	160 ²	434 (73)
	OPT	68 ²	212 (69)	158 ²	215 (70)
Contak-CD	CRT-D	66 (11)	208 (85)	160(27)	132 (54)
	ICD	66(11)	203 (83)	156(26)	135 (55)
DEFINITE	ICD	58.4 (20.3-83.9) ³	166 (72.5)	114.7 (78 - 196) ³	45 (19.7)
	OPT	58.1 (21.8-78.7) ³	160 (69.9)	115.5 (79 -192) ³	45 (19.7)
MADIT	ICD	62 (9)	92 (97)	NR	7 (7)
	OPT	64 (9)	92 (91)	NR	8 (8)

Study reference	Arm	Age- mean (SD)	Male- n (%)	QRS duration (ms)- Mean (SD)	LBBB-n (%)
MADIT II	ICD	64 (10)	623 (84)	50 ⁴	141 (19)
	OPT	65 (10)	417 (85)	51 ⁴	88 (18)
MADIT-CRT	CRT-D	65 (11)	814 (74.7)	699 (64.2) ⁵	761 (69.9) ⁶
	ICD	64 (11)	553 (75.6)	476 (65.1) ⁵	520 (71.3) ⁶
MIRACLE	CRT-P	63.9 (10.7)	155 (68)	167 (21)	NR
	OPT	64.7 (11.2)	153 (68)	165 (20)	NR
MIRACLE-ICD	CRT-D	66.6 (11.3)	142 (75.9)	165 (22)	NR
	ICD	67.6 (9.2)	141 (77.5)	162 (22)	NR
MIRACLE-ICD II	CRT-D	63.0 (12.8)	75 (88.2)	166 (25)	NR
	ICD	63.1 (12.1)	91 (90.1)	165 (23)	NR
MUSTIC	First study group	64 (11)	19 (65)	172(22)	
	Second study group	64 (8)	24 (82)	175 (19)	877
Piccirillo <i>et al</i>	ICD	65(8)	12(80)	159(8)	NR
	CRT-D	65(4)	13(81)	160(4)	NR
Pinter <i>et al</i>	CRT-D	66.3 (8.6)	28 (77.8)	NR ⁸	NR
	ICD	66.1 (8.8)	29 (80.6)	NR ⁸	NR
RAFT	CRT-D	66.1 (9.3)	758 (84.8)	157 (23.6) ⁹	68 (7.6)

Study reference	Arm	Age- mean (SD)	Male- n (%)	QRS duration (ms)- Mean (SD)	LBBB-n (%)
	ICD	66.2 (9.4)	732 (81.0)	158.3(24) ⁹	93 (10.3)
	CRT-P	66.7(7.86)	25(86.2)	91.5(10.6)	NR
RESPOND	OPT	69.3(10.2)	24(77.4)	97.8(12.9)	NR
	CRT-D	60 (12)	62 (12)	107 (12)	NR
RETHINQ	ICD	58 (14)	49 (58)	106 (13)	NR
	CRT-D	62.9 (10.6)	327 (78)	153 (21)	NR ¹⁰
REVERSE	ICD	61.8 (11.6)	152 (80)	154 (24)	NR
	CRT-D	NR ¹¹	NR	169 (16)	NR
Rhythm-ICD	ICD	NR	NR	167 (15)	NR
	ICD	60.1 (51.9-69.2) ¹	639 (77)	NR	NR
SCD-HeFT	OPT	59.7 (51.2-67.8) ¹	655 (77)	NR	NR
	CRT-P	NR ¹²	NR ¹²	NR	NR
Vector	OPT	NR ¹²	NR ¹²	NR	NR

1-Median (IQR); 2- Median; 3- Mean (range); 4- Percentage of patients with QRS interval ≥ 0.12 sec; 5- = number (percentage) of pts. With QRS duration ≥ 150 ms; 6- LBBB was analysed amongst a total of 1088 and 729 pts. In the CRT-D & ICD respectively; 7- Percentage of patients with LBBB for all the patients at baseline; 8- Eligibility criteria was QRS > 120 ms. However, data were not reported at baseline; 9- Intrinsic QRS duration. And this was analysed amongst 826 and 837 patients in the CRT-D and ICD group respectively; 10- 468 (76.7%) of all the patients in the trial had LBBB. Data not reported by intervention groups; 11- Data not provided by intervention groups. Patients ≥ 18 years were eligible to enter the trial; 12- Data not provided by intervention groups. The mean age (SD) and number (percentage) of male of the entire population = 67.1 (9.7) and 90 (62.5) respectively. NR = not reported

Table 11: Characteristics by cardiac history (n (%))

Study reference	Intervention	Prior MI	Ischaemic	History AF	Prior pacemaker	Non-sinus rhythm
AMIOVIRT	ICM	NR	0 ¹	NR	NR	NR
	OPT	NR	0 ¹	NR	NR	NR
CARE-HF	CRT-P	NR ²	165 (40)	0	0	409 (100)
	OPT	NR ²	144 (36)	0	0	404 (100)
CAT	ICD	0	NR	10 (20.4)	0	40 (79.6)
	OPT	0	NR	6 (11.3)	1 (1.9)	47 (86.8)
COMPANION	CRT-P	NR	333 (54)	0	0	617 (100)
	CRT-D	NR	327 (55)	0	0	595 (100)
	OPT	NR	182 (59)	0	0	308 (100)
Contak-CD	CRT-D	NR	164 (67)	NR	NR	NR
	ICD	NR	174 (71)	NR	NR	NR
DEFINITE	ICD	NR	0	52 (22.7)	0	NR
	OPT	NR	0	60 (26.2)	0	NR
MADIT	ICD	95 (100)	95 (100)	NR	2 (2)	NR
	OPT	101 (100)	101 (100)	NR	7 (7)	NR
MADIT II	ICD	742 (100)	742 (100)	67 (9)	NR	NR

Study reference	Intervention	Prior MI	Ischaemic	History AF	Prior pacemaker	Non-sinus rhythm
	OPT	490 (100)	490 (100)	39 (8)	NR	NR
MADIT-CRT	CRT-D	NR	598 (55)	118 ³	0	1089 (100)
	ICD	NR	401 (55)	90 ³	0	731 (100)
MIRACLE	CRT-P	NR	114 (50)	NR	0	NR
	OPT	NR	130 (58)	NR	0	NR
MIRACLE-ICD	CRT-D	NR	119 (64)	NR	NR	NR
	ICD	NR	138 (75.8)	NR	NR	NR
MIRACLE-ICD II	CRT-D	NR	47 (55.3)	NR	0	NR
	ICD	NR	59 (58.4)	NR	0	NR
MUSTIC	First study group	NR	NR	0	NR	29 (100)
	Second study group	NR	NR	0	NR	29 (100)
Piccirillo <i>et al</i>	ICD	NR	15 (100)	0	0	15 (100)
	CRT-D	NR	16 (100)	0	0	16 (100)
Pinter <i>et al</i>	CRT-D	24 (66.7)	NR	6 (16.7)	0	36 (100)
	ICD	27 (75)	NR	2 (5.6)	0	36 (100)
RAFT	CRT-D	NR	614 (68.7)	114 (12.8)	68	780 (87.2)
	ICD	NR	587 (64.9)	115 (12.7)	67	789 (87.3)

Study reference	Intervention	Prior MI	Ischaemic	History AF	Prior pacemaker	Non-sinus rhythm
RESPOND	CRT-P	0	22(75.9)	NR	NR	29 (100)
	OPT	0	28(90.3)	NR	NR	31 (100)
RETHINQ	CRT-D	NR	47 (54)	NR	0	NR
	ICD	NR	43 (51)	NR	0	NR
REVERSE	CRT-D	NR ⁴	236 (56)	NR ⁵	0	419 (100)
	ICD	NR ⁴	97 (51)	NR ⁵	0	191 (100)
Rhythm-ICD	CRT-D	NR	NR ⁶	NR	NR	NR
	ICD	NR	NR ⁶	NR	NR	NR
SCD-HeFT	ICD	NR	431	141 (17)	NR	NR
	OPT	NR	453	117 (14)	NR	NR
Vector	CRT-P	NR	NR	NR	NR	NR
	OPT	NR	NR	NR	NR	NR

1-Only pts. with non-ischaemic dilated cardiomyopathy and non-sustained ventricular tachycardia were included; **2**- 31% of patients from the entire study population had a history of MI. Data not provided by intervention groups; **3**- The number of patients who had AF was analysed for 1063 patients in the CRT-D and 717 in the ICD group; **4**- 281 (46.1%) of all the patients in the trial had a history of MI. Data not provided by intervention groups; **5**- 89 (14.6%) of all the patients in the trial had a history of AF. Data not provided by intervention groups; **6**- patients with Ischaemic and non-ischaemic HF were included. However the number (percentage) of patients who had ischaemic aetiology at baseline was not reported **NR** = not reported

3.4 Results from mortality end points

3.4.1 All-cause mortality

All-cause mortality was reported in the 22 trials (Table 12). A formal review of the impact of treatment on mortality is confounded by two key variables: differing follow up periods and interventions being used in patients with differing underlying disease profiles. A formal analysis of the impact of a range of clinical covariates forms a key element of the patient level network meta-analysis described in Section 4.

CRT-P

For CRT-P, CARE-HF found a significant reduction in the risk for all-cause mortality compared with OPT (HR = 0.60 [0.47-0.77]; P < 0.0001). In COMPANION, the effect of CRT-P compared with OPT narrowly failed to reach significance (HR = 0.76 [0.58-1.01]; P = 0.059). In MIRACLE the difference between CRT-P and OPT was not statistically significant (HR 0.73 [0.34-1.54; P=0.4]). Fox *et al.*³⁴ conducted a meta-analysis of interventions for heart failure in 2007 and concluded that CRT-P conferred a significant benefit compared to OPT in terms of impact on all-cause mortality. This finding has been conformed in a recently published meta-analysis of CRT trials (including RAFT).⁹⁶

CRT-D

For CRT-D, all-cause mortality was analysed in three trials. In COMPANION, CRT-D reduced the risk of death by 36% compared with OPT (HR = 0.64 [0.48-0.86]; P = 0.003). In RAFT, CRT-D significantly reduced mortality compared with ICD (HR = 0.75 [0.62-0.91]; P = 0.003). In MADIT-CRT, there was no significant difference in all-cause mortality between the ICD and CRT-D groups. However, MADIT-CRT was conducted in patients with mild to moderate heart failure whereas the others were conducted in patients with moderate to severe heart failure. Despite not being a formal CRT-D vs. ICD trial, REVERSE reported all-cause mortality rates but not a hazard ratio. Mortality rate was 2.2% in the CRT-ON arm and 1.6% in the CRT-OFF arm (P=0.63).

Fox *et al.*³⁴ concluded that CRT-D was highly effective in patients with moderate to severe heart failure (risk ratio 0.65 [95% CI 0.49 to 0.85]³⁴). These findings were again corroborated by the meta-analysis conducted by Wells *et al.*⁹⁶

ICD

All-cause mortality for ICD was compared with OPT in six trials. Three showed a significant reduction with ICD (MADIT, MADIT II and SCD-HeFT), and three did not (AMIOVIRT, CAT and DEFINITE). Notably, ICD reduced all-cause mortality in MADIT and MADIT II, with hazard ratios of 0.46 (0.26-0.82) and 0.66 (0.56-0.78), respectively. Previous meta-analyses have concluded ICD confers significant reduction in mortality compared to OPT (Ezekowitz *et al.* RR 0.72 [95% CI 0.63 to 0.84], Lee *et al.* RR 0.66 [95% CI 0.46 to 0.96]).^{97,98}

Table 12: Effect of interventions on all-cause mortality*

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value	Comments
AMIOVIRT				6/51	7/52	NR	0.8	p - value for binary data
CARE-HF	5.5 yrs		101/409		154/404	0.60 (0.47 -0.77)	< 0.0001	
CAT				13/50	17/54	NR*	NR	Cumulative survival after 2, 4 & 6 years of follow up provided 91% ,86%, & 73% in ICD group vs. 93% 80% & 68% in OMT group p=0.554
COMPANION	6 months	105/595	131/617		77/308	0.64 (0.48 -0.86) 0.76 (0.58 -1.01)	0.003 0.059	CRT-D vs. OPT CRT-P vs. OPT
Contak-CD		11/245		16/245		NR	NR	70 additional deaths at long term follow-up reported. However, data were not provided by intervention groups.
DEFINITE				28/229	40/229	0.65 (0.40 -1.06)	0.08	
MADIT				15/95	39/101	0.46 (0.26 - 0.82)	0.009	
MADIT II				NR	NR	0.66 (0.56 - 0.78)	<0.001	Total events reported after 8 years of follow up is 647. However, the data for each arm of treatment were not provided.
MADIT-CRT		74/1089		53/731		1.00 (0.69 -1.44)	0.99	
MIRACLE			12/228		16/225	0.73 (0.34 -1.54)	0.4	
MIRACLE-ICD		14/187		15/182		NR	NR	Cumulative survival at 6 months: CRT-D: 92.4% (95% CI 87.2%-95.3%); ICD: 92.2% (95% CI 87.2%-95.3%). P=0.96
MIRACLE-ICD II		2/85		2/101		NR	NR	
MUSTIC			1/29		2/29	NR	NR	
Piccirillo <i>et al</i>		0/16		0/15		NR	NR	
Pinter <i>et al</i>		1/36		1/36		NR	NR	
RAFT		186/894		236/904		0.75 (0.62 - 0.91)	0.003	
RESPOND			6/29		10/31	NR	NS	Median follow up of 677.5days not statistically significant for binary end point

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value	Comments
	6 months							
RETHINQ		5/87		2/85		NR	NR	COS: CRT-D: 94.2% (95% CI 86.7 to 94.6); ICD: 98.8% (95% CI 91.9 to 99.8) P = 0.11.
REVERSE		9/419		3/191		NR	NR	Data for mortality rate reported (CRT-D: 2.2%; ICD: 1.6% P=0.63)
Rhythm-ICD		9/119		3/59		NR	NR	
SCD-HeFT				182/829	244/847	0.77 (0.62 - 0.96)	0.007	Trial also had a third arm (amiodarone). HR compared to placebo. Reported hazard ratio and 95% CI for comparison of ICD vs. OPT.
Vector	6 months		1 /59		1/47	NR	NR	

*All entries n/N unless otherwise stated; **NR** = not reported; **NS** = not statistically significant

3.4.2 Sudden cardiac death

The effect of intervention on sudden cardiac death was reported in 14 of the identified trials (Table 13).

CRT-P

Despite containing no direct mechanism for preventing sudden cardiac death, CRT-P was found to significantly reduce the risk of sudden cardiac death in an extension phase of the CARE-HF study when compared with OPT (HR = 0.54 [0.35-0.84]; P = 0.005). However it did not reduce SCD over OPT in COMPANION (HR 1.21 [0.7-2.07]; P=0.5). Given that these trials were of similar size and conducted in similar patient groups, the evidence for some form of residual benefit associated with CRT-P is currently equivocal, although it is important to note that median follow up in CARE-HF was over twice as long as in COMPANION (37 months compared to 16 months) and hence the CARE-HF results may be more reflective of the long term real world treatment effect. The two smaller studies which reported information for this treatment option (MUSTIC and Vector) made no reference to the statistical significance of the results.

CRT-D

A significant effect of CRT-D on sudden cardiac death was reported in COMPANION, where CRT-D reduced the risk by 56% (HR = 0.44 [0.23-0.86]; P = 0.02) compared with OPT.

ICD

ICD therapy significantly reduced the risk of sudden cardiac death versus OPT in the DEFINITE (HR = 0.20 [0.06-0.71]; P = 0.006) and SCD-HeFT (HR= 0.40 [0.27-0.59]; P < 0.001) studies. MADIT II also proved survival benefit of ICD therapy over OPT (HR for all-cause mortality = 0.66 [0.56-0.78]; P <0.001). Although this trial did not report the mode of death, reduction in SCD is the only plausible mechanism. ICD had no significant effect on sudden cardiac death compared with OPT in the small non-ischemic cardiomyopathy AMIOVIRT study. Studies that directly compared ICD and CRT-D treatment did not report the statistical significance of the findings. Previous authors have concluded that in comparison to OPT, ICD is highly effective in preventing SCD (Ezekowitz *et al.* RR 0.37 [95% CI 0.27 to 0.50]⁹⁷, Lee *et al.* RR 0.34 [95% CI 0.23 to 0.50]⁹⁸).

Table 13: Effect of interventions on sudden cardiac death*

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value	Comments
AMIOVIRT				1/51	2/52	NR	0.7	p-value for binary data
CARE-HF			32/409		54/404	0.54 (0.35- 0.84)	0.005	
COMPANION		17/595	48/617		18/308	1.21 (0.7- 2.07)	0.5	CRT-D vs. OPT CRT-P vs. OPT
DEFINITE				3/229	14/229	0.20 (0.06 - 0.71)	0.006	Sudden deaths from arrhythmia. Some death classified as non-cardiac could have been due to arrhythmia but there was not enough information to determine the cause of death. Mode of death not reported. SCD is assumed as the mechanism. Total events reported after 8 years of follow up is 647. However, the data for each arm of treatment were not provided.
MADIT II**				NR	NR	0.66 (0.56 - 0.78)	<0.001	
MIRACLE-ICD		3/87		3/182		NR	NR	
MIRACLE-ICD II		NR		NR		NR	NR	Across both treatment groups, three deaths were as a result of cardiac arrest, while one was due to MI.
MUSTIC			1/29		1/29	NR	NR	
Piccirillo <i>et al</i>		0/16		0/15		NR	NR	
RETHINQ		0/87		0/85		NR	NR	
REVERSE		0/419		0/191			NR	
SCD-HeFT				37/829	95/847	0.40 (0.27 -0.59)	< 0.001	Sudden death from ventricular tachyarrhythmia. Hazard ratio & p - value refers to ICD vs. OPT only.
Vector	6 months		0/59		1/47	NR	NR	

* All results n/N unless otherwise stated; ** Results relates to all-cause mortality and not specifically to sudden cardiac death; **NR** = not reported;

3.4.3 Death due to heart failure

The effect of intervention on death due to heart failure was reported in eleven trials (Table 14).

CRT-P

In the two larger studies undertaken in patients with severe (NYHA III/IV) heart failure, CRT-P significantly reduced the risk of death due to heart failure compared with OPT in CARE-HF (HR = 0.55 [0.37-0.82]; P = 0.003), but the reduction was not statistically significant in COMPANION (HR = 0.71 [0.46-1.09]; P = 0.15). Given that the two studies were of similar, although not identical design, and recruited individuals who were broadly similar in terms of underlying disease status, the difference in benefit of CRT in reducing heart failure deaths between the two studies is likely to be due to the short length of follow up in COMPANION (14-16 months vs. 30+ months in CARE-HF). However, when these two studies were meta-analysed by Fox *et al.*³⁴ the resulting treatment effect was significant (risk ratio 0.62 [95% CI 0.46 to 0.83]).

CRT-D and ICD

ICD therapy is not a treatment modality which improves heart function and therefore did not significantly affect the risk of death due to HF compared with OPT in SCD-HeFT. Similarly, there was no significant effect of CRT-D compared with OPT in COMPANION. A previous meta-analysis of ICD vs. OPT in a primary prevention setting conducted prior to the publication of SCD-HeFT concluded that the benefit of ICD on non-arrhythmic death was non-significant (RR 0.95 [95% CI 0.74 to 1.21]⁹⁸)

Table 14: Effect of intervention on death due to heart failure*

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio (95% CI)	P-value
CARE-HF			38/409		64/404	0.55 (0.37 -0.82)	0.003
COMPANION		52/595	53/617		34/308	0.73 (0.47- 1.11) 0.71 (0.46- 1.09)	0.11 CRT-D vs. OPT 0.15 CRT-P vs. OPT
Contak-CD		NR ¹		NR ¹		NR	NR
DEFINITE				9/229	11/229	NR	NR
MUSTIC			0/29		0/29	NR	NR
Piccirillo et al		0/16		0/15		NR	NR
RAFT		NR ²		NR ²			
RESPOND			1 ³ /29		9 ³ /31	8.41 (1.05 - 67.3)	0.0447
RETHINQ		2/87		2/85		NR ⁴	NR ⁴
REVERSE			NR ⁵	NR ⁵		NR	NR
SCD-HeFT				72/829	66/847	1.14 (0.82 -1.60)	NS (ICD vs. OPT only)

* All results n/N unless otherwise stated; **1** - 47 patients in the trial died due to heart failure during the study treatment and long term follow up phase. This finding was not reported for each intervention group;**2**- One patient died from worsening HF in the ICD group 24 hours after device implantation;**3**- Death due to heart failure after a median follow up of 677.5 days; **4**- Cumulative freedom from death due to worsening HF: CRT - D = 97.7% (91.1 to 99.4) vs. ICD = 98.8% (91.9 to 99.8) p=0.58; **5**- Cause of death not reported by intervention groups. However 3 deaths were adjudicated to be due to progressive HF.**NR** – Not reported **NS** - not statistically significant

3.5 Heart failure related hospitalisations

Twelve trials reported the effect of intervention on incidence or risk of hospitalisation (Table 15). Measures of statistical significance were reported for six of these studies and estimates of the magnitude of any treatment effect in two (CARE-HF and MIRACLE). Discussion on the relative efficacy of the interventions on hospitalisation is therefore somewhat limited.

Compared with OPT, CRT-P significantly reduced the incidence of hospitalisation in CARE-HF (HR = 0.48 [0.36-0.64]; $P < 0.001$), COMPANION ($P = 0.02$), MIRACLE (HR = 0.50 [0.28-0.88]; $P = 0.02$) and MUSTIC ($P < 0.056$).

CRT-D significantly reduced the incidence of hospitalisation compared with OPT in COMPANION ($P = 0.03$) and compared with ICD in RAFT ($P < 0.001$) and REVERSE ($P = 0.03$).

In their 2005 systematic review of the primary prevention literature undertaken on behalf of NICE, Bryant *et al.*⁹⁹ did not identify any meta-analyses reporting the results for this end point. In contrast, regardless of whether or not the information was reported as risk ratios or rate ratios, Fox *et al.*³⁴ concluded that CRT-P was effective in terms of significantly reducing heart failure hospitalisations compared to OPT (risk ratio 0.48 [95% CI 0.37 to 0.61], rate ratio 0.60 [95% CI 0.47 to 0.65]).

Table 15: Effect of intervention on incidence of hospitalisation*

Study reference	Time point	CRT-D	CRT-P	ICD	OPT	Hazard ratio(95% CI)	P-value
CARE-HF			72 ¹ /409		133 ¹ /404	0.48 (0.36 -0.64) ¹	< 0.001
COMPANION		372/595	388/617		199/308	NR	0.03 CRT-D vs. OPT 0.02 CRT-P vs. OPT
Contak-CD		32 ² /245		39 ² /245		NR	0.352
MADIT II				148 ³ /742	73 ³ /490	NR	NR
MADIT-CRT		136 ⁴ /1089		140 ⁴ /731		NR	0.59 ¹⁰
MIRACLE			18/228 ⁵		34/225 ⁵	0.50 (0.28 -0.88) ⁵	0.02
MIRACLE-ICD		85/187		78/182		NR	NR
MUSTIC			3 ⁶ /29		9 ⁶ /29	NR	< 0.056
Piccirillo <i>et al</i>		0/16		2 ⁷ /15		NR	NR
Pinter <i>et al</i>		11/36		13/36		NR	NR
RAFT		174 ⁸ /894		236 ⁸ /904		0.68 ⁸	<0.001
REVERSE		17 ⁹ /419		15 ⁹ /191		0.47 ⁹	0.03

* All results n/N unless otherwise stated; **1-** These data refers to a mean FU of 29.4 months from unplanned hospitalisation with worsening HF; **2-** The data and p- value reported refers to the number of patients with at least one hospitalisation due to progression of HF; **3-** These data refers to patient hospitalised with HF, mean follow-up 20 months; **4-** Refers to only patients who had heart failure event during hospitalisation; **5-** Hospitalisation due to heart failure; **6-** Data refers to number of hospitalisations analysed in the first period (first 12 weeks) only; **7-** Hospitalisation due to worsening HF; **8-** The hazard ratio and P value reported in the table represent patients who were hospitalised for heart failure. A total of 1018 patients were hospitalised at least once during follow up; 509 in each treatment arm. The majority of this hospitalisation was for cardiovascular reasons. A total of 404 in the ICD group and 423 in the CRT-D group were hospitalised for a cardiac cause [HR = 1.04,p -value = 0.56] in the CRT-D & ICD group respectively.; **9-** Hospitalisation due to HF. Hazard ratio not reported except for time to first hospitalisation due to HF as can be seen in the table. No data reported for CRT -P vs. OPT.; **10 -**Study used “heart failure events” definition that required intravenous drug therapy for outpatient events or proof of decongestive therapy for inpatients.

3.6 Other clinical end points

3.6.1 Change in NYHA class

Change in NYHA class was reported in 11 studies, and was reported and analysed using a variety of different end points (Table 16 to Table 19).

CRT-P

CRT-P was associated with improvements in NYHA class outcomes versus OPT in all trials where these outcomes were reported. CRT-P was associated with a significantly lower mean NYHA class than OPT after 90 days (2.1 versus 2.7, difference in means = 0.6 [0.4-0.7]; $P = 0.001$) in CARE-HF. In RESPOND, there was a significant reduction in mean NYHA class from baseline with CRT-P compared with OPT (3.34 to 2.24; $P = 0.0001$). In COMPANION, 61% of patients receiving CRT-P had improved NYHA class at 6 months, compared with 38% on OPT ($P < 0.001$). In MIRACLE, 52% and 16% of patients treated with CRT-P improved by at least one and at least two NYHA classes, respectively, compared with 32% and 6%, respectively, with OPT ($P < 0.001$).

CRT-D and ICD

CRT-D was associated with significant improvements in NYHA end points over ICD alone in four out of five trials where this was reported. CRT-D was compared with OPT in one trial, COMPANION: 57% of patients with CRT-D had improved their NYHA class at 6 months, compared with 38% on OPT ($P = 0.001$).

In MIRACLE ICD, patients with ICD whose CRT was turned on had a mean improvement in NYHA class of one, whereas patients with ICD whose CRT was turned off showed no change ($P = 0.007$). In MIRACLE ICD II, which included only patients with NYHA class II, improvement in NYHA class from baseline was greater (difference: -0.18) in patients with CRT activated compared with CRT off (difference: 0.01; $P = 0.05$). In Rhythm-ICD, the mean change in NYHA class from baseline was -0.48 with CRT-D and -0.28 with ICD ($P = 0.048$).

In RETHINQ, 54% of patients with CRT-D had improved by at least one NYHA class, compared with 29% of those with ICD ($P = 0.006$). In Contak CD, there was no difference in NYHA class outcome between CRT-D and ICD.

Table 16: NYHA class, mean (SD) value at 90 days

	CRT-P (N=409)	OPT (N=404)	Difference in means (95% CI)	P value
CARE-HF	2.1 (1.0)	2.7 (0.9)	0.6 (0.4 to 0.7)	<0.001

Table 17: NYHA at baseline and six months (mean, SD)

	CRT-P		P value	OPT		P value
	Baseline	6 months		Baseline	6 months	
RESPOND	3.34 (0.48)	2.24 (0.99)	p<0.0001	3.12 (0.43)	3.32 (0.79)	NR

Table 18: Change in NYHA class, number of pts (%) at 6 months (CRT-P and OMT only)

Miracle	CRT-P (n=213)	OPT (n=193)	P Value
Improved by two or more classes	34 (16)	12 (6)	<0.001
Improved by one class	109 (52)	62 (32)	
No change	64 (30)	115 (59)	
Worsened	4 (2)	7 (4)	

Table 19: Change in NYHA class, number of pts. (%) (CRT-D and ICD only)

RETHINQ	CRT-D (n=76)	ICD (n=80)	P value
Improved by one class or more	41 (54)	23 (29)	0.006
No Change	31 (41)	51 (64)	
Worsened	4 (5)	6 (8)	

Table 20: Change in NYHA class, number of pts. (CRT-D and ICD only)

Contak-CD	CRT-D	ICD	P Value
<i>All patients (CRT-D N=109, ICD N=116)</i>			
Improved two classes	11	2	0.10
Improved one class	25	30	
No change	51	51	
Worsened	13	17	
<i>NYHA Class III/IV at randomisation (CRT=D N=45, ICD N=48)</i>			
Improved two classes	27	4	0.006
Improved one class	47	50	
No change	22	38	
Worsened	4	8	
<i>NYHA Class I/II at randomisation (CRT=D N=64, ICD N=68)</i>			
Improved two classes	-	-	0.84
Improved one class	9	16	
No change	72	60	
Worsened	19	24	

Table 21: Improvement at 6 months in NYHA class symptoms (%)

	CRT-D (n=497)	CRT-P (n=489)	OPT (n=199)	P value
COMPANION	57	61	38	P<0.001 (CRT-P vs. OPT) P<0.001 (CRT-D vs. OPT)

Table 22: Change in NYHA class - baseline and 6 months (median, 95% CI)

	CRT-D (n=165)	ICD (n=162)	P value
MIRACLE-ICD	-1(-1 to -1)	0(-1 to 0)	0.007

Table 23: Change in NYHA class - baseline and 6 months (mean, SD)

	CRT-D		ICD		P value
	No. of patients	value	No. of patients	value	
MIRACLE-ICD II	82	-0.18(0.61)	98	0.01 (0.63)	0.05
Rhythm-ICD	83	-0.48 (0.65)	43	-0.28 (0.63)	0.048

Table 24: Percentage of patients that worsened/improved NYHA at 12 months

REVERSE	CRT-D (n=419)	ICD (n=191)	P Value
Worsened	10	9	NR
Improved	14	15	NR

Table 25: NYHA class distribution after one year of treatment (number of pts)

Piccirillo <i>et al.</i>	ICD		CRT-D	
	Baseline	One year	Baseline	One year
NYHA class, I	0	0	0	1
NYHA class, II	0	1	0	1
NYHA class, III	5	1	5	6
NYHA class, IV	10	13	11	6

3.6.2 Change in LVEF

The effect of intervention on change in LVEF from baseline was reported in 14 studies (Table 26).

CRT-P

In MIRACLE, patients in the CRT-P arm had a mean increase in LVEF of +4.6%, compared with a mean reduction of 0.2% with OPT (P < 0.001). At 18 months of follow up, CARE-HF noted a difference in mean LVEF of +6.9% ([5.6 – 8.1] P = <0.001) between the CRT-P arm and the OPT arm. However, there was no significant difference between CRT-P and OPT in terms of LVEF change in RESPOND.

CRT-D versus ICD

CRT-D was associated with significantly greater LVEF improvement compared with ICD in Contak-CD (all patients; P=0.02 and those with NYHA class III or IV; P=0.029 difference in patients with NYHA class I or II was not significant); in

MIRACLE-ICD II (3.8% with CRT-D versus 0.8% for ICD, $P = 0.02$); and in REVERSE (mean LVEF at 12 months 31.8% and 27.0% with CRT-D and ICD respectively; P for change from baseline < 0.01). In MADIT-CRT, LVEF change was 11% with CRT-D and 3% with ICD only ($P = 0.0001$).

There was no significant difference in LVEF outcome between CRT-D and ICD in MIRACLE ICD, Pinter *et al.* or RETHINQ.

Table 26: Effect of intervention on change in LVEF

Study	Time point	CRT-D	CRT-P	ICD	OPT	P-value	Comments
	18 months						Difference in means (95% CI)
CARE-HF			NR		NR	< 0.001	+6.9 (5.6 to 8.1)
Contak-CD (all patients)		5.1 (0.7) ^a		2.8 (0.7) ^a		0.02	
Contak-CD (NYHA I/II)		4.7 (0.9) ^a		2.9 (0.9) ^a		0.16	
Contak-CD (NYHA III/IV)		6.0 (1.1) ^a		2.3 (1.2) ^a		0.029	
MADIT-CRT	12 months	11 ^d (0.05) ^a		3 ^d (0.03) ^a		0.0001	
MIRACLE			+4.6 (+3.2 to +6.4) ^b		-0.2 (-1.0 to +1.5) ^b	< 0.001	
MIRACLE-ICD	6 months	2.1 (1.2 to 4.1) ^b		1.7 (0.7 to 2.4) ^b		0.12	
MIRACLE-ICD II	6 months	3.8 (8.0) ^a		0.8 (6.2) ^a		0.02	
Piccirillo et al	12 months	Baseline: 23 (4) ^a Study end: 28 (4) ^a		Baseline: 22 (8) ^a Study end: 22 (8) ^a		ICD arm NS, CRT-D arm <0.05	
Pinter et al	6 months	3.9 (8.9) ^a		1.9 (6.8) ^a		NS	
RESPOND			6.72 (18.4) ^c		5.37 (10.4) ^c	0.7533	
RETHINQ		1.2 (-0.4 to 4.4) ^b		2.0 (0.3 to 4.2) ^b		0.83	
REVERSE	12 months	Baseline: 27.2 (6.6) ^a Study end: 31.8 (8.8) ^a		Baseline: 26.4 (6.7) ^a Study end: 27.0 (7.1) ^a		< 0.01	
Rhythm-ICD	6 months	4.3 (9.9) ^a		2.9 (6.2) ^a		NR	

a - mean (SD); **b**- median (95% confidence interval); **c**- median (interquartile range); **d** – (percentage)

3.6.3 Incidence of ventricular tachycardia/ventricular fibrillation (VT/VF)

Cross-study interpretation of results is difficult due to the lack of consistent reporting (Table 27). Nonetheless, some general points arise.

It has been proposed that CRT may prevent ventricular arrhythmias⁸³. The only trials to report a statistical analysis of the rates of VT/VF incidence between treatment arms were CONTAK-CD, MIRACLE ICD, MIRACLE ICD II and REVERSE. All compared the incidence of spontaneous VT or VF in patients on CRT-D versus ICD, and all found no significant difference between the two.

Table 27: Effect of intervention on incidence of VT/VF (n/N)

Study	CRT-D	CRT-P	ICD	OPT	P-value	Comments
AMIOVIRT			18/51	2/52	NR	In ICD group, this refers to 16 patients who received appropriate therapy for VA and 2 patients who had syncope due to VT. While in OPT, 2 patients had an ICD implanted due to documented VT
CAT			17/50	NR	NR	Refers to 11 patients who received adequate therapy for VTs > 200bpm, and 6 patients who had syncope during VT
Contak-CD	36/245		39/245		NS	Those patients in the CRT-D group who experienced VT/VF had a median of 2.5 episodes while those in the ICD group had a median of 2 episodes.
DEFINITE			NR	NR	NR	Three and fourteen patients in the ICD and OPT group had arrhythmia. Type was not specified
MADIT II			NR	21/490		Twenty one patients received a defibrillator for documented or suspected malignant VA
MIRACLE-ICD	42/187		47/182		0.47	Pertains to patients who experienced at least one episode of ventricular tachycardia or fibrillation.
MIRACLE-ICD II	19/85		26/101		0.61	Related to individuals who experienced at least one appropriately detected, spontaneous episode of VT/VF
Piccirillo <i>et al</i>	2/16		4/15		NR	Individuals receiving appropriate ICD shocks for sustained VT/ VF
Pinter <i>et al</i>	7/36		6/36		NS	Number of patient requiring therapy from their device.
RESPOND		NR/29		1/31	NR	One patient in the OMT group crossover to the CRT-P with defibrillator backup after development of a sustained ventricular tachycardia
REVERSE	54/345		24/163		0.09	There were 196 and 114 adjudicated episodes of VT/ VF in the CRT-D and ICD group respectively. Of note, the non-significant difference is likely to have arisen due to the 2:1 randomisation mechanism.
SCD-HeFT			177/829	95/847	NR	The number of individuals who had VT/VF in the OPT group could be more than the reported number.. The figure reported here refers to incidence of ventricular tachyarrhythmia leading to sudden death. In the ICD group, it refers to those who received shocks from their device for rapid VT/VF

NS - not statistically significant; **NR**- Not Reported

3.7 Health related quality of life

3.7.1 EQ-5D

Three trials collected HRQoL data using the EQ-5D instrument. Data from two of these (RAFT and MADIT-CRT) is not yet in the public domain. These data are re-discussed in the section on the IPD analysis relating to the modelling of HRQoL. Mean EQ-5D scores from CARE-HF are shown in Table 28. Patients receiving CRT-P reported significantly higher scores than those on OPT (mean difference (95% CI) 0.13 (0.08, 0.18) $p < 0.0001$). This size of difference is generally considered highly clinically significant with EQ-5D.

Table 28: Health related quality of life: EQ-5D instrument (mean (95% CI))

Study	Time point	CRT-D	CRT-P	ICD	OPT	P-value	Comments
CARE-HF	3 months		0.56 (0.52-0.59)		0.43 (0.39-0.46)	< .0001	Mean difference (95% CI) 0.13 (0.08, 0.18)

3.7.2 Change in MLWHF

Information on health related quality of life was also collected using the Minnesota Living With Heart Failure (MLWHF) instrument. While not a direct representation of the utility associated with different treatment/disease severity combinations, these data are informative as to the likely benefit of treatment on HRQoL, and hence can be used to both infer utility and to validate the results from the IPD analyses.

At six months, individuals in the COMPANION clinical trial⁵¹ with either a CRT-P or CRT-D reported an approximate 25% improvement in MLWHF ($p < 0.001$ compared to OPT). Similar impressive results were observed in the active treatment arms of the MIRACLE and MIRACLE-ICD trials (absolute changes of -18 and -13.3% respectively). Thus, CRT has a strong impact on an individual's HRQoL, and the results for CRT-D from the smaller clinical trials support this conclusion.

Information on the impact of ICD on MLWHF scores was available from ten studies. Young *et al.*⁸³ analysed data using two different methods and reported a significant improvement associated with ICD treatment in both (absolute change = -11). This change was also significantly less than observed for CRT-D. In contrast, Abraham *et al.*⁴⁴ reported a similar improvement (-10.7) but the result was not significantly different to that observed for CRT-D. It is important to note, however, that the two studies were undertaken in different patient groups and may not be directly comparable.

Higgins *et al.*⁶⁰ reported the results from the CONTAK-CD (change in MLWHF scores) by all patients and by disease severity (NYHA I/II and III/IV). This study is thus informative in assessing the impact of treatment in different patient groups. While there was no significant difference between the two treatments in the overall group ($p = 0.39$), when the results for each subgroup are assessed the impact of treatment is significant in the more severely ill patients ($p = 0.017$) and not in the less severely ill ($p = 0.26$).

Table 29: Absolute MLWHF scores by study

Study	Time point	CRT-D	CRT-P	ICD	OPT	P- value	Comments
	End of study						
CARE-HF			27.2 (24.9-29.5)		35.1 (32.6-37.6)	< 0.0001	Mean (95% CI). Individuals who died were not included in the analysis. Mean difference (95%CI) -10.1 (-6.8 -13.3)
MUSTIC	3 months		29.6 (21.3)*		43.2 (22.8)	< 0.001	Mean (SD). Data analyzed amongst 45 patients in the CRT-P and OPT group.
RESPOND	6 months		44.6 (30.0)*		62.1(27.7)*	0.0265	Mean (SD)

Table 30: Effect of intervention on change in MLWHF scores*

Study	Time point	CRT-D	CRT-P	ICD	OPT	P- value	Comments
COMPANION	6 months	-26% (28)	-25%(26)		-12% (23)	<0.001 <0.001	CRT-D vs. OPT ICD vs. OPT
Contak-CD (all patients)		-7 (2)		-5 (2)		0.39	
Contak-CD (NYHA I/II)		-1 (2)		-4 (2)		0.26	
Contak-CD (NYHA III/IV)		-16 (3)		-5 (3)		0.017	
MIRACLE	6 months		-18 (-22 to -12)		-9 (-12 to -5)	0.001	median (95% CI)
MIRACLE-ICD	6 months	-17.5 (-21 to -14)		-11 (-16 to -7)		0.02	median (95% CI)
MIRACLE-ICD II	6 months	-13.3 (25.1)		-10.7 (21.7)		0.49	
Pinter <i>et al</i>	6 months	-7.8 (20.1)*		-0.2 (13.5)*		NS	
RETHINQ	6 months	-8 (-10 to -1)		-7 (-11 to 3)		0.91	median(95% CI)
REVERSE	12 months	-8.4 (17.1)		-6.7 (15.9)		0.26	
Rhythm-ICD	6 months	-7.8 (22)		+3.4 (31)		0.009	

* All results mean (SD) unless otherwise stated; NS – Not significant

Table 31: Effect of intervention: change in MLWHF dimension scores (mean (SD))

Study	Time point	CRT-D	CRT-P	ICD	OPT	P- value	Comments
DEFINITE	Approx. 3 month			ES: -0.8 (0.1) PS: -1.5 (0.2);	ES: -0.7 (0.1); PS: -1.6 (0.2);	NS in long term HRQL	After 3 months, emotional score remained stable in both groups and physical scores decreased in both groups

3.8 Device- and procedure-related adverse events

All trials except one (RESPOND) collected and reported adverse events data. Due to differences in the methods of reporting it is difficult to directly compare and/or summarise the findings of the various trials. Adverse events reported in the trials are presented in detail in Appendix 5. Here we present a brief narrative overview, including information from previous meta-analyses.

CRT-P and CRT-D

In the five RCTs assessed for TA120 (CARE-HF, COMPANION, MIRACLE, MUSTIC-SR, CONTAK-SD), the estimated rate of perioperative death associated with CRT (CRT-P and CRT-D pooled) was 0.8% (95% CI 0.5% to 1.2 %). CRT devices were implanted successfully on average in 90.8% of patients (95% CI 89.6% to 92.0%).¹⁰⁰ The most common causes of implant failure were related to the placement of the left ventricle (LV) lead, and the most common postoperative event was lead dislodgement. The COMPANION trial reported no significant difference in the rate of device- and surgery-related adverse events between CRT-P (10% compared with optimal pharmacological therapy) and CRT-D (8% compared with optimal pharmacological therapy). In COMPANION, 69%, 66% and 61% of patients in the CRT-D, CRT-P and OPT arm respectively experienced moderate to severe adverse events from any cause (including those arising from patients' underlying condition).

In REVERSE there was a 97% overall implantation success rate, with 26 peri-procedural complications among the 642 patients (4%) who underwent an implant attempt. After implantation and during the 12-month follow-up, 101 of the 621 successfully implanted patients (16%) experienced a total of 138 procedure or system-related complications. One complication resulted in death. After implantation, and during the 24-month follow-up, 26 of the 262 successfully implanted patients experienced a total of 30 device-related serious adverse events (SAEs). The percentage of patients with SAEs in the CRT-ON versus CRT-OFF study groups were similar ($P=0.66$). At the time of study closure, 29 of the 30 post-implant, device-related serious adverse events were resolved. Because most patients in REVERSE had a primary prevention indication for an ICD, the added risk of implanting a CRT device was related to the LV lead. This

risk was relatively low, with an LV lead-related complication rate of 10% over the 12 months for the complete study population.

ICD and CRT-D

Serious adverse events due to ICDs were reported infrequently in the trials assessed for TA95³³. Recorded complications included infection, haematomas and bleeding, lead dislodgement and migration, cardiac perforation, pleural effusion and pneumothorax, and device dysfunction/malfunction of the generator.

In RAFT, during the first 30 days after device implantation, there were 13.3% device or implantation related complications among patients in the CRT-D group and 6.8% patients in the ICD group. The number of device-related hospitalisations over the entire study period was higher in the CRT-D group (20.0%), as compared with in the ICD group (12.2%). One death from worsening HF occurred in the ICD group within 24 hours of device implantation.

In MADIT-CRT there was successful implantation of a device in 98.4% of patients. During long-term follow-up after the first 30 days, serious device-related adverse events occurred with a frequency of 4.5 per 100 device-months in the CRT-D group and of 5.2 per 100 device-months in the ICD-only group. Of 1079 CRT-D patients that were included in the safety end point of MADIT-CRT, 164 patients (15.2%) experienced 214 system-related complications within 90 days post-implant. Left ventricular lead problems following implantation were reported in 4% of patients in a 30-day period. Device related infections occurred in 1% of CRT patients within 30 days of implantation. One death, due to pulmonary embolism, occurred in the CRT-D group.

Peri-implantation mechanical complications, including pneumothorax, coronary dissection, and pericardial tamponade occurred with a 1% frequency in the REVERSE trial, and 2% in MADIT-CRT.

Another problem associated with ICD implantation is inappropriate shock therapy, mostly for atrial fibrillation with rapid ventricular response but also for various other reasons. The occurrence of inappropriate shocks varies across studies in between 0.5 and 19% of patients within 30 days of implantation, and in 14% thereafter.

3.9 Long-term follow-up data on mortality

A major uncertainty in CRT and ICD therapy is the duration of any observed treatment effect on mortality. Long-term follow-up data on mortality from MADIT-II is in the public domain. For CARE-HF, a copy of a manuscript in preparation containing long-term data has been made available. These data are summarised below. Some long-term data from SCD-HeFT were presented at a recent international meeting but relative efficacy estimates (hazard ratios or relative risks) were not presented, so data from this study has not been included here.

3.9.1 CARE-HF

CARE-HF carried out long-term follow-up from 2005 until September 2009. The median potential follow-up, disregarding death or censorship, was 90 months. Median follow-up with censoring for death or loss to follow-up was 50 months in the control group and 56 months in the CRT-P group.¹⁰¹ Of 813 patients originally enrolled, 558 were alive at the end of the main study and a short post-trial observation phase. For the long-term follow-up, 111 (24% of those not known to be dead) could not be contacted, and 50 (11%) declined to participate. Of patients originally assigned to the control group (OPT), 156 were known to have received CRT during or after the trial.

In all, 222 patients in the OPT group and 192 patients assigned to CRT-P were known to have died since randomisation. The hazard ratio for death in patients originally randomised to CRT compared to those randomised to OPT was 0.768 (95% CI 0.633 to 0.931; $P = 0.007$). At five years, mortality was 43.9% in the original OPT group compared to 32.2% in those assigned to CRT. At 6.5 years mortality was 56.3% and 49.1% respectively, and at eight years mortality was 61.8% and 54.8%. The greatest divergence between the survival curves was at 3 years. No significant differences between patient subgroups were found, except that patients below the median age at randomisation survived longer. Patients assigned to CRT had a more favourable outcome regardless of age.

Therefore, a highly clinically significant survival benefit for original treatment with CRT persisted at a median of 50-56 months from randomisation and beyond, despite the fact that almost all surviving patients in the OPT group received CRT after the study.

3.9.2 MADIT II

An 8-year follow-up study was published of MADIT II.¹⁰² During the 3.5-year period of the study, ICD was associated with an average survival gain of only 0.167 years (2 months). Information on post-trial mortality as of September 2009 was obtained for all patients in the study (median follow-up 7.6 years, total follow-up of 7815 patient-years).

Of the 742 patients randomised to ICD, 22 patients did not receive an ICD and 13 had the ICD extracted during the trial. In the medical therapy arm (n=490), 27 patients crossed over to the ICD arm during the trial, and 140 received an ICD within 4 months after trial closure. Fewer than 5% of patients are thought to have crossed between treatment arms during the subsequent follow-up.

At 8 years of follow-up, all-cause mortality was 49% among patients treated with an ICD compared with 62% among non-ICD patients ($P < 0.001$). Multivariate analysis showed that ICD was associated with a significant long-term survival benefit (HR for 0- to 8-year mortality=0.66 [95% CI 0.56 to 0.78]; $P < 0.001$). ICD was found to be associated with a significant reduction in the risk of death at up to four years (HR =0.61 [95% CI 0.50 to 0.76]; $P < 0.001$), and with a continued survival benefit from 5 to 8 years (HR =0.74 [95%CI 0.57 to 0.96]; $P = 0.02$).

These findings demonstrate a sustained 8-year survival benefit with primary ICD therapy in the MADIT-II population.

4 Analysis of individual patient level data

- We carried out a meta-analysis of individual patient level data (IPD) from 13 clinical trials (12,638 patients, followed up for up to 7.5 years) – the first such analysis ever undertaken in CRT/ICD therapy.
- We believe that the power of the IPD approach means these are the best and most robust data available on the treatment effects of CRT and ICD devices in the different subgroups of patients with heart failure.

All-cause mortality

- The objective of the mortality analysis is to understand how the use of CRT-P, ICD, and CRT-D impact on the overall survival (OS) curve of different patient groups eligible for these devices.
- Synthesising IPD as opposed to aggregating published data is necessary in order to capture the differences in baseline risk and relative treatment effects across the highly heterogeneous patient population eligible for these devices.
- A baseline risk analysis was conducted in order to predict mortality risk over time for patients receiving OMT (3,477 patients, followed up for up to up to 6.1 years). This analysis found NYHA class, ischaemia, QRS duration and left ventricular ejection fraction (LVEF) all to be highly significant predictors of survival times, along with patient age and gender.
- The aim of the network meta-analysis was to estimate the relative treatment effects comparing each device to the other devices, and to OMT.
- Details of methods and analyses are presented.
- The network meta-analysis found CRT-D to have the strongest effect on all-cause mortality, with a hazard ratio of [REDACTED]
- Age, gender and QRS morphology (both QRS duration and LBBB status) were found to be independently predictive of the magnitude of benefit associated with the devices. The impact of QRS duration and LBBB is attributable to CRT.

- A summary of key findings on the treatment effects of each device type on all-cause mortality for different patient subgroups is given in Section 4.6.2

All cause hospitalisation

- For the base case, hospitalisation was modelled as number of events per month; a days per month approach was also performed as a sensitivity analysis. Hospitalisation rate in patients receiving OMT only was taken as the baseline rate.
- Treatment effects on hospitalisation rate were derived for each device in each NYHA class (NYHA I/II were pooled). These were used to create probabilities for use in the economic model.
- Across all NYHA classes, device therapy was associated with a reduction in admission rates.
- In NYHA classes I to III, ICD was associated with a [REDACTED] reduction in monthly admission rates, and CRT with a [REDACTED] reduction.
- The effect in NYHA class IV was even more pronounced, with CRT offering a [REDACTED] reduction in monthly admission rates.

Health Related Quality of Life

- As noted in Section 3.7, individual studies showed significant HRQoL improvements for devices, compared to baseline regardless of instrument used. The primary HRQoL analysis used EQ-5D data only. Potential mapping approaches using MLWHF data were not possible due to the absence of an algorithm.
- For ICD based treatment in NYHA classes I/II, improvement in MLWHF existed for approximately [REDACTED] years. In NYHA classes III/IV, the duration of benefit was approximately [REDACTED] years.
- After accounting for placebo effects, CRT had a strong impact on HRQoL [REDACTED] in NYHA classes I/II; [REDACTED] in NYHA classes III/IV).
- There was also a small positive impact of ICD therapy in patients with NYHA classes I/II [REDACTED], but not for patients with NYHA classes III/IV (hence any extension of life in these patients will have the same HRQoL as would be observed on OPT).

4.1 Introduction

As part of the joint submission, individual patient data from 12,638 patients recruited into 13 clinical trials were made available for the purpose of model construction.^{8;43;44;47;49;51;54;60;64;67;79;80;83} This is the first network meta-analysis of individual patient data ever conducted in the field of CRT/ICD devices, and as such represents a powerful tool for generating new insights into this major body of clinical data. It was made possible by the decision of all the major device manufacturers to make available their proprietary data, in the interests of obtaining the best possible information on the treatment effects and cost-effectiveness of the three device classes in different subgroups of the heterogeneous population of patients who have heart failure.

The analysis was a major undertaking, and such an approach would not be warranted for the majority of health technology assessments. However, it was felt that the nature of the evidence and the value of the information to be gained justified the resources needed. In particular, the high degree of patient heterogeneity inherent in heart failure (such as the wide difference between patients in NYHA class I and class IV) is a strong indicator for an individual patient data approach¹⁰³.

The IPD analysis aimed both to confirm the existing evidence and to address previously unanswered questions. In particular, we hoped to gain new insight into:

- What is the risk of death over time in different patients groups?
- What is the relative efficacy of each intervention compared to OMT in terms of all-cause mortality reduction, and does this differ by patient group?
- How does health related quality of life vary by device and patient group?
- How does the rate of all cause hospitalisation vary by device and patient group?

The analyses of each of these three categories are discussed separately below.

4.2 Mortality

4.2.1 Objective

The objective of the individual patient data (IPD) mortality analysis is to understand how the use of CRT-P, ICD, and CRT-D impact on the overall survival (OS) curve for different patient groups receiving these devices.

Synthesising IPD as opposed to aggregating published data is necessary in order to capture the differences in baseline risk and relative treatment effects across the highly heterogeneous patient population receiving these devices. This would not have been possible using published subgroup data: subgroup analyses were not consistently reported across trials, and even where available would not have allowed a multivariate analysis to be performed. A multivariate analysis is necessary to simultaneously assess the impact of each characteristic of a presenting patient on their expected outcome.

Previous NICE guidance and other guidelines have made recommendations regarding use of the devices in specific subpopulations based on the inclusion criteria of individual trials and reported subgroup analyses. The availability of IPD allows for a more formal synthesis of these data, in their entirety, rather than relying on a more informal qualitative synthesis of the available data. This is particularly important in the context of cost-effectiveness analysis, where it is important to not only understand which patient characteristics impact on outcomes, but to estimate the magnitude of impact of different patient characteristics.

4.2.2 Terminology

The following terminology is used throughout the discussion of the mortality analysis:

- Baseline risk – the risk of mortality for patients receiving OMT (optimal medical therapy; also referred to elsewhere as OPT).
- Treatment effect – the impact (relative to OMT) of device implantation (ICD, CRT-P or CRT-D) on mortality as measured on the hazard ratio scale.
- Covariable – a patient characteristic known at baseline that is expected to impact on either the baseline risk of mortality, the treatment effect of a device

on mortality or both.

- Baseline-risk modifier – a covariable that alters the risk of death for patients receiving OMT.
- Treatment effect modifier – a covariable that alters the hazard ratio for a device compared to OMT.

4.3 Overview of methods

4.3.1 Data

4.3.1.1 Network of evidence

All trials identified by the systematic review (see Section 3) were considered for inclusion in the network meta-analysis. The network of evidence formed by these trials is presented as Figure 12. All trials compared two devices with the exception of COMPANION which compared CRT-D, CRT-P and OMT.

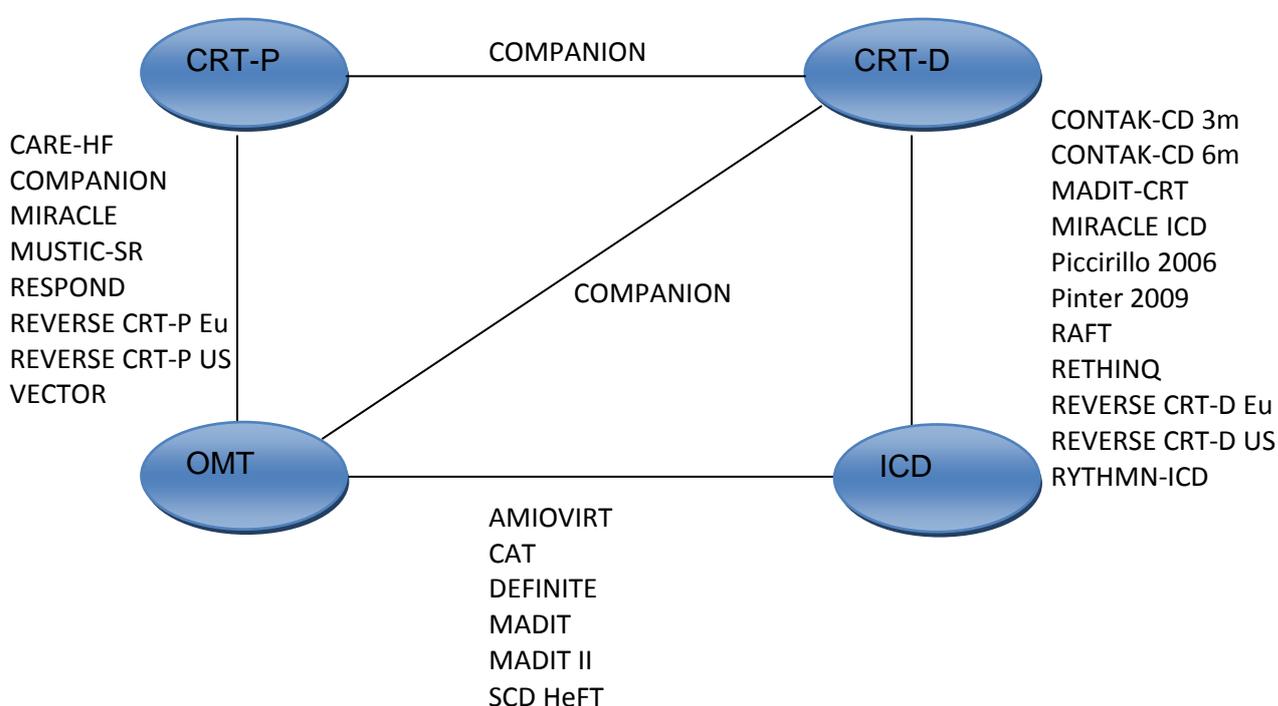
The following trial-specific study design issues should be noted when interpreting the figure:

- CONTAK-CD enrolled patients into two study designs (phases). In both study designs all patients received a CRT-D device and were randomised to CRT 'on' or CRT 'off'. Patients were initially enrolled in to a cross-over design with patients crossing over to CRT 'on' or 'off' at three months (Phase 1). However, part-way through the trial patients were enrolled into a six month parallel group trial (Phase 2). As CONTAK-CD was therefore effectively two different trials, these are included separately in the network meta-analysis as CONTAK-CD Ph 1 and CONTAK-CD Ph 2.
- MIRACLE ICD and MIRACLE ICD II, although reported in separate publications, actually describe a single trial. This is therefore labelled as MIRACLE ICD and considered as a single trial in the analysis.
- The REVERSE trial allowed physicians to select a CRT-P or CRT-D device. Patients were then randomised to CRT-ON or CRT-OFF. As the trial did not randomise patients across the four therapies they received (OMT, CRT-P, ICD, CRT-D) there is effectively a "REVERSE CRT-D" and a "REVERSE CRT-P" trial. This trial is further split in to European (EU) and US trials for the analysis due to the different protocol-specified durations of follow-up in these

geographies (24 months and 12 months respectively). There are therefore effectively four REVERSE trials in the analysis “REVERSE CRT-D US”, ”REVERSE CRT-D EU”, ”REVERSE CRT-P US”, ”REVERSE CRT-P EU”.

- The SCD HeFT trial randomised patients to three arms: conventional therapy plus placebo; conventional therapy plus amiodarone and conventional therapy plus ICD. Based on clinical advice and the all-cause mortality endpoint results from this study (amiodarone vs. placebo hazard ratio 1.06 (95% CI 0.86-1.30)) the amiodarone and placebo arms of this trial are pooled in the analysis.

Figure 12: Network of randomised controlled trials



As documented in the systematic review, the trials included were first reported between 1996 (MADIT) and 2010 (RAFT). Clinical experts were consulted to ascertain whether the devices were likely to have changed during this period in a way that would modify the relative treatment effects. The clinical experts indicated that the impact of the devices on mortality was unlikely to have changed over this period. The main technological advances have increased procedural success rates and device longevity, and reduced inappropriate shocks associated with ICD therapy.

4.3.2 Availability of IPD

We obtained IPD from 13 of the 22 trials identified by the systematic review. Data

were requested from the device manufacturers using a standardised data sheet. Boston Scientific provided data from the following trials: COMPANION, CONTAK-CD, MADIT, MADIT II; and MADIT-CRT. Medtronic provided data from: CARE-HF, MIRACLE, MIRACLE-ICD, RAFT, REVERSE, and SCD-HeFT. St. Jude Medical provided data from DEFINITE and RethinQ.

The IPD trials include 95% of the total number of patients included in the network. This reflects the fact that the trials for which IPD were not available were relatively small (see Table 32).

Table 32 describes the numbers of patients included in the analysis for each trial. These replicate the primary analyses of each trial.

The data set including the 22 trials identified by the systematic review is referred to as the 'All Trials' data set. The data set including trials for which IPD were available is referred to as the 'IPD Trials' data set.

The reasons for IPD not being available are documented below:

- CAT, Piccarillo *et al.* – these trials were not sponsored by manufacturers contributing to this submission (the former was funded by the University of Michigan and the latter's funding was not stated).
- AMIOVIRT, MUSTIC-SR, Pinter *et al.*, RHYTHM-ICD- these studies were sponsored by the submitting manufacturers (Boston Scientific, Medtronic, Guidant Corporation (part of Boston Scientific) and St Jude Medical, respectively). However, the data were not included in the analysis as they were not available (AMIOVIRT, Pinter *et al.*), or the available IPD databases were not thought to be of sufficiently reliable quality for inclusion (MUSTIC-SR, RHYTHM-ICD), where in both cases the available data sets could not be reconciled with the published data.
- VECTOR and RESPOND - the systematic review did not identify the studies until after the database had been assembled and it was not therefore feasible to include these studies in the IPD in the analysis.

Despite the unavailability of individual patient data from these studies, as shown in Table 32 the IPD contains 95% of the patients included in the RCT evidence base.

Table 32: Trials included in network meta-analysis - IPD availability

Trial / Device	CRT-D	CRT-P	ICD	OMT	Total
<i>IPD available (number of patients)</i>					
CARE-HF ⁸	0	409	0	404	813
COMPANION ⁵¹	595	617	0	308	1,520
CONTAK_CD ph1 ⁶⁰	111	0	104	0	215
CONTAK_CD ph2 ⁶⁰	134		141	0	275
DEFINITE ⁶²	0	0	229	229	458
MADIT ⁶⁸	0	0	95	101	196
MADIT-CRT ⁶⁶	1,089	0	731	0	1,820
MADIT II ⁷¹	0	0	742	490	1,232
MIRACLE ⁴³	0	228	0	225	453
MIRACLEICD ⁴⁴	272	0	283	0	555
RAFT ⁸⁰	894	0	904	0	1,798
RethinQ ⁴⁹	87	0	85	0	172
REVERSE CRT-D US ⁶⁴	227	0	104	0	331
REVERSE CRT-D Eu ⁶⁴	118	0	59	0	177
REVERSE CRT-P US ⁶⁴	0	12	0	5	17
REVERSE CRT-P Eu ⁶⁴	0	62	0	23	85
SCD-HeFT ⁴⁸	0	0	829	1,692	2,521
Total	3,527	1,328	4,306	3,477	12,638
<i>IPD Not available (number of patients)</i>					
AMIOVIRT ⁷⁹	0	0	51	52	103
CAT ⁴⁷	0	0	50	54	104
MUSTIC-SR ⁵⁴	0	29	0	29	58
Piccirillo 2006 ⁷⁴	16	0	15	0	31
Pinter 2009 ⁷⁵	36	0	36	0	72
RESPOND ⁵⁹	0	29	0	31	60
RHYTHM-ICD ¹⁰⁴	119	0	59	0	178
VECTOR ⁴⁰	0	59	0	47	106
Total	171	117	211	213	712

4.3.3 Follow-up

The longest available follow-up (primary endpoint analysis) was requested from all manufacturers in the data request form. Longer follow-up has the potential to provide more information regarding long-term baseline risk and treatment effects than the original trial publications¹.

¹ No long term follow-up was provided for CARE-HF though this has been published^{57;105}. 8

Cross-over from the control to active arm may lead to improvements in outcomes in the control arm that would not be observed in a true parallel group design. A review of the rates of cross-over in the trials suggested that use of the longest follow-up may be susceptible to bias. Cross-over was observed to be particularly high in trial designs where the active arm device was implanted for all patients with control arm patients receiving none or only part of the device functionality ('on/off' design). In these trials, almost all patients in the control arm crossed over once patients were unblinded.

Table 33 shows the proportion of patients receiving an 'upgrade' during the trial follow-up provided. An upgrade was defined as a switch from OMT to an active device (ICD, CRT-P or CRT-D); a switch from ICD to CRT-D or a switch from CRT-P to CRT-D.

Table 33: Cross-over during follow-up provided for IPD Trials

Trial	On/Off design?	% Upgrade in control arm
CARE-HF	No	13% (OMT)
COMPANION	No	34% (OMT) 7% (CRT-P)
CONTAK_CD ph1	Yes	NA
CONTAK_CD ph2	Yes	NA
DEFINITE	No	12% (OMT)
MADIT	No	NA
MADIT-CRT	No	16% (ICD)
MADIT II	No	6% (OMT)
MIRACLE	Yes	91% (OMT)
MIRACLEICD	Yes	94% (ICD)
RAFT	No	11% (ICD)
RethinQ	Yes	NA
REVERSE CRT-D US	Yes	100% (ICD)
REVERSE CRT-D Eu	Yes	98% (ICD)
REVERSE CRT-P US	Yes	100% (OMT)
REVERSE CRT-P Eu	Yes	96% (OMT)
SCD-HeFT	No	11% (OMT)

Based on this information, only the protocol specified original 'data lock' follow-up

year follow-up of MADIT II has been published¹⁰², however this was not supplied for this analysis as the follow-up data are not owned by Boston Scientific.

was included in the analysis, i.e. beyond the date or follow-up time periods specified for database-lock all patients are censored. This is expected to limit the amount of cross-over as within these periods blinding and/or protocol requirements limited the amount of cross-over observed.

The date or time period cut-offs used are provided as Table 34, along with the median follow-up times available once the database-lock cut-offs are applied. These ranged from 3 to 40 months across trials. For some trials, longer term follow-up has been reported in the literature, this information is summarised in section 3.9.

Table 34: Follow-up period used in analysis of IPD Trials dataset

Trial	Database lock	Median follow-up^a	Availability of longer follow-up in literature
CARE-HF	Sept 30 th 2004	25 months	Yes
COMPANION	Dec 1 st 2002	16 months	No
CONTAK_CD ph1	3 months follow-up	3 months	Yes
CONTAK_CD ph2	6 months follow-up	6 months	No
DEFINITE	May 25 th 2003	27 months	No
MADIT	March 24 th 1996	24 months	No
MADIT-CRT	June 22 nd 2009	29 months	No
MADIT II	Nov 20 th 2001	18 months	Yes
MIRACLE	6 months follow-up	6 months	No
MIRACLEICD	6 months follow-up	6 months	No
RAFT	Not specified	39 months	No
RethinQ	6 months follow-up	6 months	No
REVERSE CRT-D US	12 months follow-up	12 months	No
REVERSE CRT-D Eu	24 months follow-up	24 months	No
REVERSE CRT-P US	12 months follow-up	12 months	No
REVERSE CRT-PEu	24 months follow-up	24 months	No
SCD-HeFT	Oct 31 st 2003	41 months	No ^b

a) calculated from IPD, includes all patients with all patients still alive censored at database lock; **b)** 10 year follow-up of SCD-HeFT is expected to become available during the course of this appraisal.

As the dataset requested comprised the longest follow-up available for most trials, rather than the protocol specified analysis, a comparison of the deaths in each trial in the database (up to the database lock point) with the trial publications was conducted. Exact replication was possible for all trials with the exception of the MADIT trial (2 additional deaths in the ICD arm were thought to have occurred prior to database lock but have been reported afterwards) and

REVERSE (not possible to reconcile as data reported in publications¹⁰⁶ refers to two non-mutually exclusive populations).

4.3.4 Covariables considered

Previous NICE appraisals of the devices^{35,36} have made recommendations for specific subgroups of patients. It is important that our analysis captures any covariables that are likely to be baseline risk modifiers or treatment effect modifiers in order to both address heterogeneity between trials and to aid accurate prediction of cost-effectiveness in subgroups.

However, it is important to note that inclusion of unimportant covariables increases both uncertainty in parameter estimates and the number of subgroups for which predictions are made². For both of these reasons a parsimonious model is preferred.

Based on covariables used to define previous NICE recommendations, a review of existing risk scores, a review of treatment effect modifiers in previous RCTs and clinical opinion from two clinical specialists, the following covariables were identified as important for consideration in the analysis:

- Age
- Gender
- Country (US vs. non-US)
- New York Heart Association (NYHA) class
- Ischaemic aetiology
- Left ventricular ejection fraction (LVEF)
- QRS
- Left bundle branch block (LBBB)

Key variables not considered further, and the reasons for this, are provided below:

- History of MI – this is highly correlated with ischaemic aetiology. The clinical

² For example, inclusion of ischaemia (yes/no); NYHA (1/2/3/4); gender and an age covariable split in to five levels results in 80 subgroups (2 x 4 x 2 x 5).

experts consulted suggested that ischaemic aetiology may be a more reliable covariable as MIs may not be recorded in many cases. In addition, ischaemic aetiology was missing in fewer cases than history of MI (6.4% vs. 22.5%).

- History of atrial fibrillation (AF) – history of AF as opposed to current AF was not thought to be a useful differentiator. It was also thought to be potentially unreliable due to the dependence on the recording of AF in patients' medical notes.
- Sinus rhythm – this is potentially an important covariable, and is thought to modify CRT efficacy. However, of the ten CRT-P or CRT-D trials included in the IPD Trials data set, only the RAFT trial included a minority of patients with permanent atrial fibrillation³. Hence, almost all patients in these studies were in sinus rhythm (by virtue of the relationship: proportion in sinus rhythm = study population – proportion in AF)
- Mechanical dyssynchrony – these data were collected in a single study (CARE-HF) and could not therefore be considered in the analysis. In addition, this component of the CARE-HF inclusion criteria is unlikely to have driven the trial's results, as discussed in Section 4.5.4.
- Prior pacing – very few patients included in the IPD Trials had prior pacing. This was allowed in only two trials, RAFT and MADIT II (and possibly MADIT though this was never explicit). The number of patients with prior pacing in these trials is thought to be small, and patients with prior pacing could only be identified exactly in MADIT II. This covariable was therefore not included in the analysis.
- History of spontaneous VT/VF – although this was identified as a potentially important covariable, an initial review of the baseline data by the clinical experts suggested that the definitions used across trials were unlikely to be consistent and that the analysis should not therefore include this data.
- Non-sustained VT on ECG – this was not tested for in the majority of the studies (only MADIT and DEFINITE collected these data for all patients).

³ MIRACLE ICD inclusion criteria stated "Chronic atrial arrhythmias, or cardioversion or paroxysmal atrial fibrillation within previous 1 month". This is assumed to exclude all patients with permanent atrial fibrillation at the time of enrolment.

- Inducible VT on electrophysiology testing – this was not tested in the majority of the studies (only MADIT required electrophysiology testing for all patients prior to enrolment).
- Diuretic use – although potentially an important proxy for disease severity in addition to NYHA and LVEF¹⁰⁷, this covariable was not included in the analysis as it is not expected that NICE would make a recommendation contingent upon something that was subject to frequent individual titration.

Descriptors of the included covariables are provided as Table 35. The most notable differences are that patients enrolled in CRT trials have on average a higher NYHA class, more prolonged QRS and are more likely to have LBBB (as the likelihood of LBBB increases with widened QRS) than in ICD trials.

Table 35: Covariable data for IPD Trials dataset

Device	OMT	CRT-D	CRT-P	ICD	Missing (%)
Number of patients	████	████	████	████	████
Age (mean, years)	████	████	████	████	████
QRS (mean, ms)	████	████	████	████	████
LVEF (mean, %)	████	████	████	████	████
Gender (% Female)	████	████	████	████	████
US (%)	████	████	████	████	████
NYHA1 (%)	██	██	██	██	██
NYHA2 (%)	████	████	██	████	████
NYHA3 (%)	████	████	████	████	████
NYHA4 (%)	██	██	██	██	██
Ischaemic (%)	████	████	████	████	████
LBBB (%)	████	████	████	████	████

The only covariable for which a significant proportion of data is missing is ischaemic aetiology, though the proportion of data missing is still relatively low (████).

Data from the most recent Cardiac Rhythm Management UK National Audit (2010)²¹ was used to compare, where possible, the above covariable pattern with that observed in UK clinical practice. The key statistics are reproduced in Table 36.

Table 36: UK Summary data (reproduced from Cunningham et al., 2010)

Device	CRT-D	CRT-P	ICD
Age (mean, years)	67.1	71.7	63.1
QRS (prolonged, %)	77.6%	84.3%	32.1%
LVEF (mean, %)	N/A ¹	N/A ¹	N/A ¹
Gender (% Female)	16.6%	31.6%	19.9%
NYHA class I (%)	11%	2%	44%
NYHA class II (%)	18%	10%	38%
NYHA class III (%)	64%	85%	16%
NYHA class IV (%)	7%	3%	1%
Ischaemic (%)	64.5%	33.1%	66.3%
LBBB (%)	N/A	N/A	N/A

1) data reported as “Good”, “Fair” or “Poor” with no numerical quantification of each category provided

Note, that a number of these parameters, in particular the percentage in each NYHA class, have been distorted by previous NICE decisions (for example, CRT not being formally approved for use in NYHA class I/II etc.). Similarly, other data are presented in differing formats to that in the trial database (e.g. QRS reported as normal/ prolonged). There was also a high level of missing data in the UK National Audit data. Hence, direct comparison of the UK database with the trial database not always possible. Nonetheless, where a fair comparison is possible, the trial database is broadly reflective of the UK population.

4.3.5 Handling of continuous covariables

The continuous covariables (age, LVEF and QRS duration) were converted to categorical equivalents, both to ensure that the analyses provide clear recommendations for clinicians and to avoid technical issues with the cost-effectiveness model⁴. A description of the cut-offs used for each variable and the rationale for these is provided below.

- Age – age was split in to the following categories: 0-≤55, >55-≤65, >65-≤70, >70-≤75, >75. This provided a reasonable compromise between ensuring that there were sufficient patients in each category and capturing the difference in

⁴ Due to the non-linear relationship between covariables in a survival analysis and mean life years gained, inclusion of continuous covariables would necessitate simulating a large number of patients through the cost-effectiveness modelling. Using dichotomous covariables allowed use of a more parsimonious approach with fewer simulations.

prognosis and potentially treatment effects across categories.

- LVEF - Previous NICE recommendations have used cut-offs of 35% and 30%. The following categories were used to ensure an even spread across categories and to capture clinically meaningful differences in prognosis: 0%-≤20%, >20%-≤25%, >25%-≤30%, and >30%. It should be noted that only a small number of patients in the database [REDACTED] had an LVEF>35%. The >30% category is therefore representative of patients with LVEF >30%-≤35%, however to avoid excluding data the patients with LVEF>35% are retained in this category.
- QRS - Previous NICE recommendations have used cut-offs of 120ms and 150ms. The following categories were therefore used in the analysis: 0-<120ms, ≥120ms-<150ms, and ≥150ms.

4.3.6 Missing data

Data regarding study, treatment allocation, and time to death or loss to follow-up was complete for all trials. As documented in Section 4.3.3, for the covariables included in the analysis there were some missing data [REDACTED] depending on the covariable). To enable an intention to treat analysis, covariable values for these data points were imputed using multiple imputations. Details of the imputation approach are provided in Appendix six.

Multiple imputation was used for all analyses other than the exploratory analyses, which were based on complete cases only. To avoid exclusion of a substantial number of patients from the exploratory analysis, missing values of the Ischemia variable were imputed directly from the MI variable (exploratory analyses only). Use of a complete case analysis for exploratory purposes (including covariable selection) is likely to be robust for this data set as [REDACTED] of patients had complete data.

4.4 Description of analyses

4.4.1 Baseline

In order to generate estimates of baseline mortality risk, parametric survival analyses were run on a pooled data set including all patients randomised to OMT. OMT was chosen as the baseline as this allowed for inclusion of a heterogeneous

population of patients (and importantly, patients randomised to an ICD alone and a CRT-P alone).

The baseline analysis was independent of the treatment effect analysis. Although it would be possible to simultaneously analyse the baseline and treatment effects this would require a constrained functional form for the baseline hazard. Use of an unconstrained baseline has been generally preferred in meta-analysis and network meta-analysis.

The following parametric survival distributions were run for the all-cause mortality endpoint: exponential, Gompertz, log-logistic, log-normal, and Weibull. Favoured distributions were trialled with and without covariables. Initial analyses suggested that for patients with a milder prognosis, the models gave unrealistic long term predictions, with a greater proportion of patients predicted to be alive than would be expected in the general population.

An alternative approach was therefore applied whereby age was included as a time-dependent covariable. The advantage of this approach is that information is borrowed across patients in two ways:

- 1) The model parameters take account of the fact that patients who are aged 65 at five years post baseline are expected to experience a similar modification to the risk of death (controlling for other prognostic variables) as patients who are aged 65 years at baseline;
- 2) The extrapolation process uses information on the inflated risk of death associated with being in the higher age categories to inform the increase in risk of death experienced as patients progress through the model.

This approach required inclusion of separate observations for each covariate value for each patient. As age changes continuously this would have required an infinite number of observations. To maintain reasonable run times for the analysis, updating of age as a time-dependent covariable was therefore conducted every 30 days.

The different parametric models excluding covariables were compared using the following metrics, in order to identify models found to be clearly inferior:

- Visual comparison of the fitted and Kaplan Meier survival curves for fit within trial follow-up

- Visual review of the extrapolation
- Visual review of the shape of the instantaneous hazard over time
- Comparison of Akaike's Information Criteria (AIC¹⁰⁸)
- Inspection of Cox-Snell residuals¹⁰⁸

Any models found to be clearly inferior based on these tests were excluded from further consideration. All other models were trialled with the covariable set. This was conducted using a stepwise procedure based on AIC (forward and backward selection, two degrees of freedom for the penalty). The parametric models including covariables were then compared using the following metrics:

- AIC
- Cox-Snell residuals
- Tests for the acceptability of the proportional hazards assumption (exponential; gamma; Gompertz; Weibull) or accelerated failure time assumption (log-logistic; log-normal) with respect to each covariable were run
- Comparison of the fitted and Kaplan Meier curves for each quartile of the risk score (linear predictor component of the model) as recommended in Collett 2003¹⁰⁸

Results of the final model were reviewed by clinical experts for plausibility. Long term (extrapolated) predictions of the final model were reviewed against available external data and with clinical experts to ensure their plausibility.

4.4.2 Network meta-analysis – overview

The aim of the network meta-analysis was to estimate relative treatment effects comparing each device to the other devices and OMT. Network meta-analysis (also described as mixed treatment comparison) enables the combination of trials that compare different sets of treatments, and form a network of evidence, within a single coherent analysis¹⁰⁹, and to use all available direct and indirect evidence to inform a given comparison between treatments. This is important for the current appraisal where some comparisons have little direct data but a large volume of indirect data, for example only patients randomised to OMT and CRT-D in COMPANION provide direct data comparing these treatments, whereas all other trials in the network provide indirect data informing this comparison.

Network meta-analysis is based on the assumption that, on a suitable scale, we can add and subtract within-trial estimates of relative treatment effects, i.e. the difference in effect between treatments A & B (d_{AB}) is equal to the difference in effects between treatments A & C and B & C ($d_{AB} = d_{AC} - d_{BC}$)¹⁰⁹⁻¹¹¹ on a chosen scale.

Due to data availability, network meta-analyses are typically based on published aggregate data (typically from whole trials, but also from published subgroup analyses). In this context, opportunities to adjust for differences across trials which may be acting as treatment-effect modifiers are limited by data availability. The main approaches used are meta-regression and analyses of subgroup data.

As outlined in Section 4.3.2 for this submission, patient level data were made available for a large proportion of patients included in the network of evidence. This provided a unique opportunity to adjust for differences across trials in patient characteristics which may be acting as treatment-effect modifiers. This has the advantage of allowing subgroup-specific treatment effects to be estimated and potentially allowing heterogeneity or inconsistency in the network to be addressed.

4.4.3 Network meta-analysis – covariables excluded

The first analyses conducted took a more traditional form and analysed data aggregated by trial. The objective of these analyses was to understand the efficacy estimates produced by synthesising the overall evidence base without

adjustment; the extent of agreement between network meta-analysis, pairwise meta-analysis and individual trial estimates of treatment effect; and the impact of restricting the All Trials dataset to the IPD trials only.

The methods and code used in the network meta-analysis have been described previously; analyses were run using R to WinBUGS¹¹². These analyses were run without covariables. Hazard ratios were used for all IPD Trials, as these trials all reported dates of randomisation and dates of death or last follow-up for mortality.

For the non-IPD trials no hazard ratio data were reported in the trial publications, binary data were therefore included for these trials. Given the two datasets and the possibility of both fixed and random effect analyses the following four analyses were run:

1. All Trials, Fixed effects
2. All Trials, Random effects
3. IPD Trials, Fixed effects
4. IPD Trials, Random effects

Two sets of initial values were used and convergence was assessed by examining caterpillar plots and Brooks Gelman-Rubin (BGR) statistics.

Autocorrelation was also examined. The deviance information criteria (DIC) was used to compare the fit of the fixed and random effects models.¹¹³ The number of burn in simulations and model runs was determined based on inspection of these statistics for each model.

4.4.4 Network meta-analysis – Covariables included

A second set of analyses were run incorporating the covariable set as potential treatment effect modifiers. These analyses used data from the IPD Trials only and used fixed effects analyses only. A discussion of why the analysis was restricted to a fixed effects analysis is presented in appendix seven.

The network meta-analysis was run using individual patient data (IPD) analysed using a frequentist Cox proportional hazards analysis, stratified by study. The regressions included main effects for the devices; main effects for the covariables (nuisance parameters) and interactions between the devices and covariables. This method generates equivalent results to a fixed effects Bayesian network

meta-analysis using non-informative priors. The methods generate equivalent results because stratifying by trial allows the baseline hazard in each study to be independent. This method has previously been used by Tudor Smith *et al.*^{114;115} in a network meta-analysis of epilepsy trials. Covariables were selected for inclusion based on univariate analyses, a multivariate stepwise procedure and review of these exploratory analyses with the clinical experts. Proportional hazards tests were then run on the preferred model for all main effects and interaction effects. The Schoenfeld residual-based test suggested by Grambsch and Therneau was used.¹¹⁶

Further detail regarding the model used and the approach for covariable selection is provided as Appendix eight.

4.5 Results

4.5.1 Baseline risk

Firstly, parametric models were fitted without covariables. All curves exhibited a good fit and produced similar predictions within the trial period. Beyond this the exponential, Weibull and Gompertz distributions all made similar and reasonable predictions (although predicted slightly long ‘tails’). The log-normal and log-logistic distributions produced unrealistic extrapolations with approximately a fifth of the patients being alive when the average age of the patients in the cohort reached 100 years.

The AICs supported use of the exponential (AIC: 16,329), Weibull (16,329) or log-logistic (16,329) over the Gompertz (16,332) or log-normal (16,358).

Plots of the Cox-Snell residuals suggested that the models without covariables all provided a similar fit with the exception of the log-normal model which provided a poorer fit.

Examination of the instantaneous hazard indicated that it was reasonably constant over time. The exponential and Weibull distributions were therefore considered for the final model.

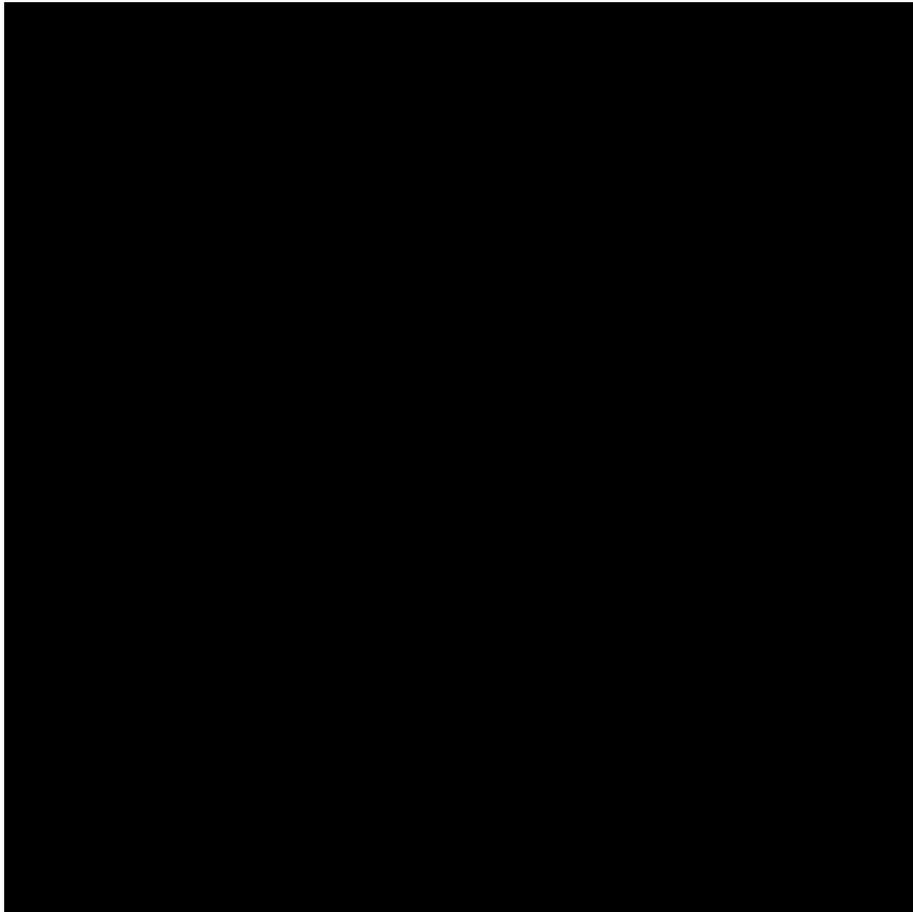
All covariables trialled were retained by the stepwise procedure and found to be highly significant predictors of baseline risk, with the exception of the US and LBBB variables. Inclusion of the covariables suggested the following conclusions (which held across the exponential and Weibull distributions):

- Age, Gender, Ischemic aetiology, and LVEF all exhibited trends in the direction and of the magnitude expected. The log hazard ratio for age indicated a linear relationship with mortality.
- NYHA classes III/IV patients as expected performed worse compared to NYHA classes I/II patients (NYHA class IV was the characteristic with the largest effect on risk of death, as expected). Patients in NYHA class II exhibited an almost identical risk of mortality compared to those in NYHA class I; these categories were therefore collapsed.
- QRS duration <120ms was associated with improved outcomes compared to QRS duration ≥150ms. Patients with QRS duration of ≥120ms-<150ms exhibited an almost identical risk of mortality compared to those with QRS duration ≥150ms. For exploratory purposes an analysis including only QRS as a continuous variable, with a quadratic form, was therefore run. This showed deterioration in mortality as QRS increased up to about 120-130ms and then a flattening out beyond this point. It was therefore judged reasonable to pool the ≥120ms-<150ms and ≥150ms categories for the purposes of the baseline risk analysis.

Both plots of the Cox-Snell residuals and the AIC statistics (15,597 for exponential model and 15,594 for Weibull model) suggested a better fit for the Weibull model.

Comparisons of the Kaplan Meier curves for patients in each quintile of the risk distribution suggest that this Weibull model is able to differentiate between patients with quite different risk profiles (see Figure 13). This presentation also shows the heterogeneity in the patient population analysed, with only ■■■ of patients in the quintile with the lowest predicted survival surviving at 4 years, compared to ■■■ of those in the quintile with the highest predicted survival.

Figure 13: Comparison of Kaplan Meier and parametric curves for patients in different risk quintiles (risk quintiles defined by the parametric model)



A Cox proportional hazards version of the preferred model was run in order to assess the suitability of the proportional hazard assumption. This suggested that one variable, age, was not conforming to the proportional hazards assumption. This is not entirely surprising as it would be expected that the increase in mortality risk for older patients would increase more rapidly over time than observed for younger patients. In addition, inspection of the predictions for a longer time horizon (see Figure 14) suggested that the model was over predicting survival in low risk patients.

Figure 14: Predictions over 50 year time horizon (by risk quintiles)



To address these issues, age was incorporated as a time-varying covariate in the analysis. Inclusion of baseline age assumes that baseline age modifies the hazard of death in a proportionate manner throughout the model. Inclusion of age as a time-varying covariate instead assumes that the impact of being at a specific age at a particular time point modifies the hazard of death in a proportionate manner.

With the application of this approach it was also considered appropriate to include age as a continuous covariable in order to allow the increase in the hazard of death associated with ageing to be applied continuously in the model. This was also thought valid as inspection of the coefficients on the age variable suggested a linear increase in the log hazard ratio over the age range in the database.

The preferred model is summarised as Table 37. This is the model for baseline mortality used in the cost-effectiveness model. For the purposes of the cost-effectiveness modelling these parameters can be converted to a survival curve using the following formulae:

$$h(t) = \exp(-(\log(scale) - \beta \cdot X) \cdot shape) \cdot shape \cdot t^{shape}$$

$$S(t) = \exp(-\int_0^t h(t) dt)$$

where $h(t)$ is the instantaneous hazard, $S(t)$ is the survival curve, β are the coefficients on the covariables and the X are the set of covariables (which can be time-dependent).

Table 37: Preferred baseline risk model

Variable	Coefficient	Hazard ratio for prognostic variable ^a	P-value
Age (per year)	█	█	█
Male gender	█	█	█
NYHA III	█	█	█
NYHA IV	█	█	█
Ischaemic aetiology	█	█	█
QRS duration <120ms	█	█	█
LVEF>20% and <=25%	█	█	█
LVEF>25% and <=30%	█	█	█
LVEF>30%	█	█	█
log(scale)	█	█	█
log(shape)	█	█	█

(a) Hazard ratio = $\exp(\beta/\text{shape})$; Na = not applicable

The impact of including age as a time-dependent covariable relative to including baseline age only, and relative to general population mortality, is shown as Figure 15 (patient shown has the average characteristics of patients in the lowest risk quintile). This shows the similar predictions associated with the models within the period of trial follow-up, and the more plausible long term predictions associated with the model that includes age as a time-dependent covariable.

An example curve for the average patient in the highest risk quintile is shown as Figure 16 to illustrate the minimal impact of the analytical approach on high risk cohorts, where a much larger proportion of events occur within the available

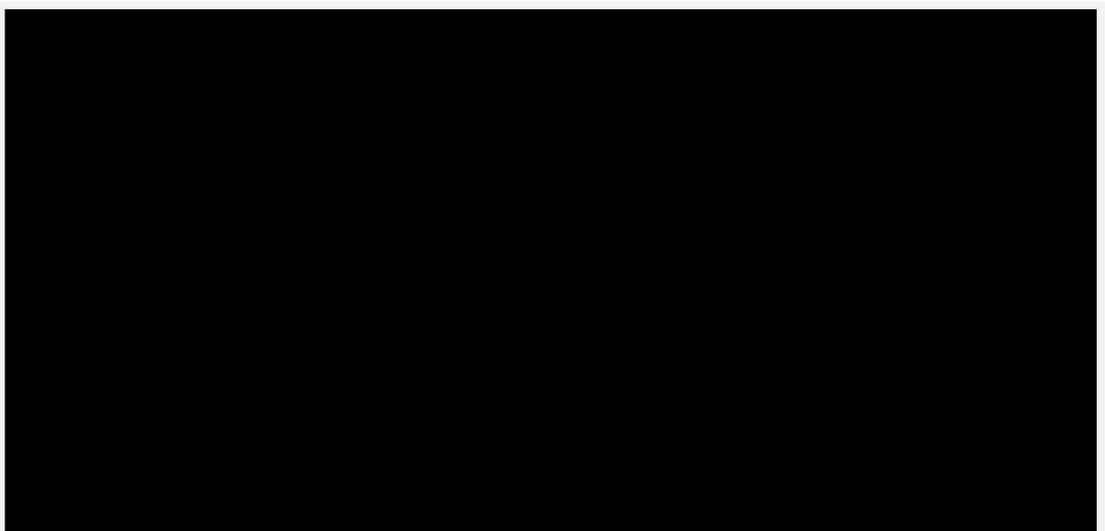
follow-up.

Predictions for sample patients were reviewed with clinicians, who supported their plausibility.

Figure 15: Example predictions, with and without age as time-dependent covariable: low risk patient (male, age 51 in NYHA class I/II, non-Ischaemic aetiology, QRS duration <120ms and LVEF between 25% and 30%)



Figure 16: Example predictions, with and without age as time-dependent covariable: high risk patient (male, age 71 in NYHA class III, ischaemic aetiology, QRS duration >120ms and LVEF ≤20%)



4.5.2 Network meta-analysis – no covariables

Figure 17 presents the results for each of the four models fitted for each pairwise comparison for which direct data is available⁵. This shows that the mean estimates from the fixed and random effects analyses for each data set are broadly similar, though confidence intervals associated with the random effects analysis are wider. The DIC assessment of model fit supported use of the fixed effect (FE) as opposed to random effect (RE) model for the All Trials (FE DIC = 59.0 vs. RE DIC = 60.8) and IPD Trials (FE DIC = 1.4 vs. RE DIC = 3.0) analyses.

Results for All Trials and IPD Trials show little difference; this is unsurprising given the small proportion of patients for whom IPD were not available (5%) but is reassuring given the reliance of subsequent analyses (including the final model that informs the cost-effectiveness analysis) on the IPD Trials.

All devices when compared to OMT deliver a statistically significant benefit (at $P=0.05$) across analyses. The magnitude of effect is also notable with hazard ratios vs. OMT (mean (95% credible interval, CrI)) of ██████████ for CRT-D; ██████████ for CRT-P and ██████████ for ICD (fixed effects analysis of All Trials).

⁵ Fixed effects models were run for 20,000 burn-in simulations and a further 50,000 iterations, random effects models were run for 100,000 burn-in simulations and a further 200,000 iterations (with thinning rate = 5).

Figure 17: Comparison of network meta-analysis results using IPD Trials and All Trials, and fixed and random effects models

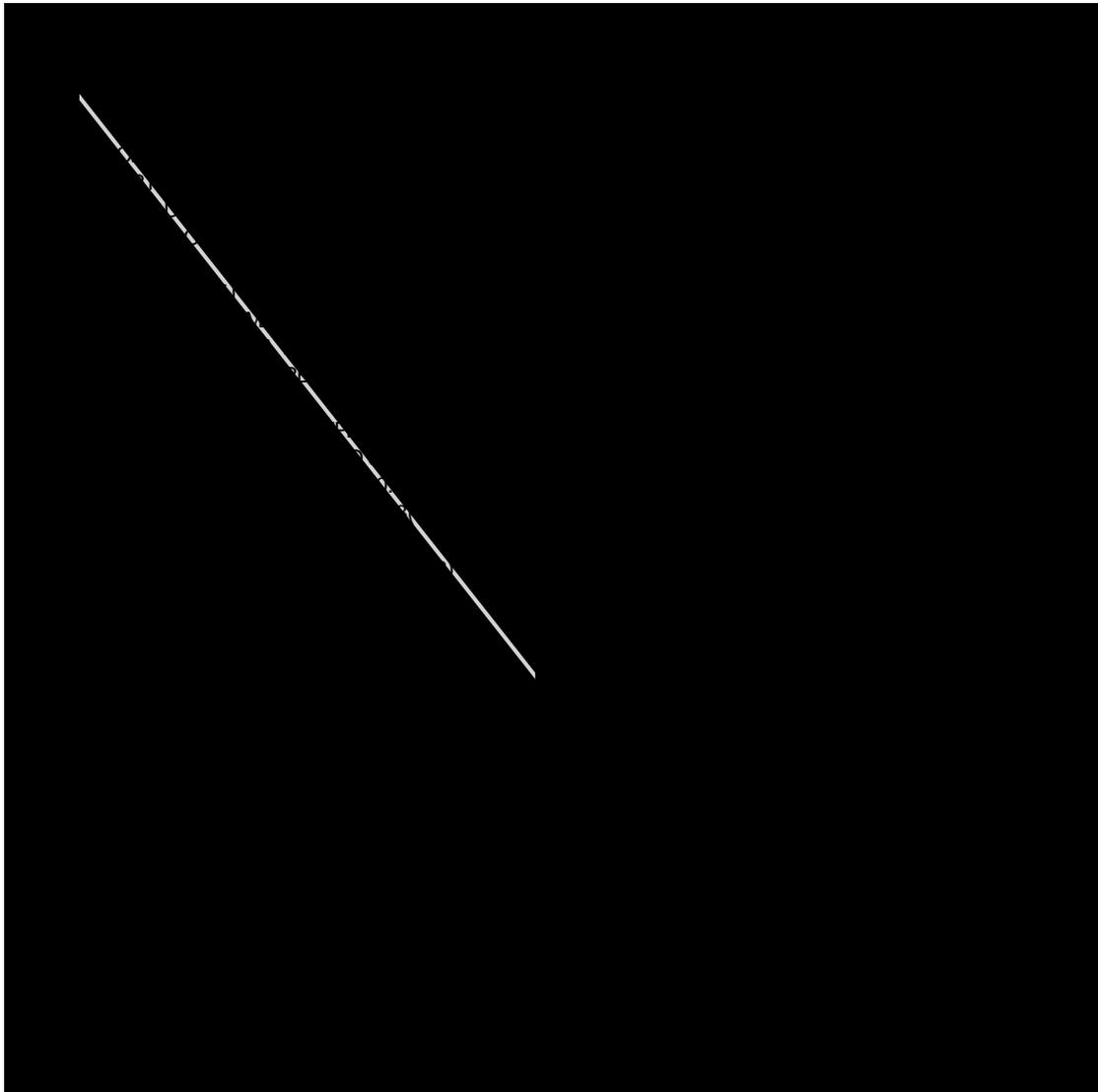
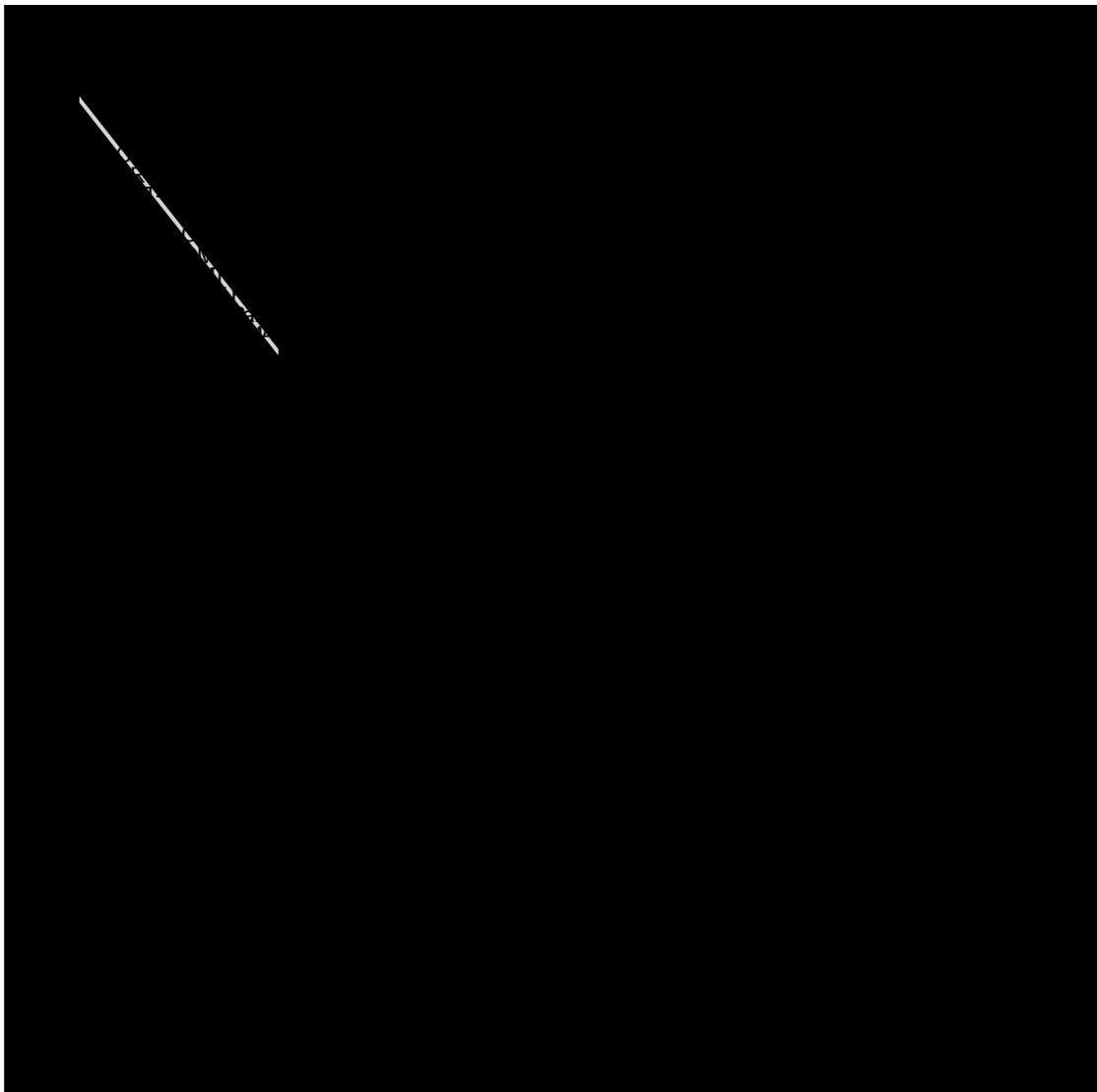


Figure 18 compares the FE results for IPD Trials (the focus of our analysis of heterogeneity) with the individual trial results and pairwise meta-analyses of the direct data for each comparison. The network appears to be reasonably consistent. Good concordance between the pairwise meta-analysis and network meta-analysis results suggests reasonable concordance between the indirect and direct data.

There is some heterogeneity within pairwise comparisons. The CARE-HF trial outperforms the other trials comparing CRT-P to OMT. This may be due to the inclusion criteria of CARE-HF, which required patients to have $QRS \geq 120ms$ and mechanical dyssynchrony OR $QRS \geq 150ms$. This inclusion criterion appears to

have resulted in almost all patients with QRS<150ms being excluded (these patients comprise only █ of the cohort compared to █ in the Companion cohort; █ in the MIRACLE cohort and █ in the REVERSE CRT-P cohort). The MADIT trial also appears to be an outlier, exhibiting much stronger effects than the other ICD vs. OMT trials. This may be due to the higher proportion of males in this trial or the requirement for prior MI (though this also applies in MADIT II), or that this simply a smaller trial than the others comparing these treatments. It may also be because background drug therapy was not as good as in subsequent trials.

Figure 18: Comparison of Fixed Effects IPD Trials analysis to individual trial results



4.5.3 Treatment effects over time

An important question is the extent to which treatment effects of the devices are

maintained over time. Tests of the proportional hazards assumption suggested no violation of this assumption (global p-value for device terms = [REDACTED]), nor did plots of the Schoenfeld residuals suggest time trends.

4.5.4 Network meta-analysis – covariable selection

The results of the univariate analyses and multivariate stepwise selection procedures are summarized in Appendix eight. Appendix nine presents the univariate analyses graphically.

The exploratory analyses were reviewed with two clinical experts and the following conclusions were reached regarding the final model:

- Clinical covariables:
 - *NYHA* – the univariate analysis suggests a somewhat diminished effect of CRT-D in patients in NYHA class IV. NYHA class was retained in only one of the multivariate models, as a treatment effect modifier for CRT-D. This result is driven by the poorer efficacy of CRT-D in NYHA class IV patients. The low statistical significance for this factor in the univariate analysis and omission from the other multivariate models may be attributable to the nine degrees of freedom lost when modelling the NYHA-device interaction. A NYHA class 4-device interaction is therefore included in a sensitivity analysis, given the plausibility of a diminished effect of CRT-D in this patient group, where the ratio of heart failure to sudden cardiac deaths becomes much higher, and therefore the benefit of the ICD component of the device is likely to be diminished.
 - *Ischaemic aetiology* – the univariate and multivariate analyses did not suggest that ischaemic aetiology impacts on the relative effects of the devices. This variable was therefore excluded from the final model.
 - *LVEF* – no clear trend with respect to LVEF was observed across the analyses. The analyses suggest a trend for increased efficacy of CRT-D in patients with lower LVEF. For CRT-P and ICD, a peak in efficacy is observed around a LVEF of 30%. This is counter intuitive (as CRT-D combines the therapies delivered by CRT-P and ICD) and suggests that the relationship between LVEF and CRT-D efficacy may have

occurred by chance. This finding was therefore not considered sufficiently robust to be included in the model.

- *QRS* – QRS duration acted in the expected direction in the multivariate and univariate analyses with patients with QRS duration ≥ 150 ms experiencing better CRT-P and CRT-D efficacy than patients with QRS duration ≥ 120 to < 150 ms. For ICD, patients with QRS duration ≥ 120 ms to < 150 ms experienced better efficacy than those with shorter and longer QRS duration. Evidence of an interaction effect was shown in all analyses where QRS duration was considered as a continuous covariable. QRS duration was therefore included in the final model.
- *LBBB* – LBBB acted in the expected direction in the multivariate and univariate analyses with patients with LBBB experiencing higher efficacy of CRT-P and CRT-D than patients with non-LBBB conduction abnormalities (right bundle branch block or non-specific intraventricular conduction delay). LBBB was therefore included in the final model.

It should be noted that the high level of collinearity between LBBB and QRS duration may explain why both covariables are not retained in all stepwise analyses.

- Non-clinical covariables:
 - *US vs. non-US* – US was retained as a covariable in three of the multivariate analyses, though it was not statistically significant in the univariate analysis. This result is likely to be in part by driven by the European RAFT trial comparing CRT-D to ICD, which provides the strongest evidence for this pairwise comparison. However, US terms were retained even once the RAFT trial was excluded. One possible hypothesis is that non-US patients tend to have a lower body mass index (BMI), which is associated with a higher risk of SCD¹¹⁷. However, due to limited collection of height data (missing in ■■■ of patients) this could not be explored robustly using the current data set. It therefore seemed safest to exclude the US term as it may be capturing systematic differences between trials conducted in US and

ex-US geographies, and its inclusion would have biased the results in favour of device therapy.

- *Age* – age acted in the expected direction in the multivariate and univariate analyses, with younger patients experiencing stronger ICD efficacy and older patient's stronger CRT efficacy. This is likely to be attributable to younger patients being relatively more likely to die from sudden cardiac death. Age was statistically significant when included as a continuous covariable in the univariate analysis, and was retained in all multivariate analyses. Age is therefore included in the final model.
- *Gender* – gender acted in the expected direction in the multivariate and univariate analyses with male patients experiencing stronger ICD efficacy and female patients stronger CRT efficacy. Again, this is likely to be attributable to males experiencing a higher likelihood of sudden cardiac death. Gender was statistically significant in the univariate analysis and retained in all multivariate analyses. Gender is therefore included in the final model.

In summary: QRS duration, LBBB, Age and Gender are included in the model as device treatment effect modifiers. A dummy variable for being in NYHA class 4 is added in a sensitivity analysis. As QRS duration and Age are continuous covariables, the dichotomisations chosen for the exploratory analyses were re-examined for their appropriateness. A quadratic model was fitted for both covariables. This showed that for QRS the efficacy of CRT-P and CRT-D increases broadly linearly between QRS durations of 120ms and 150ms and then levels off at 150ms. This suggests that the current dichotomisation is reasonable, though may miss some of the heterogeneity in response to therapy in the 120-150ms category. For age, efficacy of ICD increases and of CRT-P decreases with age, until a plateau is observed after approximately 60 years. For simplicity, age was therefore converted to a two level variable of <60 and ≥60 years. Again this may miss some of the heterogeneity in response to therapy in the <60 category. Given the uncertainty regarding the magnitude of the treatment effect modifiers it was decided that covariables should be allowed to modify all device treatment effects in the final model.

Table 38: Results of univariate analysis and multivariate automated stepwise analyses used to inform interaction effect selection

Covariable	Univariate analysis p-value ^a		Retention following multivariate automated stepwise procedure ^b			
			Device specific modifiers		All-device modifiers	
	Continuous variables dichotomised	Continuous variables retained	Continuous variables dichotomised	Continuous variables retained	Continuous variables dichotomised	Continuous variables retained
Age	■	■	■■■■■■■■■■	■■■■■■■■	■■■■	■■■■
Gender	■■■■		■■■■■■	■■■■■■	■■■■	■■■■
Country (US vs. ex-US)	■■■■		■■■■■■■■	■■■■■■■■■■		■■■■
NYHA	■■■■			■■■■■■		
Ischemic aetiology	■■■■					
LVEF	■■■■	■■■■		■■■■■■		■■■■
QRS	■■■■	■■■■■■		■■■■■■■■■■		■■■■
LBBB	■■■■■■	■	■■■■■■■■	■■■■■■	■■■■	

a - p-value for comparison of two times the difference in the log-likelihood for the model containing Device and Covariable main effects but no interaction, and the model containing Device and Covariable main effects and the Device*Covariable interaction (Chi-square test used). **b** - For the multivariate exploratory analysis, patients randomised in to CRT-D or CRT-P trials with QRS<120ms were excluded as the very low number of deaths (five in total in patients randomised to CRT-P and CRT-D) made any modelling of these patients unstable. This decision was replicated in the final analyses. This results in ■■■ patients being excluded from RethinQ; ■■■ from CONTAK-CD; ■ from CARE-HF; ■ from RAFT and ■ from MADIT-CRT. * p-value<0.05. ** p-value<0.01

4.5.5 Network meta-analysis – preferred model

The preferred model is presented in Table 39, which shows the model parameters used in the cost-effectiveness model, and Figure 19 which show the predicted treatment effect for each subgroup, along with the associated confidence intervals. It should be noted that the analysis including treatment effect modifiers presented in this section is inherently more uncertain than the analysis without covariables presented in section 4.5.2. This is due to the increased number of parameters required to capture heterogeneity in treatment effects across patients with different characteristics. This illustrates the compromise between increasing the precision of the point estimates for specific subgroups, and minimizing the uncertainty in the treatment effects.

In general, caution should be taken not to over-interpret individual subgroups since anomalies may arise as a result of patient level characteristics not accounted for. Of further note is that the conclusions refer to the effect of treatment above and beyond the baseline risk observed for a given clinical covariate pattern (see Table 37). Nonetheless, the following broad conclusions can be drawn from these figures:

- **QRS duration <120ms**
 - Benefit of ICD apparent in males of any age
 - In females, the benefit of ICD appears to be restricted to patients aged <60 years
- **QRS duration ≥120ms to <150ms without LBBB**
 - CRT-D offers an advantage over CRT-P regardless of gender or age.
 - ICD may offer a similar benefit to CRT-D in males, with CRT-D the preferred option in females.
 - In males CRT-P may offer minimal benefit. The benefit in women of all ages is far more pronounced
- **QRS duration ≥150ms without LBBB**
 - CRT-D offers an advantage over CRT-P regardless of age of gender
 - ICD may offer a similar benefit to CRT-D in males <60 years, with

CRT-D preferred to ICD in all other groups.

- In males <60 years CRT-P may offer minimal benefit and in females ≥60 years ICD may offer limited benefit. As with the results for QRS duration between 120 and 149ms, the benefits of CRT-P in all other patient groups are more pronounced.

- **QRS duration ≥120ms-<150ms or QRS duration ≥150ms with LBBB**

- CRT-D offers an advantage over CRT-P regardless of age or gender.
- While ICD and CRT-D both offer similar and substantive benefit in males <60 years, the benefits associated with CRT-D are slightly greater
- In general, CRT-D offers greater benefit than ICD in females (compared to males) of all ages regardless of QRS duration
- In females ≥60 years ICD may offer limited benefit.
- In males <60 years CRT-P offers modest benefit if QRS duration is ≥120ms-<150ms and far greater benefit if QRS duration is 150ms or more.

The parameters used in the sensitivity analysis including NYHA class IV as a treatment effect modifier are presented in Appendix ten.

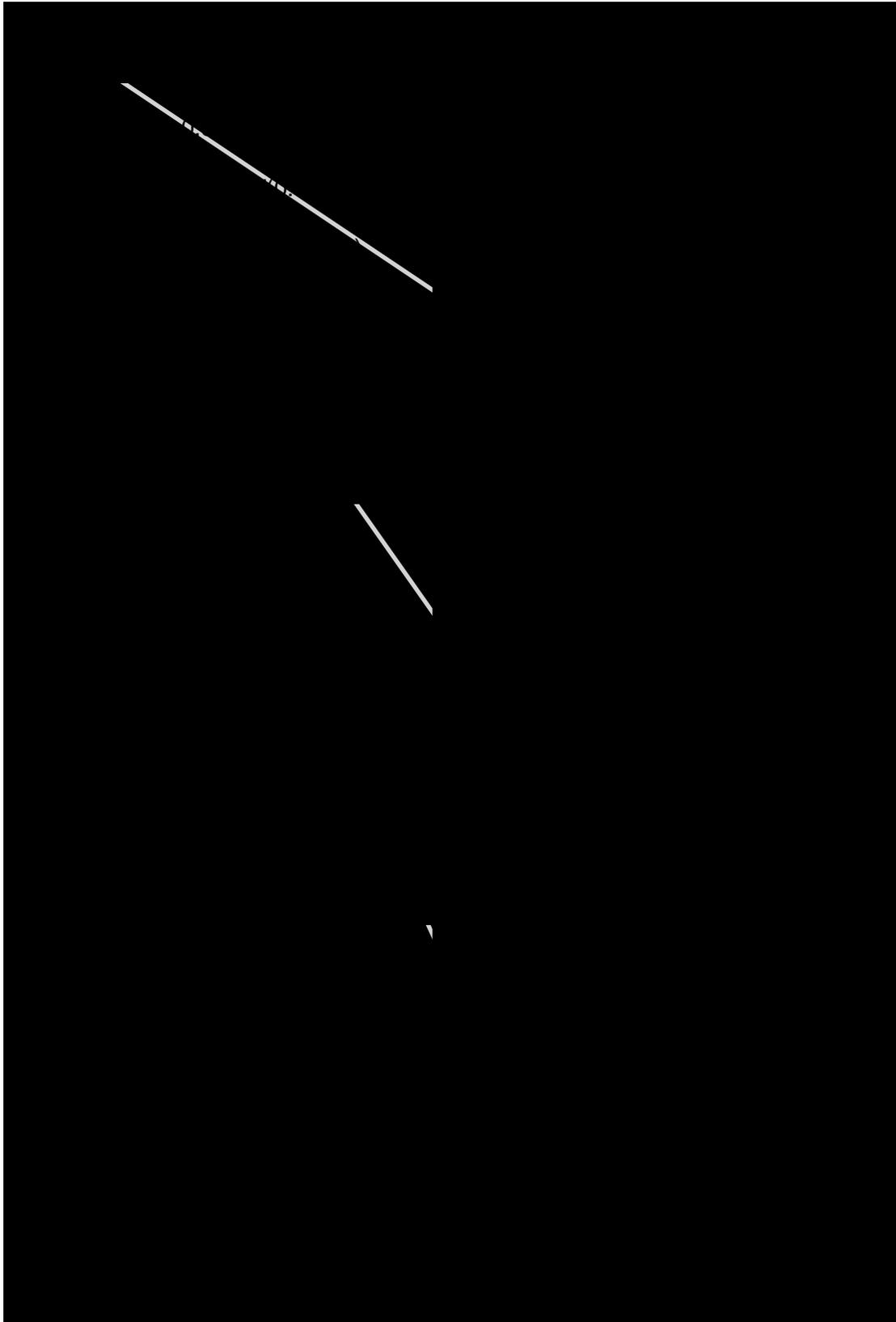
Table 39: Preferred model for IPD network meta-analysis

Variable ^a	Hazard ratio	P-value
ICD	■	■
CRT-P	■	■
CRT-D	■	■
QRS<120	■	■
QRS≥120	■	■
LBBB	■	■
AGE≥60	■	■
GENDER=M	■	■
ICD*QRS<120	■	■
ICD*QRS≥120	■	■
ICD*LBBB	■	■
ICD*GENDER=M	■	■
ICD*AGE≥60	■	■
CRT-P*QRS≥120	■	■
CRT-P*LBBB	■	■
CRT-P*GENDER=M	■	■
CRT-P*AGE≥60	■	■
CRT-D*QRS≥120	■	■
CRT-D*LBBB	■	■
CRT-D*GENDER=M	■	■
CRT-D*AGE≥60	■	■

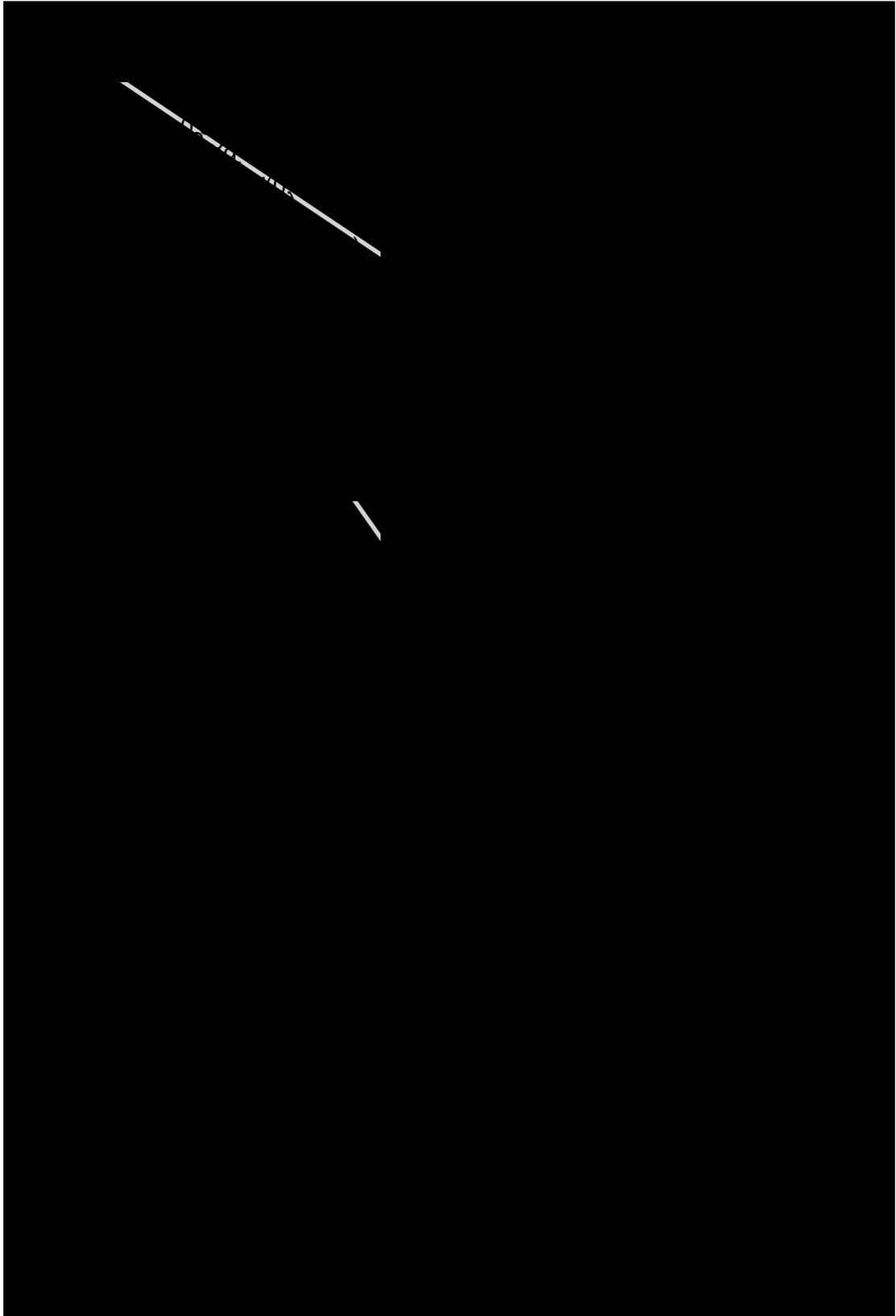
a – Reference category is a patient receiving OMT, <60 years of age, female, QRS duration ≥150ms and non-LBBB conduction abnormality. NB: main effects for covariables greyed out as not included in cost-effectiveness model.

Figure 19: Forest plot of results of analysis adjusting for covariables (LBBB)

(a) Non LBBB patients



(b) LBBB patients



4.6 Discussion of results

4.6.1 Baseline

The analysis of mortality risk for all patients randomised to OMT in the database (3,477 patients, followed up for up to up to 6.1 years) found NYHA class, ischaemia, QRS duration and LVEF all to be highly significant predictors of survival times, along with patient age and gender.

The risk equation developed was able to differentiate between the highly heterogeneous prognoses of patients included in the trials. For patients predicted to be in the upper 20% with respect to survival time, four year survival was [REDACTED]. For patients predicted to be in the lowest 20%, four year survival was [REDACTED].

Inclusion of age as a time-dependent covariable in the analysis appeared to produce realistic predictions of survival both within the database follow-up period and when extrapolated over patient lifetime.

4.6.2 Network meta-analysis

A network meta-analysis was conducted including data from all studies identified by the systematic review – contingent on availability (12,638 patients followed up for up to 7.5 years).

- The analysis found CRT-D to have the strongest effect on all-cause mortality with a hazard ratio of [REDACTED] for CRT-D vs. OMT.
- Treatment effects for the individual devices were [REDACTED] for CRT-P vs. OMT and [REDACTED] for ICD vs. OMT (fixed effects analysis of All Trials).
- These results are similar to those published previously¹¹⁸, and support the strong effect of all devices on the all-cause mortality endpoint.

Given the high level of heterogeneity in the patient groups under consideration, a series of analyses were conducted exploring the impact of patient characteristics on the magnitude of benefit associated with the devices. These analyses identified patients' age, gender and QRS morphology (both QRS duration and LBBB pattern) to be independently predictive of the magnitude of benefit associated with the devices. Younger patients and male patients appear more likely to benefit from ICD; the opposite is true for CRT. This is likely to be due to

the relatively higher rate of sudden cardiac death relative to other causes in younger and male patients^{119;120}. The impact of QRS duration and LBBB is attributable to the CRT mechanism. The evidence for NYHA class IV as an effect modifier is equivocal but does suggest poorer efficacy of CRT-D in NYHA 4 patients.

A summary of the key findings is presented below. These conclusions all refer to patients with LVEF<35% and all NYHA classes:

- **QRS duration <120ms**
 - Benefit of ICD apparent in males of any age
 - In females, the benefit of ICD appears to be restricted to patients aged <60 years
- **QRS duration ≥120ms to <150ms without LBBB**
 - CRT-D offers an advantage over CRT-P regardless of gender or age.
 - ICD may offer a similar benefit to CRT-D in males, with CRT-D the preferred option in females.
 - In males CRT-P may offer minimal benefit. The benefit in women of all ages is far more pronounced
- **QRS duration ≥150ms without LBBB**
 - CRT-D offers an advantage over CRT-P regardless of age of gender
 - ICD may offer a similar benefit to CRT-D in males <60 years, with CRT-D preferred to ICD in all other groups.
 - In males <60 years CRT-P may offer minimal benefit and in females ≥60 years ICD may offer limited benefit. As with the results for QRS duration between 120 and 149ms, the benefits of CRT-P in all other patient groups are more pronounced.
- **QRS duration ≥120ms-<150ms or QRS duration ≥150ms with LBBB**
 - CRT-D offers an advantage over CRT-P regardless of age or gender.
 - While ICD and CRT-D both offer similar and substantive benefit in males <60 years, the benefits associated with CRT-D are slightly greater

- In females ≥ 60 years ICD may offer limited benefit.
- In males < 60 years CRT-P offers modest benefit if QRS duration is $\geq 120\text{ms}$ - $< 150\text{ms}$ and far greater benefit is GRS duration is 150ms or more.

The main limitation of the analysis is likely to be the power of the analysis to detect significant treatment effect modifiers. Our exploratory analyses suggested that country (US vs. non-US) may be predictive of relative treatment effects: We hypothesise that some of this effect may be attributable to other systematic differences between trials conducted in different geographies, and that some may be attributable to patients with a low-normal body mass index being at higher risk of both heart failure death and sudden cardiac death^{117;121;122}. Further research is required to confirm this hypothesis. However, if it is correct it would suggest that patients in the UK may experience a stronger benefit from the devices. All future trials in heart failure should collect baseline data on both height and weight. Our analyses also suggested some impact of LVEF on the relative treatment effect of CRT-D; however, the lack of consistency in the impact of LVEF on relative treatment effects across devices make this an area of uncertainty.

It should be noted that the power of this analysis to detect treatment effect modifiers is likely to be low for relatively modest effect modifiers.

Further work to ascertain whether a competing risks framework would be a viable and preferred approach in this context is warranted.

The trial data on which this analysis is based extends to 7.5 years. The treatment effect beyond this point is therefore uncertain. Given this, additional published long term follow-up data were reviewed in order to establish the durability of the device treatment effects. Two trials reporting extensive long-term follow-up were identified in the literature: CARE-HF; and MADIT II, only one of which was in the public domain at time of submission preparation¹⁰². These studies are discussed in detail in section 3.9.

For the cost-effectiveness modeling we have therefore used the hazard ratios estimated from the network meta-analysis for a period of 7.5 years (the maximum follow-up included in the network meta-analysis). Beyond this period we have assumed that the hazard ratio converges to 1.0 linearly over a 20 year period.

4.7 All cause hospitalisation

4.7.1 Data availability

Data were available from 11 of the 13 clinical trials for the purpose of this analysis.^{8;39;43;48;49;51;60;64;67;80;83} In general, information is available for all interventions across all disease severity groups in the first year. Longer term data are dominated by patients with mild heart failure and/or those in receipt of either an ICD or no treatment.

4.7.2 Analyses performed

Hospitalisation can be modelled in one of two ways: expected number of events per month or expected number of days per month spent in hospital. For completeness, we have included both in the economic model, with the number of events per month forming the base case approach and days per month a sensitivity analysis (on the basis that the latter may be associated with greater across-country variability).

For each of the two approaches, a common strategy is used:

- i) Estimate the baseline rate (i.e. as experienced by patients on OMT) using baseline clinical parameters as explanatory variables.
- ii) Estimate the device specific treatment effect using all available data and clinical parameters as treatment effect modifiers.

In order to avoid double counting of events we have removed all hospitalisation events that occurred in the 60 days post randomisation, as these are accounted for separately in the economic model. (see section 5.5.3). In order to align the results of the hospitalisation analyses with those from the mortality analyses, information was only included for all patients who were not censored for any reason (death, device explant, trial mandated crossover, etc.).

All analyses were performed in STATA v.12 (StataCorp, College Station, TX: StataCorp LP), and accounted for intra-patient correlation and included time as a covariable.

4.7.3 Estimation of baseline hospitalisation rate (rate with OPT)

4.7.3.1 Methods

Given that the data are count data, the conventional regression based approaches^{123;124} used to predict events by a range of clinical covariates are as follows:

- Poisson regression (PRM)
- Negative binomial regression (NBRM)

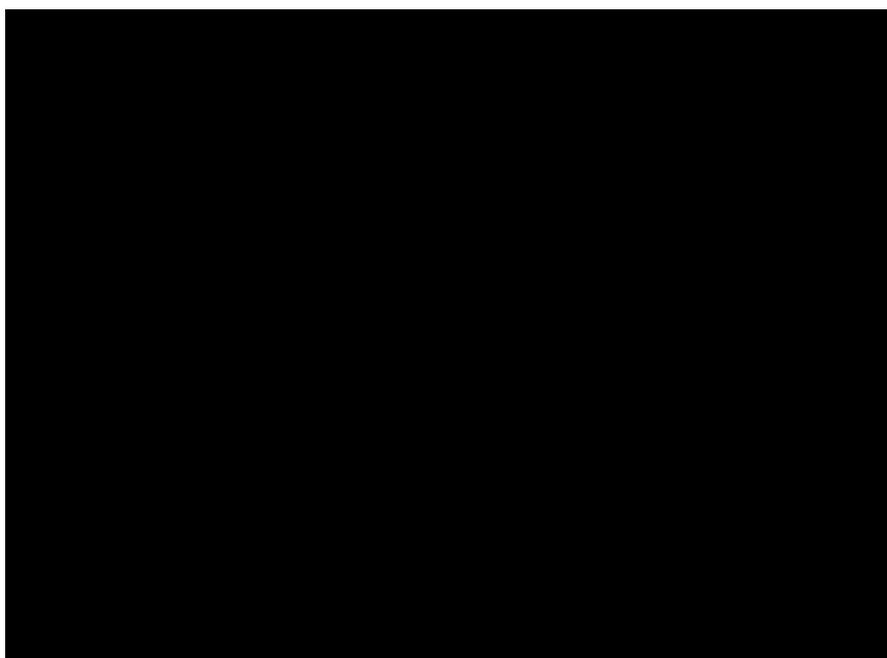
The covariates of interest are those used in the mortality analysis (section 4.1) with the exception of LBBB which was not expected to modify hospitalisation rates and also baseline age (defined as a continuous variable as this was considered a likely predictor of hospitalisation). Goodness of fit was assessed via the Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC) and two times log-likelihood score (2LL). The selection of final clinical parameters was made via a stepwise process using a cut-off threshold of 0.05 for inclusion. NYHA class was described as having three rather than the conventional four categories (I and II were pooled), because of data scarcity in patients classified as NYHA class I.

Regardless of which goodness of fit criterion was used, the NBRM model was deemed a better fit to the data than the PRM model. The final model used is described in Table 40. A comparison of the observed and predicted values is presented in Figure 20.

Table 40: NBRM results used to predict all cause hospitalisation in OPT arm (baseline risk)

Covariable	β Coefficient	Std. error	Z score	e^{β}
NYHA III				
NYHA IV				
Ischaemic aetiology				
QRS 120-150ms				
QRS >150ms				
Age				
Constant				

Figure 20: Comparison of observed vs. fitted baseline hospitalisation rates (events per month)



4.7.3.2 Results and discussion

The derived monthly probabilities are shown in Table 41, using an assumed starting age of 66 (the average age across all studies included in the hospitalisations analysis).

Table 41: Monthly probability of hospitalisation by covariate pattern (OPT)

	NYHA I/II	NYHA III	NYHA IV
Non-Ischaemic aetiology			
QRS <120ms	████	████	████
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████

Ischaemic aetiology			
QRS <120ms	████	████	████
QRS 120-149ms	████	████	████
QRS ≥150ms	████	████	████

The previous appraisal of ICDs by Buxton *et al.*³³ did not report hospitalisation rates, so it is not possible to compare the results of our analysis with those

previously used. However, it is possible to compare the derived NYHA class III/IV rates for OPT, CRT-P and CRT-D with those previously derived. Fox *et al.*³⁴ used 28 day values of HF related hospitalisation of 3.81% for OPT. These results should be interpreted with care as the values are based on historical CRT trials conducted in patients who were mostly NYHA class III and had a QRS complex ≥ 150 ms. Ischaemic aetiology was also an inclusion criterion in some of these studies. The results presented in Table 41 also correspond to rates over a slightly longer period (30.44 days [a calendar month] as opposed to 28 days) and are for all cause as opposed to HF related hospitalisation.

Nonetheless, comparison of the values for QRS ≥ 120 ms and NYHA class III/IV with the OPT values in Fox *et al.*³⁴ demonstrates that the values generated are in line with those used in the previous NICE appraisal.

The value of the present analysis lies in its quantification of risk in patients with both more and less severe HF than previously used, and also the inclusion of age related differences in hospitalisation. In particular, the derived value for patients with the worst possible covariate pattern (NYHA class IV, QRS duration ≥ 150 ms and ischaemic aetiology) is approximately twice that used in the previous appraisal.

Corroborative evidence for the plausibility of this result can be drawn from a recently presented analysis of data elicited from patients with NYHA class III/IV heart failure, mitral regurgitation and a general poor prognosis.¹²⁵ While not directly comparable, these patients can be thought of as at high risk of hospitalisation, and the derived monthly value in this patient group was approximately 8.5%.

4.7.4 Estimation of treatment effect on hospitalisation rate

4.7.4.1 Methods

The underlying approach used to estimate the impact of treatment on the rate of hospitalisation is similar to that used in a fixed effects network meta-analysis. Briefly, study specific intercepts were included as well as device related main effects. We also included NYHA class, ischaemic aetiology and baseline age as potential treatment effect modifiers, and explored whether the interaction between either NYHA class or ischaemic aetiology and choice of device had a significant impact on hospitalisation.

Choice of modelling approach was again made using BIC, AIC and 2LL scores, and variables were included at a significance level of $P=0.05$. Since the underlying data were still count data, the approaches assessed were again PRM or NBRM.

As with the baseline risk, the most appropriate approach to modelling the data was the NBRM. The final model used, after removal of all irrelevant covariates (study intercepts, main effects where interactions are included, etc.) from the table is presented in Table 42.

Table 42: Negative binomial model used to predict the impact of treatment on all cause hospitalisations per month

Covariable	β Coefficient	Std. error	Z score	e^{β}
Device = ICD				
Device = CRT-P				
Device = CRT-D				
Device = CRT-P and NYHA = III				
Device = CRT-P and NYHA = IV				

Of note, the interaction terms relating to treatment and ischaemic aetiology were not significant and hence, while predictive of baseline risk, aetiology grouping has no significant impact on treatment efficacy.

4.7.4.2 Results and discussion

The derived treatment effects are presented in Table 43.

Table 43: Derived all cause hospitalisation treatment effects

	NYHA I/II	NYHA III	NYHA IV
ICD			
CRT-P			
CRT-D			

Despite information being available from a number of trials in a large number of patients, the results presented above require careful interpretation. In particular, in the underlying data set there were very few patients with NYHA class I/II who

received a CRT-P device, and a small number who were NYHA class IV (particularly amongst patients randomised to ICD). In line with the overall submission strategy we have therefore not generated results for these devices in these patient groups.

Clinically, it is highly unlikely that the use of CRT-D will result in a smaller treatment effect than the use of CRT-P in a given patient group, as both receive CRT therapy. In addition, as noted above, the majority of studies from which data were drawn are ICD/CRT-D studies, where the primary endpoints related to mortality and not hospitalisations. It is therefore conceivable that events were either not reported or incompletely recorded in these trials, leading to increased noise in the underlying dataset. This result is therefore highly likely to be a construct of the data used, and clinically plausible assumptions will be made in the model to reinstate face validity. The values used in the model, together with the justification, are presented in Table 44.

Table 44: All cause hospitalisation treatment effects used in the model (events per month)

	Value	Justification
ICD		
NYHA I/II	████	Results from IPD analysis clinically plausible
NYHA III	████	Results from IPD analysis clinically plausible.
NYHA IV	N/A	Device not assessed in this patient group
----- CRT-P -----		
NYHA I/II	N/A	Device not assessed in this patient group
NYHA III	████	Results from IPD analysis clinically plausible
NYHA IV	████	Results from IPD analysis clinically plausible
----- CRT-D -----		
NYHA I/II	████	Results from IPD analysis clinically plausible
NYHA III	████	Results from IPD analysis not clinically plausible. Assumed same as CRT-P value given common component (CRT)
NYHA IV	████	Results from IPD analysis not clinically plausible. Assumed same as CRT-P value given common component (CRT)

4.7.4.3 Device specific values used in the model

The full list of monthly transition probabilities used in the model for each intervention is presented in Table 45 to Table 47. An assumed starting age of 66 was again used in all calculations.

Table 45: Monthly all cause hospitalisation transition probabilities (ICD, events per month)

	NYHA I/II	NYHA III	NYHA IV
Non-ischaemic aetiology			
QRS <120ms	████	████	N/A
QRS >120ms, ≤150ms	████	████	N/A
QRS >150ms	████	████	N/A
Ischaemic aetiology			
QRS <120ms	████	████	N/A
QRS >120ms, ≤150ms	████	████	N/A
QRS >150ms	████	████	N/A

Table 46: Monthly all cause hospitalisation transition probabilities (CRT-P, events per month)

	NYHA I/II	NYHA III	NYHA IV
Non-ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	N/A	████	████
QRS >150ms	N/A	████	████
Ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	N/A	████	████
QRS >150ms	N/A	████	████

Table 47: Monthly all cause hospitalisation transition probabilities (CRT-D, events per month)

	NYHA I/II	NYHA III	NYHA IV
Non-ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	██████	██████	██████
QRS >150ms	██████	██████	██████
Ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS >120ms, ≤150ms	██████	██████	██████
QRS >150ms	██████	██████	██████

Comparison of the derived values with those used in previous NICE appraisals is again only possible for CRT-P and CRT-D. In their 2007 model, Fox *et al.*³⁴ used a common four weekly value of 2.49% for heart failure related hospitalisations for both devices. This was derived using relative risk estimates based on data from up to five studies at different time points, but without any correction for the different follow up periods.

Nonetheless, when an assumed 90%/10% distribution of NYHA III/IV is made (the approximate mix of all trials included in the Fox *et al.*³⁴ model and applied to the non-ischaemic values for the widest QRS duration, again in line with historical trials) the pooled monthly estimate would be ██████. Hence, allowing for different units of time, the all cause hospitalisation values derived using the IPD based approach are very similar to the HF hospitalisation related values used in previous appraisals.

4.7.5 Conclusions from the IPD analysis of all cause hospitalisation

The significant ($p < 0.05$) predictors of hospitalisation in patients on OMT were NYHA class, aetiology, age and QRS duration. All of these would be expected *a priori* to impact on hospitalisation, and so our results retain face validity. All three devices were estimated to reduce the rate of hospitalisation. Only NYHA class was found to be a significant effect modifier, and only for the CRT-P device, with patients in higher NYHA classes experiencing a stronger treatment effect. We also used two different approaches to analysing the data, and the results from

both are internally consistent.

Across all NYHA classes, device therapy was associated with a reduction in admission rates.

In NYHA class I to III, ICD was associated with a [REDACTED] reduction in admission rates, and CRT with a [REDACTED] reduction. The effect in NYHA class IV is even more pronounced, with CRT offering a [REDACTED] reduction in admission rates (although the data used to inform this result are sparse).

A patient who is hospitalised places a burden on local resources and is likely to have a reduction in general well-being. Thus, treatments that reduce hospitalisation will be attractive to both local finance managers and patients.

The key value of the IPD approach used in our analysis is that it allows results to be generated for a range of clinical variables. This in turn allows for a more nuanced approach to identifying clinical benefit. By virtue of working with data from multiple clinical trials, we are also able to identify any benefits that would not have been identifiable had a single study been used. We were also able to identify and correct for any placebo or Hawthorne effects inherent in the clinical trial data.

Because of the level of data available and the ability to use clinical and patient characteristics to define the admission rate, the results from this analysis are the best and most robust currently available. The data were completely aligned with the mortality analysis, and so derived event rates were based on the same follow up data as survival rates.

That our results are more nuanced and more useful in terms of medical decision making can be seen by comparing them with those from the previous CRT appraisal. The latter generated pooled event rates for patients who were NYHA class III/IV, and did not account for ischaemic aetiology. The monthly values from the “worst case scenario” in the current analysis are nearly twice those from previous analyses, meaning that the previously generated rates were not reflective of what is actually happening in clinical practice.

4.8 Health related quality of life

The purpose of this analysis is to inform the utility values used in the economic model. It is useful first to briefly review values used in other models. We then present the modelling methods used, followed by the results and conclusions from the HRQoL analysis (see Section 4.8.9).

4.8.1 Review of results from the literature review

The review of published HRQoL data (Section three) is highly supportive of the following hypotheses:

- i) The impact of treatment is dependent on whether an individual is classified as NYHA class I/II or NYHA class III/IV.
- ii) Use of an implanted CRT device significantly improves HRQoL in patients with severe HF.
- iii) Use of an ICD device neither significantly improves nor worsens HRQoL of patients with severe HF.
- iv) The impact of CRT therapy in patients with mildly symptomatic HF is more modest than in severe HF, possibly due to a ceiling effect, and there may be no differences between device types in impact on HRQoL in these patients.

The economic model from the previous NICE appraisal of CRT used NYHA class specific utility scores.³⁴ Our review of the impact of treatment on the underlying disease (expressed as either change in NYHA score from baseline or improvement in NYHA class), when used in combination with the NYHA specific utility scores, further supports these hypotheses.

4.8.2 Overview of values used in previous models

As mentioned above, in their submission dossier to the previous CRT appraisal, PenTAG used NYHA class specific utility values, which were combined with the results from the CARE-HF trial to estimate the change in utility over time.³⁴ In contrast, in the original assessment of ICD therapy Buxton *et al.*³³ used a common utility score for ICD and OPT (0.75), with the rationale being 'based on UK sample data'.

Among the non-UK HTA based models, the values used for each intervention in a selection of studies are summarised in *Table 48*. Although not a systematic review of the literature, trends emerge from the information provided, principally that ICD and OMT have commonly been assumed to have the same impact on an individual's health related quality of life.

Table 48: Overview HRQoL modelling approaches used in previous economic models

Study	Interventions	Method used
Calvert <i>et al.</i> ¹²⁶	CRT-P, OPT	Advanced statistical techniques and mapping algorithm used to derive treatment specific long term utility scores
Feldman <i>et al.</i> ¹²⁷	CRT-P, CRT-D, OPT	Derived via a mapping algorithm applied to MLWHF scores
Al-Khatib <i>et al.</i> ¹²⁸	ICD/ OPT	Common value of 0.88 used for both interventions. Source unstated in text
Linde <i>et al.</i> ¹²⁹	CRT, No CRT	Trial based analysis of NYHA mix over time combined with PenTAG NYHA values
Mark <i>et al.</i> ¹³⁰	ICD, OPT	A common utility weight of 0.85 was used for both treatments based on a regression analysis of time trade off data
Sanders <i>et al.</i> ¹³¹	ICD, OPT	Common value of 0.88 applied to both treatments
Yao <i>et al.</i> ¹³²	CRT-P, CRT-D, OPT	NYHA class specific utility scores

4.8.3 Overview of approach used in current model

The approach used in the current model is as follows:

- i) Estimate UK specific age and gender population utilities.
- ii) Derive a disease specific decrement using the patient level EQ-5D data, with a range of clinically plausible variables used to parameterise the regression equation. The derived decrements will be compared to the population norms in order to derive an estimate of the impact of disease beyond natural background ageing in different subgroups.
- iii) Derive treatment specific increments associated with each device at first follow up visit by NYHA class. For the purposes of this model we have used an NYHA codification of I/II, III and IV.

- iv) Estimate the period of time over which the benefit of treatment is experienced. Individuals will experience a tailing off in treatment related benefit up to this point and thereafter will revert to baseline (OMT) utility (i.e. no benefit).

Point iv) is where the current approach differs from all previous analyses. As can be seen from Section 4.4.2, all other researchers, even those using regression based approaches, have assumed that the benefit of treatment is constant over time. In previous NICE appraisals, the time horizon used in the ICD model was 20 years, with the constant utility applied in all years. In the CRT appraisal, the NYHA mix at 18 months was assumed to hold in all future cycles. Hence, the current approach is more conservative than any previous analysis.

Despite patient level MLWHF data being available in multiple trials at multiple time points, we chose not to use these for any of the primary HRQoL analyses. The rationale for this decision was two-fold. Firstly, as noted in the most recent version of the NICE reference case, there is a strong desire for preference weights to be derived using the EQ-5D instrument¹⁰³. The second reason was the criticisms raised during the previous NICE appraisal of CRT of the mapping algorithm devised by Havranek *et al.*¹³³, in particular its poor predictive accuracy ($R^2=0.1$). Similarly, a multiple imputation approach such as used by Calvert *et al.* in the previously published CARE-HF model¹²⁶ was rejected due to inadequate imputation accuracy arising from high levels of missing data in the dependent variable. The level of data for the key variable (EQ-5D) was “block missing” (i.e. not collected in most studies from which data were available).

Nevertheless, we have analysed the MLWHF data, with a view to using the results to support any modelling assumptions made, and in particular to estimate the duration of treatment benefit.

Each of the four components of the base case analysis is discussed separately below.

4.8.4 Modelling EQ-5D population preference weights

The key data source for estimating UK specific age and gender EQ-5D population norms is a study by Kind *et al.* of 3,395 individuals resident in the UK.¹³⁴ The raw data are reproduced in Table 49 and the results of regression equations using the mid-point of these ranges as the time variable are presented in Table 50. The

values were used to generate all population estimates in all model cycles.

Table 49: Age and gender specific UK EQ-5D population norms (mean, SD.) reproduced from Kind et al. ¹³⁴

Age band	Male	Female
Under 25	0.94 (0.12)	0.94 (0.12)
25-34	0.93 (0.16)	0.93 (0.15)
35-44	0.91 (0.17)	0.91 (0.15)
45-54	0.84 (0.27)	0.85 (0.23)
55-64	0.78 (0.28)	0.81 (0.26)
65-74	0.78 (0.28)	0.78 (0.25)
75+	0.75 (0.28)	0.71 (0.27)

Table 50: Regression coefficients used to model age specific population utility

Group	Coefficients			R² statistic
	Constant	Age	Age squared	
Male	1.0257	-0.0036	N/A	0.9413
Female	0.9643	-0.0002	-0.00004	0.9872

4.8.5 Estimating the impact of baseline disease severity on HRQoL

EQ-5D data were available from three studies for the purpose of this analysis (N=4,432).^{8;67;80} The raw data are presented graphically in Figure 21 and the distribution of individuals across the NYHA groups is shown in Table 51.

Figure 21: Histogram of baseline EQ-5D data across all three clinical trials

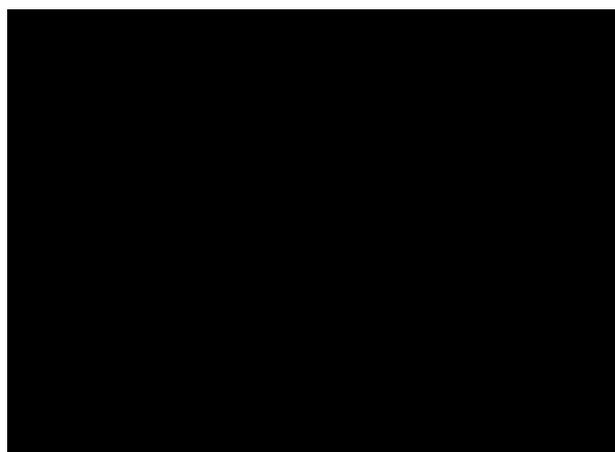
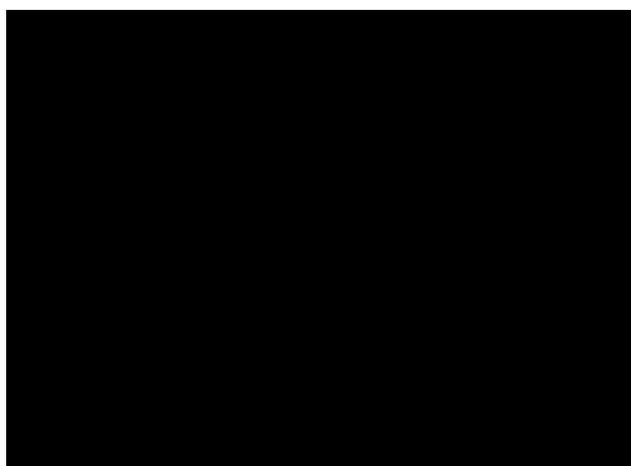


Table 51: Distribution of baseline EQ-5D observation counts by NYHA class

Class	Count	Percentage of total
I/II	██████	██████
III/IV	██████	██████

A large number of individuals ██████ reported a score of 1 (implying perfect health), and the majority of the individuals in whom EQ-5D data were collected had mild to moderate heart failure (see Table 51). In order to derive decrements, the data were transformed to a proportional change from unity (see Figure 22). Since the transformed data are in count format, standard regression techniques can be applied to estimate the impact of different baseline clinical variables on HRQoL.

Figure 22: Histogram of baseline EQ-5D data across all three clinical trials expressed as proportional change from unity



The regression techniques introduced in Section 4.7.3 (modelling of hospitalisation) were assessed for candidacy, with a negative binomial model being used in the final analysis. The justification for this choice is presented in Appendix 12.

The final negative binomial model is presented in Table 52. Variable selection was again made on the basis of stepwise methods using an inclusion threshold of 0.05.

Table 52: NBRM Coefficients used to predict baseline utility decrement

Covariable	β Coefficient	Std. error	Z score	e^{β}
NYHA = III	████	████	██	████
NYHA = IV	████	████	██	████
Age	████	████	██	████
Ischaemic aetiology	████	████	██	████
Gender= Male	████	████	██	████
Constant	████	████	██	██

* Variable included despite not being significant on the basis of the underlying disease. Lack of significance likely to have arisen due to small patient counts.

Validation

Due the combination of treatment options, clinical variables and time, as well as the distribution of patients across the covariate patterns, the analysis of patient level EQ-5D data was particularly challenging, and interpretation of the model outputs is not straightforward. Validation of the approach is also challenging, since all of the available data have been used in the construction of the model. Nevertheless, generating results for all patient covariate patterns allows for a simple sanity check. Non-ischaemic subgroups are presented in Table 53 and ischaemic subgroups in Table 54. A common assumed starting age of 66 has been used in all calculations, giving an average age and gender adjusted UK population norm utility score of 0.7902 for females and 0.7900 for males.

Table 53: Comparison of indicative individuals with population equivalents (non-ischaemic aetiology)

Decrements from unity				
NYHA	Gender	Pop Norm	Derived	Disease specific component*
I/II	Male	0.2100	████	████
I/II	Female	0.2098	████	████
III	Male	0.2100	████	████
III	Female	0.2098	████	████
IV	Male	0.2100	████	████
IV	Female	0.2098	████	████

* Corresponds to difference between population norm and derived value. To be interpreted as the impact of disease above and beyond what would naturally occur.

Table 54: Comparison of indicative individuals with population equivalents (ischaemic aetiology)

Decrements from unity				
NYHA	Gender	Pop norm	Derived	Disease specific component*
I/II	Male	0.2100	████	████
I/II	Female	0.2098	████	████
III	Male	0.2100	████	████
III	Female	0.2098	████	████
IV	Male	0.2100	████	████
IV	Female	0.2098	████	████

* Corresponds to difference between population norm and derived value. To be interpreted as the impact of disease above and beyond what would naturally occur.

Broadly speaking, and allowing for the relatively complex approach used as well as the nature of the underlying data the following general statements appear to hold in relation to the derived values:

- i) The size of the disease specific decrements increases through the NYHA classes.
- ii) Individuals in NYHA class I/II have effectively the same HRQoL as an age equivalent member of the general public.
- iii) Patients with ischaemic aetiology have a slightly worse HRQoL than those with

non-ischaemic aetiology.

iv) Slight differences exist between the values generated for males and females.

Overall, this is all what would be expected given the nature of the underlying disease. A simpler validation is to compare the decrement-derived absolute EQ-5D values with the raw, mean EQ-5D data from the three trials that collected it. A summary of the relevant trial information is presented in Table 55. Absolute values for each covariate combination range from approximately 0.8 for patients who are in NYHA class I/II to approximately [REDACTED] for those who are in NYHA class IV and have an ischaemic aetiology of heart failure.

Table 55: Summary EQ-5D statistics from the three clinical trials in which data was collected

Study	N	Mean	Std. Dev	Min	Max
CARE-HF	741	0.6031	0.28204	-0.59	1.00
MADIT-CRT	1787	0.7958	0.19214	-0.43	1.00
RAFT	1789	0.7512	0.19492	-0.145	1.00

The derived absolutes are within an acceptable level of tolerance for inclusion into the three studies, though again the external value of this comparison is limited due to the comparison of results from a regression analysis with the input data. However, it does show that the zero inflated negative binomial model has internal validity.

Overall, the approach used generates clinically plausible results.

4.8.6 Estimating impact of treatment on HRQoL

EQ-5D data were used in the HRQoL analysis, but the EQ-5D instrument was used in only three of the trials. For this reason, it was felt appropriate to refer to the larger MLWHF data set to corroborate the results in those instances where clinically counter-intuitive results were generated for particular subgroups.

The impact of treatment on a patient level can be calculated as the difference between baseline and first follow up period (with the 90 day data from CARE-HF assumed to reflect what would have been observed at 180 days, the follow-up available for the other trials). As discussed in section three of the review of clinical efficacy, the impact of treatment is likely to depend on NYHA class and

the choice of treatment. In total 3,736 observations were available to inform the analysis.

As highlighted in Table 51, the majority of individuals are in NYHA I/II at baseline. Further confounding variables are that two of the four treatment options (ICD and CRT-D) are only used in RAFT and MADIT-CRT, and the other two exclusively used in CARE-HF. Furthermore, when device use is viewed by NYHA group, only [REDACTED]. Hence, there is a weak network of studies available to inform any meaningful regression analysis.

We have therefore used the IPD data to generate mean changes from baseline for each device type by NYHA group. The results are presented in Table 56. Results for ICD in patients who are NYHA IV and CRT-P in patients who are NYHA I/II have not been generated.

Table 56: Mean changes from baseline in EQ-5D at six months by device and NYHA group (mean, s.e.)

	NYHA = I/II		NYHA = III		NYHA = IV	
	N	Change	N	Change	N	Change
OPT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
ICD	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CRT-P	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CRT-D	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

* Significant at 95% confidence level

The results for several patient groups appear highly counter-intuitive given the nature of the underlying disease and the interventions being used. Most obvious of these are the results for all NYHA IV patients, and for CRT-D in NYHA III. The latter are particularly striking given the positive results for CRT-P in the same patient group and the use of a common treatment component.

4.8.6.1 Exploratory analysis: change in MLWHF at 6 months

In order to assess whether or not the counter-intuitive results are real or artefacts of the EQ-5D data and modest patient counts, an identical analysis was performed for all MLWHF data. The results from this analysis are presented in

Table 57.

Table 57: Mean changes from baseline in MLWHF at six months by device and NYHA group (mean, s.e.)

	NYHA = I/II		NYHA = III		NYHA = IV	
	N	Change	N	Change	N	Change
OPT	████	████████████████	████	████████████████	██	████████████████
ICD	████	████████████████	██	████████████████	██	████████████████
CRT-P	██	████████████████	██	████████████████	██	████████████████
CRT-D	██	████████████████	██	████████████████	██	████████████████

Overall, far more data were available for this analysis than for the analysis of EQ-5D data. Assuming that MLWHF is a fair representation of an individual’s health related quality of life the following conclusions can be drawn:

- i) The impact of CRT-D and CRT-P on HRQoL in patients who are in NYHA class III or NYHA class IV is both substantial and very similar.
- ii) CRT-P has at least as large an impact on HRQoL in patients who are in NYHA class I/II as either ICD or CRT-D.
- iii) Regardless of NYHA class, individuals who do not get any form of device achieve at best a modest change in HRQoL.

This last point suggests that some form of placebo effect, or continuing improvement due to OPT is occurring, meaning that a correction needs to be made to all values used for all devices to ensure that this effect is not included (i.e. a ‘difference in difference’ approach is required).

4.8.7 Values used in the model

On the basis of the above analyses of six month data, as well as information presented in the systematic review section of the dossier, the values used in the model and the justification for the choices are presented in Table 58. In generating these values, we have deducted the OMT NYHA class III value from all estimates (see Table 56) to account for any trial based placebo effects. In effect, we have used a difference in differences approach to generating the final values used.

Table 58: Treatment specific utility increments used in the economic model

	Value	Justification
NYHA = I/II		
OPT	██████	No clinical reason why an individual already on optimized medication would have a change in utility
ICD	██████	Value derived from IPD analysis ██████. Systematic review highly suggestive of ICD therapy have a positive impact in this patient group
CRT-P	████	Cost-effectiveness results not generated for this treatment option
CRT-D	██████	Value derived from IPD analysis ██████. Systematic review and MLWHF analysis highly suggestive of CRT-D therapy have a positive impact in this patient group
NYHA III		
OPT	██████	No clinical reason why an individual already on optimized medication would have a change in utility
ICD	██████	Result from IPD analysis not significantly different to zero. Literature review supportive of no benefit from ICD treatment in this patient group
CRT-P	██████	Value derived from IPD analysis ██████. Literature review concluded that there was a benefit of this treatment option in this patient group, supported by MLWHF analysis
CRT-D	██████	Assumed same as value used for CRT-P. IPD results for this treatment option derived from very small patient numbers. No clinical reason why this should perform any different to CRT-P. Analysis of MLWHF and literature review strongly supportive of therapeutic benefit in this patient group
NYHA IV		
OPT	██████	No clinical reason why an individual already on optimized medication would have a change in utility
ICD	████	Cost-effectiveness results not generated for this treatment option
CRT-P	██████	Not enough information available to inform meaningful analysis. Assumed same as for NYHA III. Analysis of MLWHF data supportive of this assumption
CRT-D	██████	Not enough information available to inform meaningful analysis. Assumed same as for NYHA III. Analysis of MLWHF data supportive of this assumption

4.8.8 Estimation of HRQoL treatment benefit duration

4.8.8.1 Relevant long term published data

In a long term retrospective analysis of the CARE-HF HRQoL data, Cleland *et al.*⁵⁶ used a previously published algorithm³¹ to estimate the magnitude of benefit

at 18 months and study end. The key results are reproduced in Table 59. The observed 3 monthly difference estimate was, unsurprisingly, very similar to that generated using the IPD analysis and was maintained for at least 18 months (the minimum follow up period) until study end. Interpretation of “end of study” is not obvious, but median follow up was 29.6 months. We have thus interpreted the results as saying that the benefit lasted for at least 2.5 years.

Table 59: CARE-HF based long term EQ-5D gains (mean, 95% CI) reproduced from Cleland et al.⁵⁶

Time point	OPT	CRT-P	Difference	P-value
Baseline	0.60 (0.57, 0.63)	0.60 (0.58, 0.63)	N/A	N/A
3 months	0.61 (0.59, 0.64)	0.69 (0.66, 0.72)	0.08 (0.04, 0.11)	<0.0001
18 months	0.52 (0.48, 0.54)	0.61 (0.58, 0.64)	0.10 (0.06, 0.15)	<0.0001
End of study	0.43 (0.39, 0.46)	0.56 (0.52, 0.59)	0.13 (0.08, 0.18)	<0.0001

4.8.8.2 Additional IPD analyses

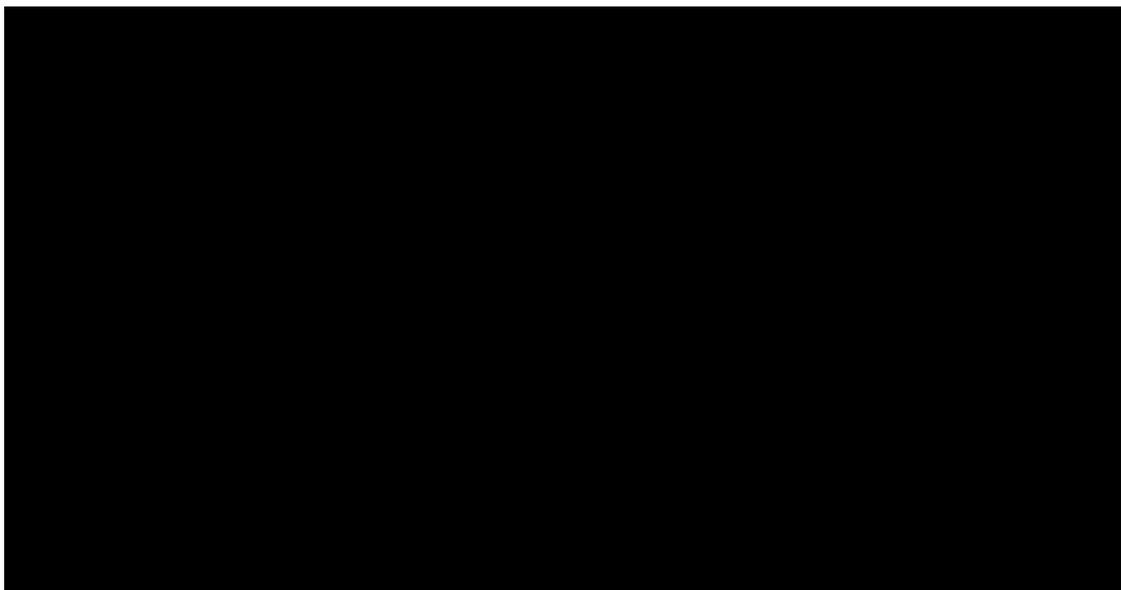
Long term MLWHF data from all studies and all devices was used to inform change from baseline estimates at three-monthly periods, and as a conservative assumption it was decided to limit the duration of treatment benefit on HRQoL. More technically, we identified the time point at which the mean change from baseline was zero. The purpose of this analysis was to estimate how far beyond 2.5 years treatment related HRQoL benefit might exist.

In general, not enough data in patients who were in NYHA class IV were available to inform a meaningful analysis. Similarly, minimal data existed for CRT-P patients post 18 months in all NYHA classes, so again no meaningful long term analysis could be performed. The ‘difference in difference’ values for NYHA class I/II and NYHA class III for ICD and CRT-D (mean device value minus mean OMT value) are plotted in Figure 23 and Figure 24. With the exception of ICD in NYHA I/II, benefit is still being experienced (on average) ██████ years after device insertion

Figure 23: difference in difference (device-OPT) long term change in MLWHF (NYHA I/II)



Figure 24: difference in difference (device-OPT) long term change in MLWHF (NYHA III)



4.8.8.3 Value used in model

In order to be conservative in our assumptions we have assumed a health related quality of life benefit of five years for all devices in all NYHA classes.

The impact of truncating this benefit period is explored in sensitivity analyses.

4.8.9 Conclusions from the HRQoL analysis

In our analysis of the EQ-5D data, after accounting for placebo effects, CRT had a strong impact on HRQoL [REDACTED] in NYHA class I/II; [REDACTED] in NYHA class III/IV).

There was a small positive impact of ICD for patients in NYHA class I/II [REDACTED], but not for patients in NYHA class III/IV (hence, any extension of life in these patients will have the same HRQoL as would be observed on OPT.

The key clinical parameters that had a significant ($p < 0.05$) impact on baseline HRQoL were NYHA class, aetiology, age and gender. Of these, NYHA class is a surrogate for disease severity, and aetiology status a proxy for previous MI. In addition, age and gender are known modifiers of HRQoL in the general population. Hence, the results have face validity. However, the direction of impact of age and gender is opposite to what would be expected in the general population, albeit very slightly. This should be viewed as a limitation of the analysis and is reflective of the data used and not the analytical approach.

From the patient perspective, improvements in quality of life are arguably as important as life extension. As noted in Section 3.7, individual studies showed significant HRQoL improvements regardless of whether a generic (EQ-5D) or disease specific (MLWHF) instrument was used. These studies report results at the aggregate level (i.e. for all patients in a study) and not at a patient level.

The benefits of the IPD based approach for estimating treatment effects on HRQoL are similar to those discussed for all cause hospitalisation. Again, the HRQoL analysis is completely aligned with the mortality data, meaning that the same patient exposure data were used. Hence, the results presented here represent the best, most robust evidence as to the magnitude of HRQoL benefit for each intervention.

Interestingly, while no direct mapping algorithm exists to generate EQ-5D preference weights solely from MLWHF scores, the IPD analyses of data for this disease specific instrument can be used to inform the duration of HRQoL benefit.

- In patients who were in NYHA class I/II and had ICD based treatment,

improvement in MLWHF existed for approximately █ years (contingent on the individual being alive).

- In patients who were in NYHA class III/IV, contingent on being alive, the duration of benefit was approximately █ years.

Hence, our analyses show that HRQoL benefits are likely to be maintained for many years after initial implant. This result is in line with recently published information from the CARE-HF study.

5 Assessment of cost-effectiveness

- This section presents the methods and inputs used to model cost-effectiveness.
- The modelling approach used is described. Note that full details of the methods used to model mortality, hospitalisation and HRQoL are described in Section 4.
- The values used in the model are presented, along with explanations of how they were sourced or derived.
- Long term (>10 year) time to device replacement data from approximately 40,000 UK implants was used to inform device failure rates for all three interventions. Predicted median time to replacements for ICD, CRT-P and CRT-D are 7.1, 10.3 and 5.8 years respectively.
- We have used conservative assumptions throughout. In particular, in contrast to previous models, we have assumed that any treatment effects on mortality or HRQoL are not constant but diminish over time.
- Initial implant costs for ICD, CRT-P and CRT-D are £15,248, £8,281 and £17,849 respectively.

5.1 Description of modelling approach

The model has two 'health states': alive and dead. The rationale for this approach is that, in the patient population of interest, death is the main clinical event. By modelling death directly via a series of covariate based regression equations (for baseline risk and treatment effect), we were able to use the long term data available and to explore the impact of patient-level heterogeneity. This approach also allowed for a coherent regression-based approach to modelling HRQoL and all-cause hospitalisation that was aligned with the mortality analysis. Of the other approaches to modelling HRQoL that we considered, the use of a clinical surrogate (i.e. time-dependent progression through NYHA classes) was rejected due to the technical difficulties it would entail, as well as the loss of predictive accuracy.

The first regression equation is used to predict the probability of death in patients who receive OMT but no device, based on a range of clinical covariates. These probabilities are used in combination with treatment effects derived via network meta-analyses to derive device specific death probabilities. The methods used to define this approach are described in detail in section 4.2

Conditional on being alive at a given time point, two additional equations are used to predict the probability of experiencing a hospitalisation event, and the level of HRQoL (utility). The methods used are described in detail in section 4.3 and section 4.4. In addition, all living patients potentially incur other costs related to device replacement, background medication and routine clinical visits.

The analysis follows NICE methodological guidance issued in 2008.¹⁰³ A lifetime time horizon has been used for the model in combination with a one month cycle length, and all costs and benefits (QALYs) incurred or accrued for each treatment option are calculated. Annual discount rates of 3.5% and a half cycle correction are applied to both costs and benefits in all calculations. A strict UK NHS perspective has been used in all cost calculations.

5.2 Mortality

The method used to model mortality is described in detail in section 4.2

5.3 Event probabilities

5.3.1 All cause hospitalisation

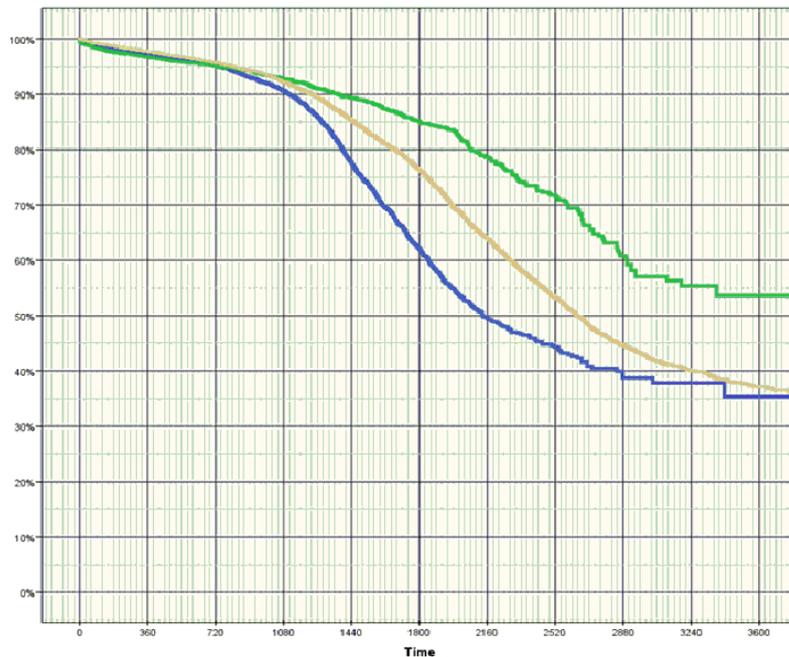
The method used to model all cause hospitalisation is described in detail in section 4.3

5.3.2 Device lifetime (time to first replacement)

UK device longevity estimates were derived from an analysis of all implants with verified life status from 1/1/2000 until 14/4/2011. This was performed on behalf of the Association of British Healthcare Industries (ABHI) by Dr. David Cunningham, Director of the Central Cardiac Audit Database (CCAD) (supplied via personal communication). The results are presented as Kaplan-Meier plots in Figure 25. Approximately 40,000 implants were used to inform the analysis (ICD:22,259 CRT-P:7,968 CRT-D:10,062). The data were uncensored, meaning that all device replacements, however soon after initial implant, were included. Given that CCAD

is run by the NHS Information Centre, and the large number of implants from which data was available, the device longevity estimates represent the best currently available.

Figure 25: UK device longevity data (Jan 2000 to April 2011, time unit: days)



Legend: Blue=CRT-D, Yellow=ICD, Green=CRT-P

In order to include the information in the model, we electronically extracted the above data into Microsoft Excel[®] (Microsoft Corporation, Redmond, WA) and fitted Weibull parametric functions. No data were excluded from the curve fitting process. The Weibull curve was chosen since it is commonly used to model such data and often offers a good fit (both in terms of within-data accuracy and long term predictive plausibility). In the case where the fitted Weibull curve was deemed unrealistic (i.e. either within data period accuracy was poor or extrapolated survival clinically implausible), a broader range of commonly used functions would be used (exponential, log-normal, log-logistic) and the “best” fit chosen from this wider set.

Comparisons of the observed and fitted Weibull functions for CRT-P and ICD are presented in Figure 26 and Figure 27. The fitted curves were a reasonable approximation with clinical face validity, and no other alternatives were considered. Since the curve fitting process was undertaken in Excel, goodness of fit is assessed via the R^2 statistic (>0.97 for both curves).

Figure 26: Parametric function fitted to UK CRT-P implant data

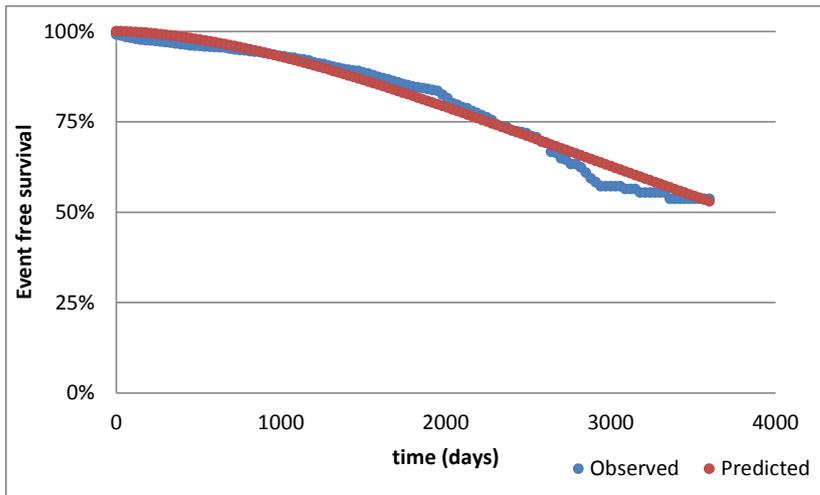
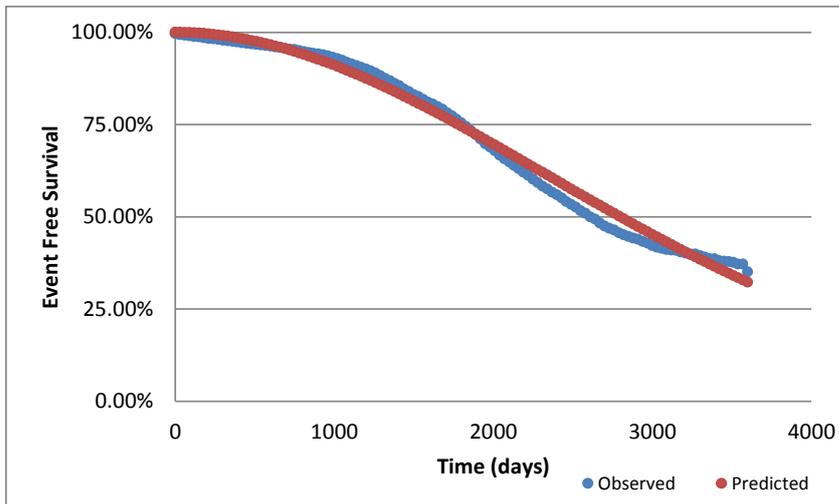


Figure 27: Parametric function fitted to UK ICD implant data



The Weibull curve used to model the CRT-D data was not as good a fit to the data as those used for ICD and CRT-P and so the wider range of curves were fitted. A comparison of the observed CRT-D data and fitted exponential, Weibull, log-logistic and log-normal functions is presented in Figure 28. No curve completely captures the observed data. We also considered, but rejected, a piecewise curve fitting approach since this generated clinically implausible device longevity estimates. Hence, we have used the Weibull function in the base case for reasons of extrapolative plausibility (see Figure 29). Of note, the final choice generates the lowest estimate of mean device longevity, and can therefore be considered conservative.

Figure 28: Parametric function fitted to UK CRT-D implant data

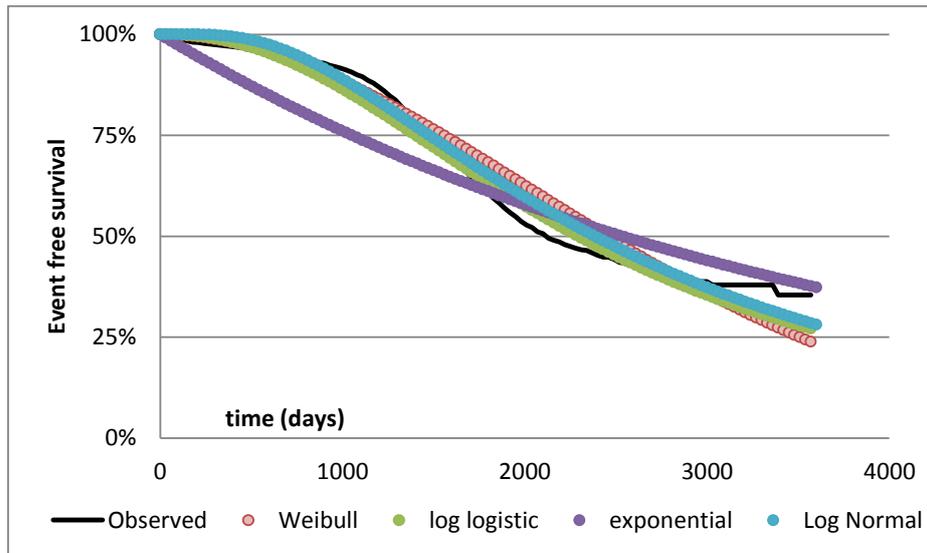
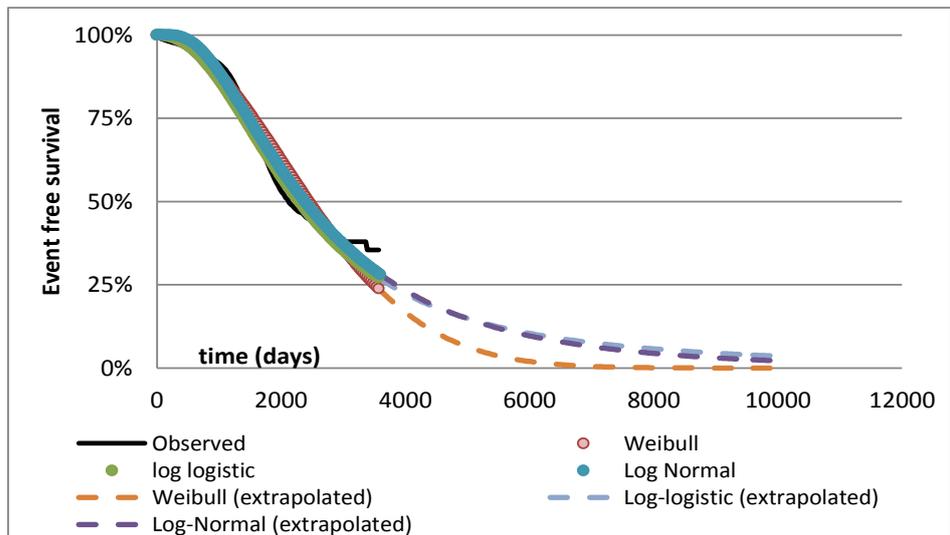


Figure 29: Extrapolation of parametric functions: CRT-D data only



Cycle specific cumulative survival probabilities were used to estimate device specific failure probabilities using conventional formulae.¹³⁵ Values were not applied to the first two cycles (i.e. 60 days) in the model because of the approach used to model adverse events.

5.3.3 Device lifetime (time to subsequent replacements)

As can be seen from Figure 25 above, device replacement will be uncommon during expected survival, with the exception of those with mild heart failure. We have therefore assumed, for completeness and given the complexity of the underlying cost-effectiveness model and the need to avoid ‘tunnel states’ (states where patients can only remain for one cycle), that conditional on having already

had one replacement, the probability of subsequent replacements (i.e. second and subsequent) in any given cycle is constant for each device type. Device specific median survival estimates derived from the Cunningham dataset were used to inform these transition probabilities.

The values used in all model cycles are presented in Table 60.

Table 60: Parameters used to derive time to second and subsequent device replacement estimates

Treatment option	Median time to failure (days)	Derived monthly rate of replacement (second/ subsequent)
ICD	2600	0.00039
CRT-P	3780*	0.00027
CRT-D	2115	0.00047

* Failure curves not crossed 50% value at end of follow up period. Hence, median value from fitted curve used.

5.3.4 Device related adverse events (short term)

The nature of the costing approach used to derive total initial implant costs is based on a mixture of wholesale prices (for devices and leads) and HRG tariffs which cover all additional costs (inpatient care, short term adverse events etc.). Thus, to avoid double counting we have not explicitly included short term device related adverse events separately in the model.

5.3.5 Infection rates (post battery replacement)

Infection following device replacement is a relatively uncommon but serious device-related adverse event, and has therefore been included in the model for all procedures subsequent to the initial implant. The proportion of patients experiencing this event was based on information derived from 1,744 North American individuals who were included in the REPLACE registry.¹³⁶ Overall, 14 major events were reported in all generator replacements (0.8%). This value has been applied to all devices in the first cycle following battery replacement.

5.4 Resource use

5.4.1 Reasons for hospitalisation

In a review of 322 incident cases of heart failure in England, Cowie *et al.* noted that 50.1% of subsequent hospitalisations related to worsening heart failure and the remainder are explained by multiple other reasons.¹³⁷

In addition, lead-related complications can be expected to occur in every month and will result in time in hospital. The most up to date information on this event comes from the REPLACE registry. In this database, of the 1,031 individuals without a planned lead related procedure, a total of 11 severe lead related events occurred (1.07%) across all hospitalisations.¹³⁸ The proportion of patients hospitalised for reasons other than worsening heart failure or lead related complications is the remainder (100% minus 50.1% minus 1.07%).

A summary of the values by hospitalisation type used in the model is presented in Table 61. As with the derivation of device related adverse events, common logic has been applied to exclude lead related events from patients on OMT. These values are used in combination with the costs presented in Section 5.5 to generate an average cost per hospitalisation event.

Table 61: Distribution of reasons for hospitalisations by intervention

	OPT	ICD	CRT-P	CRT-D
Heart failure related	50.1%	50.1%	50.1%	50.1%
Lead related	0%	1.07%	1.07%	1.07%
Other reasons*	49.9%	48.83%	48.83%	48.83%

* Values calculated as the residual of the other two

5.4.2 Background medication

A summary of the proportion of patients using a range of heart failure medications, by NYHA class, is presented in Table 62. The source for this information is a combination of the clinical studies identified in the systematic review (see Section 3) and expert opinion. Common values are applied to all four interventions in each month of the model (conditional on being alive), on the basis of baseline NYHA values.

Table 62: Background medication by NYHA class

	NYHA I	NYHA II	NYHA III	NYHA IV
Atorvastatin	20%	20%	20%	20%
Simvastatin	55%	55%	55%	55%
Warfarin	10%	15%	25%	40%
Clopidogrel	15%	15%	15%	15%
Ramipril	90%	90%	90%	90%
Carvedilol	85%	85%	75%	70%
Spirolactone	0%	30%	30%	30%
Digoxin	5%	25%	25%	25%
Furosemide	75%	80%	90%	95%
Eplerenone	0%	30%	30%	30%

5.4.3 Other resource use parameters

We have assumed that patients will require bi-annual device related outpatient visits for ICD patients and quarterly visits for CRT (CRT-D or CRT-P) patients.

5.5 Costs

5.5.1 Optimal pharmacological medical therapy (OMT)

5.5.1.1 Doses used in all calculations

OPT for HF is composed of a range of drugs both for heart failure treatment and primary and secondary prevention. An OPT regimen is taken by all patients, regardless of whether they receive a device in addition. In order to estimate the cost per cycle of pharmacological therapy, we used the British National Formulary (BNF)¹³⁹ to find the recommended daily dose for each commonly used drug (Table 63). Where a range of doses was possible, we have used those typically used in routine clinical practice as the basis of all costings.

Table 63: Recommended doses

Drug	Dose (mg/day)	Source
Atrovastatin (Liptor®)	10	British National Formulary ¹³⁹
Simvastatin	20	British National Formulary ¹³⁹ Value represents clinical practice
Warfarin	1	British National Formulary ¹³⁹
Clopidigrel	75	British National Formulary ¹³⁹ Value represents clinical practice
Ramipril	10	British National Formulary ¹³⁹
Carvedilol	25	British National Formulary ¹³⁹ Value represents clinical practice
Spirolactone	25	British National Formulary ¹³⁹ Value represents clinical practice
Digoxin	125 ^a	British National Formulary ¹³⁹ Value represents clinical practice
Furosemide	60	British National Formulary ¹³⁹ Value represents clinical practice
Eplerenone	25	British National Formulary ¹³⁹ Value represents clinical practice

a) Dosing measured in μg and not mg per day

5.5.1.2 Purchase costs for pharmacological therapy

Information on the costs of various combinations of pack size and tablet concentration was available from the BNF (Table 64). An average of these costs was calculated based on the cost per tablet, which was then combined with the mean dose to derive an estimate for the cost per cycle of each drug and the mean monthly cost of pharmacological treatment by NYHA class in (Table 65).

The drug cost allocated in any given month to each patient alive, regardless of treatment option, is predicated on their baseline NYHA class.

Table 64: Purchase costs

Drug	Tablets per pack	Tablet dose	Pack price	Source
Atrovastatin (Liptor®)	28	10mg	£13.00	BNF ¹³⁹
Simvastatin	28	10mg	£0.90	BNF ¹³⁹
	28	20mg	£1.01	
	28	40mg	£1.32	
	28	80mg	£2.29	
Warfarin	28	0.5mg	£1.49	BNF ¹³⁹
	28	1mg	£0.93	
Clopidigrel	30	75mg	£3.40	BNF ¹³⁹
	28	75mg	£3.17	
Ramipril	28	1.25mg	£1.10	BNF ¹³⁹
	28	2.5mg	£1.18	
	28	5mg	£1.25	
	28	10mg	£1.41	
Carvedilol	28	3.125mg	£1.10	BNF ¹³⁹
	28	6.25mg	£1.25	
	28	12.5mg	£1.37	
	28	25mg	£1.84	
Spirolactone	28	25mg	£1.55	BNF ¹³⁹
	28	50mg	£2.11	
	28	100mg	£2.46	
Digoxin	28	62.5	£2.03	BNF ¹³⁹
	28	125	£1.12	
	28	250	£1.13	
Furosemide	28	20	£0.81	BNF ¹³⁹
	28	40	£0.84	
	28	500	£4.05	
Eplerenone	28	25	£42.72	BNF ¹³⁹

Table 65: Total cost of treatment per 1 month model cycle

	NYHA I	NYHA II	NYHA III	NYHA IV
Total cost per cycle	£14.28	£22.21	£22.13	£22.30

5.5.2 Hospitalisation events

As noted in Section 4, two approaches to estimating all cause hospitalisation were used: mean number of events per month and mean number of days per month. Hence, two different costing approaches are required.

The NHS Schedule of Reference Costs (SRC) provides numerous estimates of the cost of hospitalisation, including those specific to HF patients.¹⁴⁰ These are further subcategorised by whether the admission is elective or non-elective, whether it is an inpatient, outpatient or day case, and whether or not the patient experiences complications.

The cost of a hospitalisation event for HF hospitalisations using EB03H and EB03I was calculated as a weighted average of whether or not the patient experienced complications. For non-HF hospitalisations, it was calculated as a weighted average of all costs except EB03H and EB03I. The number of recorded NHS attendances for each currency code was used as the weights in these calculations.

In order to align the 'day costs' with the tariff values reported in the NHS SRC, we have used a weighted average mean length of stay from all relevant currency codes, in combination with total costs, to get the relevant daily cost. The approach used was to divide total cost by mean length of stay. We acknowledge that this approach may be slightly unreflective of the true daily cost incurred in the NHS, but reiterate that it is not used in all base case analyses. Base case results are generated using the total tariff values and the expected number of events per month approach to costing.

A similar approach was used to derive the 'day in hospital (leads)' value, but using the total cost of a lead event as the numerator.

The cost of an outpatient visit was taken from the most recent version of the Personal Social Services Research Unit (PSSRU) review of unit costs of health and social care.

The relevant costs used in the model are reported in Table 66.

Table 66: Hospitalisation event costs

Item	Cost	Source
Day in hospital (HF)	£655.71	NHS SRC ¹⁴⁰
Day in hospital (non-HF)	£699.50	NHS SRC ⁵⁸
Day in hospital (leads)	£794.41	NHS SRC ¹⁴⁰
HF hospitalisation event	£2,295	NHS SRC ¹⁴⁰
Non-HF hospitalisation event	£2,448	NHS SRC ¹⁴⁰
Outpatient visits	£110.00	PSSRU 2010, Table 15.5 ¹⁴¹

5.5.3 Device system costs

5.5.3.1 Device average selling prices

The previous NICE appraisal of CRT used data from the now defunct Purchase and Supplies Agency (PASA) which referred to a cost year of 2004/2005. As the data are 8 years old we did not use this in the current model. A relevant HRG code exists for CRT-P implantation (EA07Z), which includes device acquisition, and procedure costs, but the existing HRG code for ICD implantation does not include device acquisition costs and does not distinguish between CRT-D and ICD implantation. It was therefore decided to source the most recent UK NHS specific average selling prices from the manufacturers via the Association of British Healthcare Industries (ABHI). These prices are an aggregate across all sponsors (manufacturers) of this submission for all ICD, CRT-P and CRT-D devices and leads (either as systems or devices/leads only) sold in the UK to the NHS. The data are the most accurate and up-to-date available and were elicited solely for the purpose of model parameterisation. The values provided by the ABHI are presented in Table 67 and refer to a cost year of 2011.

5.5.3.2 UK tariff prices (device implantation)

As noted above, a complete tariff exists for CRT-P implantation (HRG: E07Z - £8,281) which we have assumed, given the device acquisition cost, covers all relevant costs associated with the implant procedure. This tariff value is assumed to be sufficient to cover both procedural and acquisition costs. We know this is

the case, however, by virtue of payment based results (PbR) documentation which makes clear which devices are excluded from tariff – ICD and CRT-D.

Tariff values also exist for ICD non-purchase costs (HRG: EA12Z – £5,556) and lead revisions/ interventions not requiring a new device (HRG: EA39Z - £2,748). We have assumed that the ICD value is equally applicable to both ICD and CRT-D implants and that EA12Z will be used in all upgrade/ replacement operations. These values (ICD/CRT-D) have been used in combination with the relevant ASPs (as provided by the ABHI, see above) to generate all implant costs.

Table 67: ICD and CRT system costs

Item	Cost	Source
<i>System costs</i>		
CRT-P whole system costs (device and leads)	£3,411	ABHI (data on file)
CRT-D whole system costs (device and leads)	£12,293	ABHI (data on file)
ICD whole system costs (device and leads)	£9,692	ABHI (data on file)
CRT Leads	£510	ABHI (data on file)
CRT-P pulse generator	£2,600	ABHI (data on file)
CRT-D pulse generator	£11,752	ABHI (data on file)
ICD generator	£9,149	ABHI (data on file)
<i>UK Tariff values</i>		
CRT-P	£8,281	HRG E07Z
ICD non-purchase costs	£5,556	HRG EA12Z
Revisions not requiring new device	£2,748	HRG EA39Z

5.5.3.3 Additional costs incurred treating infection

As per Fox *et al.*³⁴ we have assumed that device related infection involves:

- 1) Explanation of the exiting device
- 2) Device reimplantation
- 3) Additional time in hospital
- 4) An additional outpatient visit

1), 3) and 4) are discussed above. In absence of data on excess bed day costs,

we have inflated the derived value in Fox *et al.*³⁴ to current equivalents using the HCHS Pay and Prices index (value used £3,139).

5.5.3.4 Values used in the model

The total cost values used in the model for all procedures are presented in Table 68.

Table 68: Device costs used in the model

Item	Cost	Components
Initial implant operation (ICD)	£15,248	ABHI system costs (incl. leads) and UK tariff EA12Z
Initial implant operation (CRT-P)	£8,281	UK Tariff E07Z
Initial implant operation (CRT-D)	£17,849	ABHI system costs (incl. leads) and UK tariff EA12Z
Replacement (ICD)*	£14,705	ABHI system costs (excl. leads) and UK tariff EA12Z
Replacement (CRT-P*)	£8,281	UK Tariff E07Z
Replacement (CRT-D)*	£17,308	ABHI System costs (excl. leads) and UK tariff EA12Z
Device related infection (ICD)	£18,964	See section 5.5.3.3
Device related infection (CRT-P)	£12,541	See section 5.5.3.3
Device related infection (CRT-D)	£21,568	See section 5.5.3.3
Battery replacement (ICD)	£12,004	ABHI generator costs (excl. leads) and UK tariff EA39Z ¹
Battery replacement (CRT-P)	£8,381	UK Tariff ¹
Battery replacement (CRT-D)	£14,672	ABHI generator costs (excl. leads) and UK tariff EA39Z ¹

* Values solely used in the calculation of device related infection costs; 1) Values adjusted to account for the small proportion who experience an infection related event.

5.6 Health related quality of life

The approach used to incorporate subgroup specific HRQoL into the model is described in detail in Section 4.4. When measured by improvements from baseline in MLWHF score, treatment related benefits exist for many years. Further, Cleland *et al.*¹⁰¹ applied a mapping algorithm to the data from the CARE-HF study and showed that, when expressed as EQ-5D preference weights, there were significant benefits associated with both CRT-D and CRT-P at 18 months and study end ($p < 0.001$ for both results).

However, expert clinical advice indicated that benefits would be unlikely to be

apparent forever in all patients. Hence, in contrast to the analyses undertaken by Buxton *et al.*³³ and Fox *et al.*³⁴, we have not assumed a constant lifetime ‘treatment effect’ for any of the three devices. Instead, we have assumed that the benefit observed at six months is maintained up to five years and thereafter begins to recede in a linear manner over the time period five to ten years. After ten years we have used the conservative assumption that, conditional on being alive, an individual with a CRT or ICD device will have no additional HRQoL benefit over an identical person receiving OPT.

5.7 Other parameters

The remaining parameters used in the model are presented in Table 69

Table 69: Remaining model parameters

Item	Value	Source
Discount rate (costs)	3.5% p.a.	NICE Reference Case ¹⁰³
Discount rate (benefits)	3.5% p.a.	NICE Reference Case ¹⁰³
Time Horizon	80 years	Effective lifetime horizon
Gender	Subgroup specific	
Starting age	Subgroup specific	

6 Results from the cost-effectiveness analysis

Results of the base case deterministic cost-effectiveness analysis are presented for 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology (24 subgroups for patients with LBBB and 24 subgroups for patients without). All individuals are assumed to have LVEF \leq 35%. Ischemia did not substantively impact on cost-effectiveness; the results presented below are therefore applicable to both ischemic and non-ischemic patients.

In many cases, there is little difference between the best and second best options (when viewed in terms of incremental cost-effectiveness ratios), and there may be other issues that clinicians wish to take into account. Thus there seems to be a reasonable case for building clinical flexibility into the recommendations in those cases where the ICER differences between technologies are small and the uncertainty as to which is the preferred device is high.

NYHA class I/II

- QRS duration < 120ms: the ICERs are below £25,200 per QALY gained, when accounting for the number of patients in each group, ICD is still likely to be an acceptable use of resources.
- QRS duration 120-149ms: ICD is cost-effective (all ICERs below £17,100 per QALY gained). For CRT-D in patients with LBBB all ICERs are below £24,400 per QALY gained, meaning CRT-D is cost-effective.
- QRS duration \geq 150ms, with or without LBBB: CRT-D is, overall, a cost-effective treatment.

NYHA class III

- QRS duration <120ms: ICD generates ICERs below £30,000 per QALY gained and is hence cost-effective

- QRS duration >150ms: CRT-P is cost-effective. Compared to CRT-P, CRT-D generates ICERs below £30,000 per QALY gained, and is cost-effective. ICD is either dominated or extended dominated.
- QRS duration 120-149ms: CRT-P is cost-effective. CRT-D generates ICERs between £23,900 and £27,400 per QALY gained relative to CRT-P, and provides significantly greater mortality reductions, so is likely to be an acceptable use of resources (i.e. cost-effective).

NYHA class IV

- QRS duration < 120ms: no comparative analysis was possible in this patient group.
- QRS duration ≥120ms: Compared to OPT, CRT-P represents value for money in NYHA class IV patients: all ICERs are close to or below £20,000 per QALY gained and hence cost-effective. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

Comparison with previous appraisals

- For CRT, the ICERs are nearly always lower than in the previous appraisal (except in NYHA class IV). In particular, the ICERs for CRT-D vs. CRT-P in NYHA class III are 30% to 50% lower than the accepted 2007 value.
- For ICD, the ICERs generated are similar to those in the previous appraisal generated assuming no EP testing in patients where ICD is recommended (NYHA class I/II, LVEF <35% and QRS <150ms).
- ICER improvements are likely to be due to lower real-terms device costs, increased device longevity, and better estimates of the impact of treatment on mortality and HRQoL.

Sensitivity analyses

- Sensitivity analyses were performed to explore alternative modelling assumptions and potential changes in the UK NHS. Most generated ICERs lower than, or similar to, the base case, confirming that the base case was indeed conservative.

- The base case assumed that treatment effects on mortality or HRQoL are not constant but diminish over time. When constant treatment effects for mortality and quality of life were explored, ICERs in all patient groups were lower than in the base case. In particular, the ICERs in patients who are NYHA class III with a QRS >150ms are reduced to no more than £24,600 regardless of LBBB status.
- When performing a “Real world scenario” for patients in NYHA class III (i.e. CRT-D vs. OPT), the highest ICER generated was £22,400 per QALY gained. The scenario is necessary due to the high risk of SCD and hence defibrillation. Defibrillation based therapy was cost-effective in this scenario.
- The scenario analysis surrounding the use of NYHA class as a treatment effect modifier resulted in the decisions for patients in NYHA I, II or IV being unchanged. The greatest impact of the alternative assumption was in NYHA class III, where the ICERs for CRT-D vs. CRT-P in patients regardless of LBBB status are now at most £26,700 per QALY gained. Hence CRT-D was cost-effective in this patient group in this scenario.

Recommended decision rules

- The aim was to generate simple decision rules to allow cardiologists to provide the most cost-effective intervention to a given patient. These recommendations make no distinction between ischemic and non-ischemic aetiology and can be summarised as follows:
- For patients without LBBB (LVEF <35%):
 - In NYHA class I/II, QRS < 150ms: ICD should be used. For QRS ≥150ms, the patient should be given CRT-D.
 - NYHA class III: where indicated, doctors should be allowed to use either CRT-D or CRT-P, with CRT-D the preferred device because of the incidence of SCD in this population. Patients with QRS < 120ms should be offered an ICD.
 - NYHA class IV: CRT-P is the treatment of choice (where indicated).

- For patients with LBBB (LVEF <35%):
 - NYHA class I, II or III: the treatment choice is CRT-D.
 - NYHA class IV: CRT-P device is the preferred option (where indicated).

6.1 Base case deterministic analysis

Results were generated in a two-stage process. In the first, both for patients with and without LBBB, cost and QALY estimates were derived for all relevant comparators in all 4,992 patient profiles (4 NYHA * 2 aetiology status (ischaemic/ non-ischaemic) * 3 QRS categories * 4 LVEF categories* LBBB status (yes/no)* 2 gender groups * 13 age categories⁶).

In the second stage, these were collapsed to 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology. To provide results for each of these groups, it was necessary to aggregate over patients with different LVEFs, genders and ages. Results were aggregated over different LVEF values represented in the clinical trials as LVEF was not a strong predictor of cost-effectiveness across this range, and its inclusion would have increased the number of subgroups. Results were aggregated over age and gender categories as it is not expected that NICE would make different recommendations according to age or gender. The patient counts in the trial database for each LVEF-, age- and gender-defined patient profile were used as weights in the calculation of weighted average costs and QALYs for the 24 subgroups for each LBBB category.

The list of fully incremental base case results is presented in Table 70 for patients who do not have LBBB and in Table 71 for patients who do have LBBB. The deterministic CRT-D vs. ICD vs. OPT ICERs for patients with NYHA III are presented in Table 73 for both patient groups.

The labels in the columns titled 'CE-Sequence' detail the order in which interventions

⁶ Age is described using 5- year bands starting at 35, with the top band being 'greater than 85'

appear on the cost-effectiveness frontier, starting from the origin (least costly and least effective) and moving in a 'north east' direction to take in more effective and more costly options. The ICERs represent the relevant values for each indication along the frontier. Note that when fewer than four interventions are considered for a given subgroup, the values in both empty columns will be represented as "N/A". Similarly, where no patients were identified for a given combination (e.g. with LBBB and QRS duration <120ms), values of N/A are reported in all boxes.

Table 70: Deterministic base case results (patients without LBBB)⁷

NYHA Class	Etiology	QRS Duration	N	C-E Sequence				ICERs			
				1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	66	OPT	ICD	N/A	N/A	Referent	£24,304	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	11	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,619	N/A
I	Non-Ischemic	>=150ms	8	OPT	ICD	CRTD	N/A	Referent	£18,074	£1,080,057	N/A
I	Ischemic	<120ms	272	OPT	ICD	N/A	N/A	Referent	£24,016	N/A	N/A
I	Ischemic	>=120, <150 ms	216	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,234	N/A
I	Ischemic	>=150ms	106	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,086	N/A
II	Non-Ischemic	<120ms	710	OPT	ICD	N/A	N/A	Referent	£25,110	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	232	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,016	N/A
II	Non-Ischemic	>=150ms	141	OPT	ICD	CRTD	N/A	Referent	£20,312	£27,175	N/A
II	Ischemic	<120ms	788	OPT	ICD	N/A	N/A	Referent	£23,884	N/A	N/A
II	Ischemic	>=120, <150 ms	756	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,749	N/A
II	Ischemic	>=150ms	470	OPT	ICD	CRTD	N/A	Referent	£20,697	£22,777	N/A
III	Non-Ischemic	<120ms	255	OPT	ICD	N/A	N/A	Referent	£29,402	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	150	OPT	CRTD	ICD	CRTD	Referent	Ext Dominated	£19,760	£27,336
III	Non-Ischemic	>=150ms	109	OPT	ICD	CRTD	CRTD	Referent	Dominated	£13,227	£24,350
III	Ischemic	<120ms	438	OPT	ICD	N/A	N/A	Referent	£26,923	N/A	N/A
III	Ischemic	>=120, <150 ms	426	OPT	CRTD	ICD	CRTD	Referent	£19,670	Ext Dominated	£24,796
III	Ischemic	>=150ms	192	OPT	ICD	CRTD	CRTD	Referent	Dominated	£14,392	£25,734
IV	Non-Ischemic	<120ms	5	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	12	OPT	CRTD	CRTD	N/A	Referent	£17,324	£30,624	N/A
IV	Non-Ischemic	>=150ms	9	OPT	CRTD	CRTD	N/A	Referent	£16,304	£33,901	N/A
IV	Ischemic	<120ms	42	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	52	OPT	CRTD	CRTD	N/A	Referent	£24,366	£43,500	N/A
IV	Ischemic	>=150ms	10	OPT	CRTD	CRTD	N/A	Referent	£18,065	£37,802	N/A

⁷ Patients in NYHA I, non-ischaemic, QRS>150ms nearly all of one type – elderly males

Table 71: Deterministic base case results (patients with LBBB)

NYHA Class	Etiology	QRS Duration	N	C-E Sequence				ICERs			
				1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	21	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,021	N/A
I	Non-Ischemic	>=150ms	33	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,118	N/A
I	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	76	OPT	ICD	CRTD	N/A	Referent	£19,989	£24,343	N/A
I	Ischemic	>=150ms	165	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,335	N/A
II	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	385	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,608	N/A
II	Non-Ischemic	>=150ms	1,308	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,794	N/A
II	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	477	OPT	ICD	CRTD	N/A	Referent	£20,640	£21,277	N/A
II	Ischemic	>=150ms	982	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,479	N/A
III	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	189	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,550	£23,831
III	Non-Ischemic	>=150ms	775	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,798	£27,592
III	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	355	OPT	ICD	CRTP	CRTD	Referent	Dominated	£15,449	£25,540
III	Ischemic	>=150ms	773	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,408	£29,912
IV	Non-Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	22	OPT	CRTP	CRTD	N/A	Referent	£14,715	£31,920	N/A
IV	Non-Ischemic	>=150ms	81	OPT	CRTP	CRTD	N/A	Referent	£12,076	£35,660	N/A
IV	Ischemic	<120ms	0	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	38	OPT	CRTP	CRTD	N/A	Referent	£22,340	£41,695	N/A
IV	Ischemic	>=150ms	97	OPT	CRTP	CRTD	N/A	Referent	£17,722	£46,445	N/A

Table 72: Deterministic base case results (NYHA III, CRT-D vs. OPT)

Pt. Group	ΔCosts	ΔQALYs	ICER (£/QALY gained)
<i>Individuals without LBBB</i>			
Non-Ischaemic, QRS between 120 and 149ms	£25,771	1.24	£20,850
Non-Ischaemic, QRS ≥150ms	£26,060	1.45	£17,968
Ischaemic, QRS between 120 and 149ms	£23,476	1.05	£22,412
Ischaemic, QRS ≥150ms	£24,730	1.27	£19,352
<i>Individuals with LBBB</i>			
Non-Ischaemic, QRS between 120 and 149ms	£27,019	1.56	£17,323
Non-Ischaemic, QRS ≥150ms	£27,514	1.79	£15,341
Ischaemic, QRS between 120 and 149ms	£24,073	1.20	£20,096
Ischaemic, QRS ≥150ms	£24,778	1.42	£17,514

Further to the additional NYHA III analyses presented in Table 72, as was noted in the introduction and in the definition of the decision problem, SCD remains the most

common form of death in this patient group. This would imply that, if CRT-D were unavailable, then clinicians would have a preference for ICD over CRT-P. This argument is supported by both the latest ESC and NICE guidelines.^{4,5} Such a decision would be acceptable given the large overlap between guidance issued in TA95 and TA120. The relevant results presented in Table 70 and Table 71 were therefore regenerated with CRT-P removed as a treatment option (see Table 73).

Table 73: Deterministic base case results (NYHA III, CRT-D vs. ICD vs. OPT)

Pt. Group	ΔCosts (vs. OPT)		ΔQALYs (vs. OPT)		ICER (£/QALY gained)	
	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D
<i>Individuals without LBBB</i>						
Non-Ischaemic, QRS between 120 and 149ms	£20,912	£25,771	1.06	1.24	£19,760 ^a	£27,336 ^b
Non-Ischaemic, QRS ≥150ms	£19,732	£26,060	0.76	1.45	Dominated	£17,968 ^a
Ischaemic, QRS between 120 and 149ms	£19,006	£23,476	0.76	1.05	Dominated	£22,412 ^a
Ischaemic, QRS ≥150ms	£19,113	£24,730	0.70	1.28	Dominated	£19,352 ^a
<i>Individuals with LBBB</i>						
Non-Ischaemic, QRS between 120 and 149ms	£20,101	£27,019	0.74	1.56	Dominated	£17,323 ^a
Non-Ischaemic, QRS ≥150ms	£19,302	£27,514	0.50	1.79	Dominated	£15,341 ^a
Ischaemic, QRS between 120 and 149ms	£18,650	£24,073	0.64	1.20	Dominated	£20,096 ^a
Ischaemic, QRS ≥150ms	£17,790	£24,778	0.41	1.42	Dominated	£17,514 ^a

a) vs. OPT; b) vs. ICD;

6.1.1 Interpretation of base case results

Due to the varying number of treatment options assessed in each of the 48 patient groups, the results presented above require careful consideration and interpretation. In general, the discussion focuses on the most cost-effective option in each group for a given cost-effectiveness threshold. However, in many cases, there is little difference between the best and second best options (when viewed in terms of incremental cost-effectiveness ratios), and there may be other issues that clinicians wish to take into account. Thus there seems to be a reasonable case for building clinical flexibility into the recommendations in those cases where the ICER differences between technologies are small and the uncertainty as to which is the preferred device is high.

6.1.1.1 Patients with mild to moderate heart failure (NYHA class I/II)

QRS duration <120ms

Due to the definition of LBBB there are no patients with LBBB and QRS <120ms, and so all patients for whom CRT treatment was not indicated (QRS<120ms) are assumed to not have LBBB. The analysis performed was a pairwise comparison of ICD to OPT. The results were very similar in all patient groups (NYHA class I/II, ischaemic and non-ischaemic aetiology), with the ICER ranging from £23,884 to £25,110 per QALY gained.

There is good clinical evidence supporting the use of ICD devices in this patient group (see Section 3), and this is recognised both in previous NICE guidance and in international guidelines. Importantly, no difference in cost-effectiveness between ischaemic and non-ischaemic were observed.

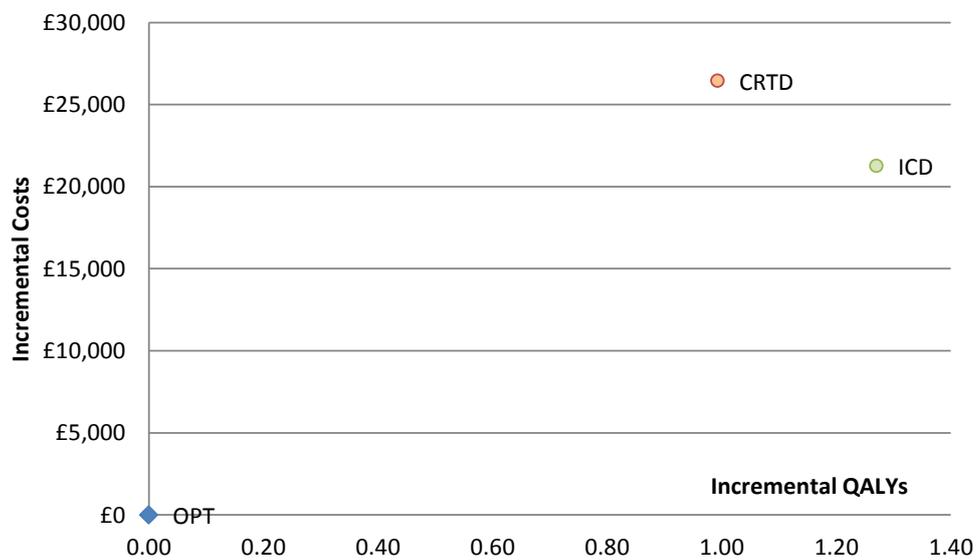
The ICERs are no more than £25,200 per QALY gained meaning that ICD therapy is still likely to represent an acceptable (cost-effective) use of health care resources in NYHA class I/II patients with or without ischaemia, with LVEF \leq 35% and with QRS \leq 120ms.

QRS duration 120ms to 149ms

In this group the interventions of interest are CRT-D, ICD and OPT, and the choice of intervention depends on LBBB status. The results from the network

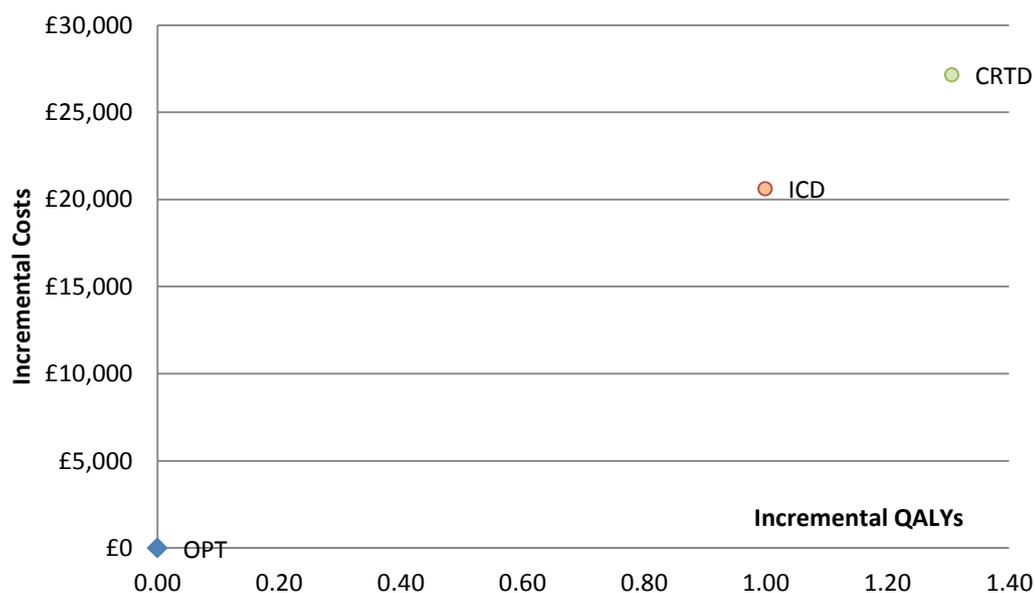
meta-analysis indicate that, in patients without LBBB, ICD and CRT-D are likely to be similar in terms of clinical efficacy with differences driven by parameter uncertainty and slight variations in patient mix (e.g. by age and gender). Thus, given the additional implant cost for CRT-D, this results in ICD being the dominant technology. The cost-effectiveness frontier for the patient group with the most patients in the trial database (NYHA class II and ischaemic aetiology, n=756) is presented in Figure 30. In all relevant patient groups the ICERs generated were below £20,000 per QALY gained (£16,234 to £17,016).

Figure 30: CE frontier (NYHA II, ischaemic aetiology, no LBBB)



LBBB was shown to be a strong treatment effect modifier in this patient group (pooled hazard ratio [redacted]), and the results from the network meta-analysis indicate that CRT-D is more clinically effective than ICD in patients with LBBB. The cost-effectiveness frontier for the most common patient profile in the trial database (NYHA class II, ischaemic aetiology, n=472) is presented in Figure 31. Similar frontiers are generated for all other relevant patient groups. In all relevant patient groups the ICERs generated were below £25,000 per QALY gained (£20,608 to £24,343).

Figure 31: CE frontier (NYHA II, ischaemic aetiology, LBBB)



ICD is a cost-effective treatment option in NYHA I/II patients with QRS duration 120-149ms and no LBBB and LVEF≤35%.

For CRT-D all ICERs are below £25,000 per QALY gained in LBBB patients (£20,608 to £24,343), meaning that CRT-D is a cost-effective intervention for NYHA class I/II patients with QRS duration 120-149ms with LBBB and LVEF ≤35%.

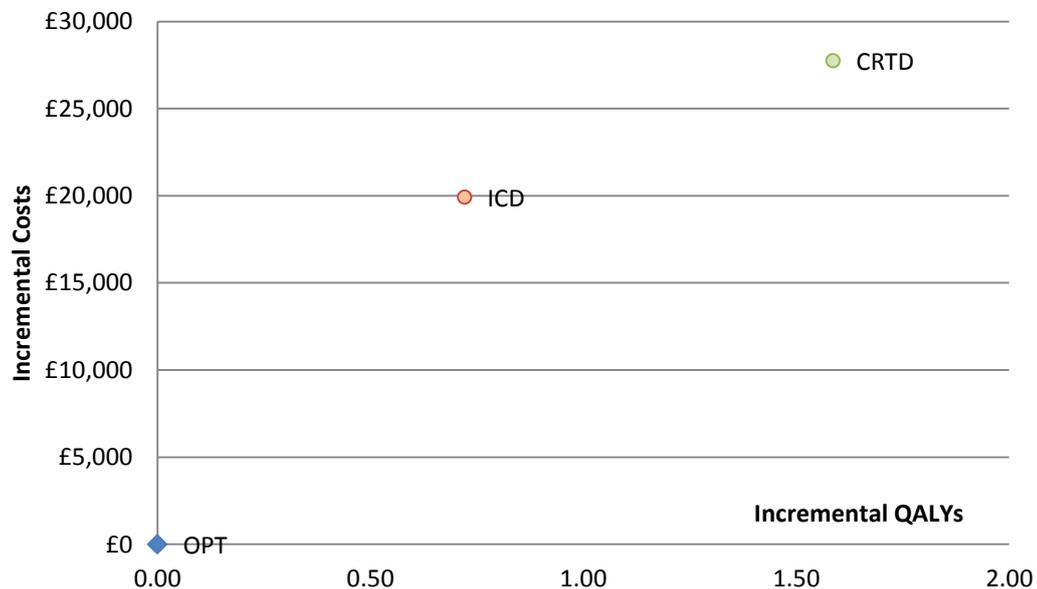
QRS duration at least 150ms

In patients with LBBB the argument presented above applies to those with QRS duration ≥ 150 ms also, and the conclusions identical: CRT-D is a cost-effective intervention for this patient group (ICER range £17,335 to £18,118).

In patients without LBBB the interpretation is more subtle, as there were very small patient numbers in some profiles (in particular those with NYHA class I and non-ischaemic aetiology, n=8). The results generated for these groups are likely to be influenced by non-decision variables (age, gender, etc.), and so the results should be viewed 'in the round'. Across all four patient groups, and accounting for the fact that the great majority of patients had ischaemic aetiology, CRT-D emerges as a cost-effective treatment option (relevant ICERs ranging from £21,086 to £27,175 per QALY gained).

The cost-effectiveness plane for the most populated group (NYHA class II, ischaemic aetiology, n=470) is presented in Figure 32.

Figure 32: CE frontier (NYHA II, ischaemic aetiology, LBBB)



Overall, CRT-D is a cost-effective treatment for NYHA class I/II patients with QRS duration ≥ 150 ms, with or without LBBB and with LVEF $\leq 35\%$.

6.1.1.2 Patients with moderate to severe heart failure (NYHA III)

QRS duration less than 120ms

The pairwise comparison of ICD to OPT results in cost-effectiveness ratios greater than £20,000 per QALY gained but lower than £30,000 per QALY gained (£26,923 to £29,402). The numbers generated were similar to those previously deemed acceptable by NICE in their positive recommendation for ICDs. They were predicated on the assumption used in our model that ICD confers no additional quality of life benefits over OPT, which may be unnecessarily pessimistic (see section 4.4.8).

QRS duration between 120 and 149ms

In contrast to the situation for NYHA I/II heart failure, four treatment options exist for this patient group. Across all patient groups, and regardless of LBBB status (with the exception of patients who are non-ischaemic and without LBBB), ICD

does not lie on the cost-effectiveness frontier, and is either dominated or extended dominated by other treatment options. Relative to the other treatment groups, the patient count in this outlier group is modest (n=150), so the results are again likely to have been driven by the distribution of non-decision variables. The cost-effectiveness planes for the largest non-LBBB and LBBB populations are presented in Figure 33 and Figure 34, respectively.

Figure 33: CE frontier (NYHA III, ischaemic aetiology, non-LBBB)

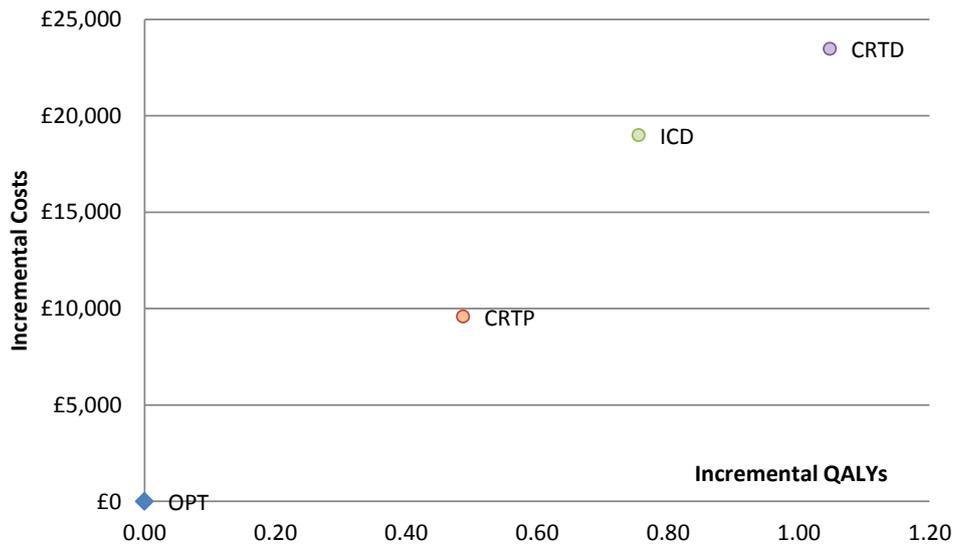
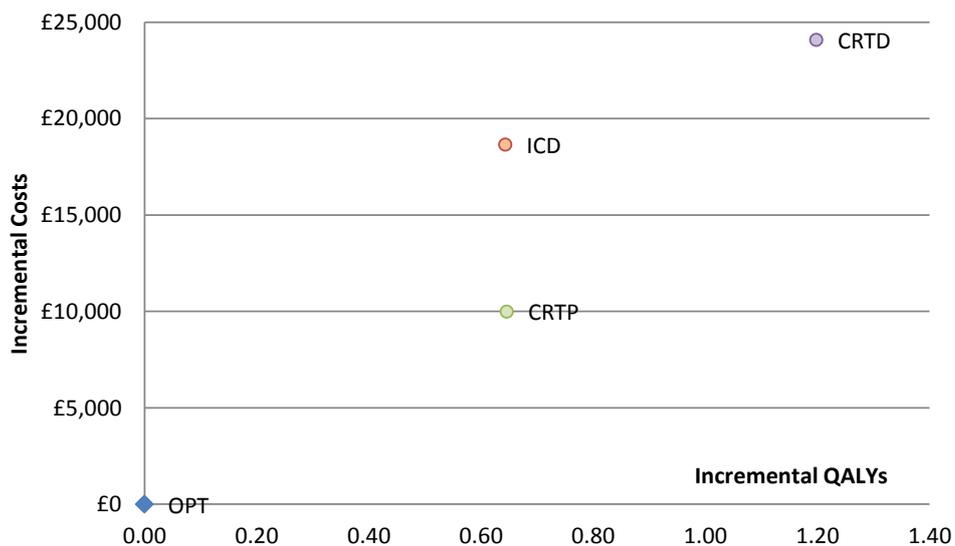


Figure 34: Cost-effectiveness frontier (NYHA III, ischaemic aetiology, with LBBB)



The ICERs generated for the pairwise comparison of CRT-P vs. OPT are similar to those generated by Fox *et al.*³⁴ in the previous NICE appraisal, and are all

below £20,000 per QALY gained. Hence, the current analysis confirms the previous findings. Of note, the ICERs generated in patients with LBBB are within £10,000-16,000 per QALY gained.

For the comparison of CRT-D to CRT-P, the ICERs generated are within the range of £23,831 to £27,336 per QALY gained). This is markedly lower than the value on which the previous positive recommendation was based (circa £40,000 per QALY gained).

The results of the NMA showed that CRT-D was significantly more effective than CRT-P in this patient group in terms of reducing all-cause mortality, and CRT-D is currently recommended for use in this group in all major clinical guidelines.^{2;4}

The ICERs generated for the “real world” comparisons of CRT-D to OPT and CRT-D vs. ICD vs. OPT (i.e. as per current clinical practice) were all close to or below £20,000 per QALY gained. The need for this analysis was predicated on ICD being higher up in the clinical decision tree because of SCD being a major cause of mortality in this group, and also on the overlap between current ICD and CRT guidance, which means that clinicians are free to use any of the four treatment options.

All of the ICERs generated in this patient group are either close to, or markedly lower than, those deemed acceptable in the previous CRT appraisal.

CRT-P is a cost-effective treatment option in NYHA class III patients with QRS 120-149ms and LVEF ≤35%.

CRT-D generates ICERs slightly below £30,000 per QALY gained relative to CRT-P in this group, and provides significantly greater mortality reductions.

Overall, CRT-D in this patient group is likely to be a cost-effective use of the health care budget in the UK in NYHA class III patients with QRS 120-149ms and LVEF ≤35%.

QRS duration greater than 150ms

The overall picture in this group is similar to that in patients with a QRS duration

between 120 and 149ms. The only point of interest is that the ICERs for patients with LBBB are at the upper end of acceptable cost-effectiveness. This is driven by the marginally stronger interaction between LBBB and CRT-P efficacy compared to that between LBBB and CRT-D efficacy. This in turn leads to a small improvement in the efficacy of CRT-D compared to CRT-P in LBBB patients. However, as highlighted in section 1.1.6 SCD is still the main cause of mortality in this patient group meaning that there is a clinical need for CRT-D in this group.

Given the complexity of the model being fitted to the data, and in particular the large number of parameters being estimated, this difference is likely to be artificial and non-significant. We reiterate that CRT-D offered a significant reduction in all-cause mortality (see section 4.2) and so is a clinically efficacious treatment option in this group.

The result of this, as noted above, is a reduction in the ICER for CRT-P compared to OPT, and thus an increase in the ICER for CRT-D compared to CRT-P. The real world comparisons of CRT-D to ICD and/or OPT generated ICERs below £20,000 per QALY gained, which is supportive of CRT-D being cost-effective in this patient group.

Compared to OPT, CRT-P is a cost-effective treatment option in NYHA III patients with QRS >150ms and LVEF ≤35%.

Compared to CRT-P CRT-D generates ICERs close to £28,000 per QALY gained in this group. ICD is either dominated or extended dominated.

In the “real word scenario” the ICER generated for the comparison of CRT-D to OPT (ICD being dominated) is at most £20,096 per QALY gained.

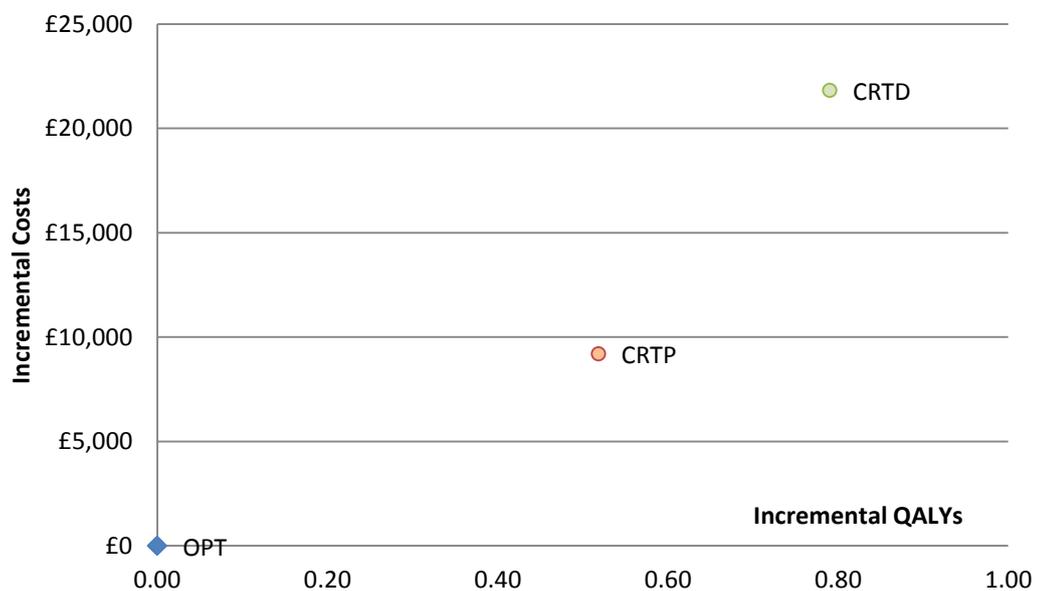
Overall, CRT treatment (both CRT-P and CRT-D) in this patient group are likely to be a cost-effective use of the health care budget in the UK in NYHA III patients with QRS >150ms and LVEF ≤35%.

6.1.1.3 Patients with severe heart failure (NYHA IV)

In general, compared to those discussed in previous results sections, all patient counts in the subgroups are modest with the largest group containing 97 individuals (QRS duration ≥150ms, ischaemic aetiology and LBBB). Hence, the

results are highly likely to be driven by small differences in patient level characteristics such as age, gender, LVEF etc. The cost-effectiveness plane for the largest patient group (LBBB, Ischaemic aetiology, QRS duration ≥ 150 ms) is presented in Figure 35. When compared to OPT, CRT-P is a cost-effective treatment option with ICERs in the range £12,076 to 24,366 per QALY gained. When compared to CRT-P, CRT-D is unlikely to be cost-effective at conventional decision thresholds with ICERs in the range £30,624 to £46,445 per QALY gained.

Figure 35: CE frontier (NYHA IV, ischaemic aetiology, LBBB, QRS>150ms)



Compared to OPT, CRT-P represents good value for money in NYHA IV patients: all ICERs are close to or below £20,000 per QALY gained and so the treatment option is cost-effective. For the comparison of CRT-D to CRT-P, all ICERs are above £30,000 per QALY gained.

6.1.1.4 Comparison with results generated in previous appraisals

As part of the 2007 appraisal of CRT in patients with NYHA class III/IV heart failure, the model developed by Fox *et al.*³⁴ generated ICERs of approximately £16,700 per QALY gained for the comparison of CRT-P to OPT, and approximately £40,100 per QALY gained for CRT-D compared to CRT-P. The equivalent values generated in the current analysis are nearly always lower than

the previous values in all subgroups. In particular, the ICERs for CRT-D compared to CRT-P in NYHA class III patients are approximately 30% to 50% lower than the accepted 2007 value.

The ICERs that are higher than those used in previous guidance concern patients with NYHA IV heart failure. We believe that this is because the IPD based model allowed us to separate out NYHA class III and IV patients, and thus generate more nuanced results by more accurately identifying which devices are clinically effective in which patients and by enabling more accurate modelling of baseline risk.

The 2006 review of ICDs in primary prevention³³ generated a range of ICERs, with final values of between £33,000 and £46,000 per QALY gained if EP testing is not used. Assuming that EP testing is used to identify high risk patients, the ICERs ranged from £21,000 to £23,000 per QALY gained. EP testing is not included as a covariable in the current analysis, meaning that direct comparison with these historical results is not possible. The ICERs generated for ICD therapy in the nearest applicable groups (NYHA I/II, LVEF <35% and QRS <150ms) are similar to those generated previously when this test is used.

Given that EP testing was only conducted for all patients in one small ICD trial, it would not have been possible to produce evidence based estimates stratified according in this way. Perhaps more importantly, the ICERs presented in the previous appraisal referred to patients with previous MI only. The current analysis did not find substantive difference in the cost-effectiveness of ICD according to whether patients were ischemic or not, suggesting that separate recommendations for ischaemic and non-ischaemic patients are not required.

Thus, the ICERs from the current model are again markedly lower than were generated in the models developed during TA95 and TA120. The reasons for these improvements are likely to be a result of a combination of the following:

- Real term reduction in procedure costs (see section 1.7)
- Increases in device longevity compared to those used in previous models (see section 5.3.2 for current values)
- Better estimates of the impact of treatment on mortality (see section 4.2)

- Better understanding of the impact of treatment on HRQoL (see section 4.4)

Note that all three interventions received restricted positive recommendations in the previous appraisals on the basis of the above mentioned ICERs.

A final note concerns comparison of the results from this analysis with those from previous published cost-effectiveness studies, in particular those derived using information from SCD-HeFT and MADIT II.^{130;142} Accepting the inherent problems in comparing the results of different models developed in different jurisdictions (hence reflecting different resource use patterns), different perspectives and different discount rates, the results from the two studies indicated that ischemic etiology is likely to impact on cost-effectiveness.

It is important to note that the discussion around the use of ischemic etiology surrounds its use as a decision variable. As can be seen from the results presented in Table 70 and Table 71, for a given LBBB/QRS/NYHA patient profile, the results vary by etiology. What is not clear is to what degree these results are driven by etiology as opposed to other variables (age, gender, BMI etc). It is also important to note that in all cases, the ICERs are below £30,000 per QALY gained for both groups suggesting that etiology should not be used to decide who does and does not get a given treatment.

6.2 Deterministic sensitivity analyses

6.2.1 Removal of treatment effect tapering (mortality)

The base case results were generated using the conservative assumptions that any treatment effects observed in the patient level data are not constant and diminish over time. This is in contrast to the assumptions used in both the *Fox et al.*³⁴ CRT model and the *Buxton et al.*³³ ICD model (with the latter accounting for the ageing process by way of multipliers for each decile above 60 years). We therefore explored the impact on cost-effectiveness of the use of constant treatment effects.

The results generated using this alternative modelling approach are presented in Table 74 and Table 75.

Table 74: Deterministic sensitivity analysis – constant mortality treatment effect (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£16,789	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£11,492	N/A
I	Non-Ischemic	>=150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,268	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£18,759	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,258	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,944	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£17,058	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,240	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£14,870	£20,863	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£18,587	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,792	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,513	£19,396	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,457	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	Ext Dominated	£16,380	£58,164
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,583	£20,620
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,614	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£19,460	Ext Dominated	£23,391
III	Ischemic	>=150ms	OPT	CRTD	ICD	CRTD	Referent	£14,043	Ext Dominated	£23,297
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£17,201	£29,674	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£16,155	£32,552	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£24,316	£42,879	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,964	£36,827	N/A

Table 75: Deterministic sensitivity analysis – constant mortality treatment effect (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,840	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,725	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£16,756	£20,704	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,375	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,108	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,862	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£17,406	£17,951	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,548	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,751	£19,294
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£9,085	£21,682
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£15,174	Ext Dominated	£23,633
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,107	£26,979
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£14,453	£29,557	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£11,880	£32,921	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£22,302	£41,139	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,666	£45,471	N/A

Broadly speaking, and as would be expected, extending survival by assuming a constant treatment effect results in the ICERs in all patient groups being lower than in the base case. However, the resulting treatment decisions for patients with NYHA classes I, II or IV are unchanged. The greatest impact of the alternative assumption lies in patients who are NYHA class III, where the ICERs for patients with LBBB for the comparison of CRT-D to CRT-P are now at most £26,979 per QALY gained.

The exception to this pattern is in non-ischaemic NYHA III patients who have a QRS duration ≥ 120 ms but no LBBB. This was the only NYHA III group for whom ICD was on the cost-effectiveness frontier in the base case, based on a modest number of patients in this subgroup (n=150). In this group, the aggregate treatment effect for ICD was greater than that for CRT-D ([REDACTED]) and hence, when this treatment effect is applied for the duration of the patient's lifetime, ICD becomes relatively more cost-effective. We note, however, that the difference in treatment effects is small and unlikely to be statistically significantly different.

The conclusion from this analysis is that the choice of the most cost-effective intervention(s) in this particular small patient group is very uncertain and, dependent on the assumptions made surrounding treatment efficacy, either CRT-D or ICD could be the preferred cost-effective option.

6.2.2 Removal of treatment effect tapering (HRQoL)

The results generated when all observed short/ medium term utility benefits are assumed to hold for all model cycles are presented in Table 76 and Table 77. In this scenario, ICD no longer appears on the cost-effectiveness frontier for patients who are NYHA class III, non-ischaemic, QRS duration between 120ms and 149ms and have no LBBB. Further, all ICERs in patients with QRS duration ≥ 120 ms are, on the whole, lower than in the base case, although the impact is modest. The derived results for patients who are NYHA class I/II with a QRS less than 120ms are very similar to those derived using the base case assumptions.

Table 76: Deterministic sensitivity analysis – constant HRQoL treatment effect (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,580	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,475	N/A
I	Non-Ischemic	>=150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,847	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,134	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,001	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,086	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,180	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,781	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,012	£28,961	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,995	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,500	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,393	£24,034	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£29,402	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£16,868	Ext Dominated	£18,982
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,558	£22,833
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,923	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£18,010	Ext Dominated	£23,535
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£13,060	£24,196
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£16,523	£29,338	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£15,486	£32,322	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£23,769	£42,278	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,388	£36,335	N/A

Table 77: Deterministic sensitivity analysis – constant HRQoL treatment effect (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,021	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,118	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,734	£25,637	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,335	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,608	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,794	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,315	£22,445	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,479	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£10,510	£22,085
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£8,611	£25,619
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£14,264	£24,177
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£10,687	£28,253
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£13,473	£30,040	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£11,415	£33,638	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£21,929	£40,622	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,399	£45,086	N/A

6.2.3 Removal of tapering of HRQoL and mortality treatment effect

The results generated using these combined assumptions are presented in Table 78 and Table 79.

Table 78: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£16,422	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£11,418	N/A
I	Non-Ischemic	>=150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,147	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£18,159	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,072	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,944	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£16,605	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£12,106	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£14,699	£21,949	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£17,986	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,593	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,263	£20,432	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,457	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£16,254	Ext Dominated	£16,388
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£10,992	£19,106
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,614	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£17,802	Ext Dominated	£22,067
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,722	£21,706
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£16,382	£28,295	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£15,316	£30,851	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£23,707	£41,543	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,266	£35,237	N/A

Table 79: Deterministic sensitivity analysis – constant HRQoL and mortality treatment effect (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,840	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,725	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£16,549	£21,774	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,375	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,108	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£12,862	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£17,145	£18,878	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,548	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£9,863	£17,626
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£7,970	£19,810
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£13,985	£22,192
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£10,370	£25,215
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£13,244	£27,534	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£11,191	£30,712	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£21,882	£39,976	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,327	£43,955	N/A

Across all patient groups, the number of groups where CRT-D is likely to be recommended increased at a willingness to pay threshold of £30,000 per QALY gained. Of note, in patients who are NYHA III, ICD no longer appears on the cost-effectiveness frontier in any patient group. The ICER for the comparison of CRT-D to CRT-P in patients with NYHA III is at most £25,200 per QALY gained.

6.2.4 Use of alternative NYHA-based IPD results

As noted in Appendix 10, there is empirical evidence and a plausible clinical argument for CRT-D having a lower mortality treatment effect in patients with NYHA class IV compared to NYHA classes I/II/III. The results derived when the economic model is run using the estimated all-cause mortality treatment effects based on the grouping of NYHA class IV vs. NYHA class I-III patients are presented in Table 80 and Table 81.

This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups, especially NYHA class III, are lower than in the base case, with no meaningful CRT-D ICER being above £23,200 per QALY

gained.

Table 80: Deterministic sensitivity analysis –alternative all-cause mortality treatment effects (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,367	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,147	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,090	£1,095,407	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,243	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,795	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,874	£21,337	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,183	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,512	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£18,936	£27,571	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,109	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,276	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,270	£23,936	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£29,464	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	£19,108	£21,754
III	Non-Ischemic	>=150ms	OPT	CRTP	ICD	CRTD	Referent	£13,661	Ext Dominated	£21,186
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,678	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	Ext Dominated	£21,363
III	Ischemic	>=150ms	OPT	CRTP	ICD	CRTD	Referent	£14,854	Ext Dominated	£22,737
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£17,337	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£15,974	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£24,152	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTP	N/A	Referent	Dominated	£17,570	N/A

Table 81: Deterministic sensitivity analysis – alternative all-cause mortality treatment effects (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,137	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,800	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,925	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,142	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,714	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,547	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,848	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,284	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£14,496	Ext Dominated	£17,158
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£10,186	£20,894
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£18,127	Ext Dominated	£18,787
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,834	£23,125
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£15,928	£129,051	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	Dominated	£12,142	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£24,113	£884,903	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	Dominated	£17,694	N/A

6.2.5 Increase in device longevity

The estimates of device lifetime are based on data from approximately 40,000 UK implants analysed by an independent research group (CCAD) and are higher than those used in previous models. This is in line with the hypothesis that ongoing technological improvements have resulted in devices lasting longer. In order to explore the impact of a continuation of this process we increased all mean device longevity by 10% by applying a scaling factor to the device specific lambda coefficient used to derive time dependent transition probabilities. The results of this analysis are presented in Table and Table 83.

Table 82: Deterministic sensitivity analysis – 10% increase in device longevity (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,855	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,313	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,747	£1,078,112	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,545	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,916	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,725	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£24,657	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,698	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,928	£27,095	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,419	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,421	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,292	£22,581	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£28,825	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	Ext Dominated	£19,380	£27,099
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£13,029	£23,894
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,447	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£19,438	Ext Dominated	£24,301
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£14,201	£25,218
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£17,137	£30,042	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£16,124	£33,258	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£24,195	£42,839	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,891	£37,118	N/A

Table 83: Deterministic sensitivity analysis – 10% increase in device longevity (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,725	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,862	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,593	£24,147	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,044	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,306	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,536	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,233	£21,103	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,187	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,347	£23,422
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£9,647	£27,103
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£15,262	£25,030
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,269	£29,304
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£14,529	£31,341	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£11,933	£34,980	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£22,186	£41,050	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,599	£45,705	N/A

The impact on the ICERs was, overall, very modest. This is likely to be because of the very low replacement probabilities in the initial three to five year period, with the rate increasing rapidly thereafter. Slowing down the replacement rate in the population when notable proportions of the cohort are dead will have a small overall impact. We also ran the model using alternative parametric functions for the CRT-D replacement rates and the impact was again modest (results not shown). Hence, the model is insensitive to changes in this parameter.

The alternative scenario - a reduction in device longevity - was deemed highly implausible and so was not performed.

6.3 Results presented by LVEF category

All patients in the IPD dataset had LVEF of no greater than 35%, and are thus relatively uniform in this respect. In all regression analyses this parameter was viewed as categorical. Although LVEF below 40% is an important determinant of sudden cardiac death in clinical trials, this uniformity may have meant that its predictive effect was not apparent in the patient level data analysis of HRQoL or all-cause hospitalisation, and so it is not an important predictor of cost-effectiveness in our model. We have therefore not included results stratified by LVEF in the dossier, but the results can be identified in the economic model.

6.4 Probabilistic sensitivity analysis

The method we used to generate deterministic cost-effectiveness results has the advantage that it fully, and correctly, incorporates patient level heterogeneity into the analysis. The downside for this approach is that the model takes a long time to loop through all patient profiles. This computational expense means that a full PSA would take several months to execute. A probabilistic analysis for a given individual patient profile requires approximately five minutes.

We have, however, performed PSA simulations on individual patient profiles and compared these with the corresponding deterministic results to ensure that they are concurrent. These profiles were selected to reflect the baseline characteristics of the MADIT-CRT trial and are reported in Appendix 16.

6.5 Discussion of cost-effectiveness results

The motivating factor in this analysis was to generate simple, clinically appropriate decision rules which can be applied quickly in clinical practice and would allow cardiologists to provide the most cost-effective intervention to a given patient. We have worked closely with two highly respected UK cardiologists (Dr. Chris Plummer and Prof. Martin Cowie) to ensure that the methods, inputs, results and general direction of the project are aligned with current clinical thinking and practice.

To this end, where assumptions were made, we have endeavoured to be cautious in our choices:

- The effects of treatment on two key parameters (reduction in all-cause mortality and improvement in health related quality of life) were modelled to diminish over time.
- This approach was chosen as a conservative way of reflecting the uncertainty regarding long term device benefits.

In order to generate the pooled cost-effectiveness ratios we took into account the impact of gender, age, LVEF, QRS duration, aetiology, LBBB status and NYHA class. In the final analysis we did not present results stratified by age and gender since these were deemed to be 'non-decision variables'. The precedent for this approach was set in the previous CRT appraisal where, despite evidence presented to the Appraisal Committee that cost-effectiveness depended on the starting age used in the model, this was not included in the final guidance.

Of the other variables, our analysis showed that the aetiology of heart failure (ischaemic or non-ischaemic) did not have a significant impact on cost-effectiveness: the results generated for each group, when differences in patient counts were accounted for, were very similar. The exploratory analysis undertaken whereby results were stratified by LVEF category (not presented) showed that this variable had little impact. The discussion henceforth does not distinguish between LVEF categories, and all results are predicated on having a LVEF of at most 35% (the inclusion criteria in the trials from which our data were taken).

The results from the economic model should also be viewed in the context of the

results from the network meta-analysis, and in particular the summaries of treatment efficacy presented in section 4.5.5. Of note, however, is the fact that the cost-effectiveness results represent pooled results across males and females as well as different age groups. The results also combine quantity and quality of life in each of the pooled groups meaning that the results from each of the subgroups cannot be directly compared. Nonetheless, the results from the clinical efficacy analysis identified increased efficacy for CRT-D and reduced efficacy for ICD as QRS duration increased. The analysis also indicated CRT-D having greater efficacy in patients with LBBB as opposed to those without.

6.5.1 Summary of findings

A summary of the most cost-effective interventions with an ICER below £30,000 per QALY gained is presented for all key analyses in Table 84 (for patients without LBBB) and Table 85 (for patients with LBBB). The numbers given are the ICERs, with the technology that generated the ICER in brackets. The treatment choices presented in these tables are in line with the key conclusions from the analysis of clinical efficacy presented in detail in section 4.5.5 and summarised above.

In generating these tables, we have used the results for individuals with ischaemic aetiology, but the results for patients with non-ischaemic aetiology were very similar. As the additional deterministic sensitivity analyses reported in Appendix 15 only had modest impacts on the ICERs, we have excluded them from these tables.

The majority of the sensitivity analyses performed to explore alternative modelling assumptions and future changes to the UK health care sector produced ICERs results lower than, or similar to, those generated in the base case, confirming that the base case was indeed conservative.

Table 84: Summary of most cost-effective ICERs across all analyses (ischaemic individuals without LBBB)

Subgroup	Base Case	Constant mortality treatment effect	Constant HRQoL treatment effect	Constant mortality and HRQoL treatment effects	NYHA as treatment effect modifier	Mean device longevity increased by 10%
NYHA I , QRS <120ms	£24,016 (ICD)	£18,759 (ICD)	£23,134 (ICD)	£18,159 (ICD)	£24,243 (ICD)	£23,545 (ICD)
NYHA II, QRS <120ms	£23,884 (ICD)	£18,587 (ICD)	£22,995 (ICD)	£17,986 (ICD)	£24,109 (ICD)	£23,419 (ICD)
NYHA III, QRS <120ms	£26,923 (ICD)	£24,614 (ICD)	£26,923 (ICD)	£24,614 (ICD)	£26,678 (ICD)	£26,447 (ICD)
NYHA IV, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA I, QRS ≥120ms, <150ms	£16,234 (ICD)	£13,258 (ICD)	£16,001 (ICD)	£13,072 (ICD)	£15,795 (ICD)	£15,916 (ICD)
NYHA II, QRS ≥120ms, <150ms	£16,749 (ICD)	£13,792 (ICD)	£16,500 (ICD)	£13,593 (ICD)	£16,276 (ICD)	£16,421 (ICD)
NYHA III, QRS ≥120ms, <150ms	£24,796 (CRT-D)	£23,391 (CRT-D)	£23,535 (CRT-D)	£22,067 (CRT-D)	£21,363 (CRT-D)	£24,301 (CRT-D)
NYHA IV, QRS ≥120ms, <150ms	£24,336 (CRT-P)	£24,316 (CRT-P)	£23,769 (CRT-P)	£23,707 (CRT-P)	£24,152 (CRT-P)	£24,195 (CRT-P)
NYHA I, QRS ≥150ms	£21,086 (CRT-D)	£17,944 (CRT-D)	£21,086 (CRT-D)	£17,944 (CRT-D)	£21,337 (CRT-D)	£20,725 (CRT-D)
NYHA II, QRS ≥150ms	£22,777 (CRT-D)	£19,396 (CRT-D)	£24,034 (CRT-D)	£20,432 (CRT-D)	£23,936 (CRT-D)	£22,581 (CRT-D)
NYHA III, QRS ≥150ms	£25,734 (CRT-D)	£23,297 (CRT-D)	£24,196 (CRT-D)	£21,706 (CRT-D)	£22,737 (CRT-D)	£25,218 (CRT-D)
NYHA IV, QRS ≥150ms	£18,065 (CRT-P)	£17,964 (CRT-P)	£17,388 (CRT-P)	£17,266 (CRT-P)	£17,570 (CRT-P)	£17,891 (CRT-P)

Table 85: Summary of most cost-effective ICERs across all analyses (ischaemic individuals with LBBB)

Subgroup	Base Case	Constant mortality treatment effect	Constant HRQoL treatment effect	Constant mortality and HRQoL treatment effects	NYHA as treatment effect modifier	Mean device longevity increased by 10%
NYHA I , QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA II, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA III, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA IV, QRS <120ms	N/A	N/A	N/A	N/A	N/A	N/A
NYHA I, QRS ≥120ms, <150ms	£24,343 (CRT-D)	£20,704 (CRT-D)	£25,637 (CRT-D)	£21,774 (CRT-D)	£18,925 (CRT-D)	£24,147 (CRT-D)
NYHA II, QRS ≥120ms, <150ms	£21,277 (CRT-D)	£17,951 (CRT-D)	£22,445 (CRT-D)	£18,878 (CRT-D)	£18,848 (CRT-D)	£21,103 (CRT-D)
NYHA III, QRS ≥120ms, <150ms	£25,540 (CRT-D)	£23,633 (CRT-D)	£24,177 (CRT-D)	£22,192 (CRT-D)	£18,787 (CRT-D)	£25,030 (CRT-D)
NYHA IV, QRS ≥120ms, <150ms	£22,340 (CRT-P)	£22,302 (CRT-P)	£21,929 (CRT-P)	£21,882 (CRT-P)	£24,113 (CRT-P)	£22,186 (CRT-P)
NYHA I, QRS ≥150ms	£17,335 (CRT-D)	£14,375 (CRT-D)	£17,335 (CRT-D)	£14,375 (CRT-D)	£16,142 (CRT-D)	£17,044 (CRT-D)
NYHA II, QRS ≥150ms	£17,479 (CRT-D)	£14,548 (CRT-D)	£17,479 (CRT-D)	£14,548 (CRT-D)	£16,284 (CRT-D)	£17,187 (CRT-D)
NYHA III, QRS ≥150ms	£29,912 (CRT-D)	£26,979 (CRT-D)	£28,253 (CRT-D)	£25,215 (CRT-D)	£23,125 (CRT-D)	£29,304 (CRT-D)
NYHA IV, QRS ≥150ms	£17,722 (CRT-P)	£17,666 (CRT-P)	£17,399 (CRT-P)	£17,327 (CRT-P)	£17,694 (CRT-P)	£17,599 (CRT-P)

6.5.2 Cost-effective interventions by patient group

A summary of the choice of cost-effective interventions in each patient group is presented in Table 86.

*Table 86: Summary of cost-effectiveness recommendations arising from our analysis**

NYHA	QRS <120ms	QRS 120-150ms	QRS >150ms
I	ICD	ICD (No LBBB) CRT-D (with LBBB)	CRT-D (Both LBBB groups)
II	ICD	ICD (No LBBB) CRT-D (with LBBB)	CRT-D (Both LBBB groups)
III	ICD	CRT-D/ CRT-P (both LBBB groups)	CRT-D/ CRT-P (both LBBB groups)
IV	OPT	CRT-P (Both LBBB groups)	CRT-P (Both LBBB groups)

* all individuals also have LVEF<35% and no myocardial infarction within the past 4 weeks; the results apply to both ischaemic and non-ischaemic patients.

6.5.2.1 Patients without LBBB (LVEF <35%)

- **In NYHA class I/II patients without LBBB who have a QRS duration of less than 150ms, ICD should be used. When the QRS duration is ≥ 150 ms the patient should be given CRT-D.**
- **For NYHA class III patients, where indicated, doctors should be allowed to use either a CRT-D or a CRT-P device since both are clinically- and cost-effective interventions, with CRT-D being the preferred device due to the incidence of SCD in this population. NYHA class III patients with QRS duration less than 120ms should be offered an ICD.**
- **CRT-P is the treatment of choice in patients who are NYHA class IV and QRS duration of at least 120ms.**

6.5.2.2 Patients with LBBB (LVEF <35%)

For patients with LBBB the key decision variable is NYHA class:

- **For patients in NYHA class I, II or III the treatment of choice is CRT-D. CRT-P is also to be a treatment option for patients who are in NYHA class III**
- **For those in NYHA IV a CRT-P device is the preferred option.**

It is interesting to note that clinical opinion provided during the development of the model indicates that in both LBBB groups, the findings highlighted above are the choices being made in routine clinical practice. Guidance reflecting the findings we present would be in line with the expectations of the clinical community, meaning that implementation would likely be high and budgetary impact low, given that this cost is already likely to be borne by the NHS under current financing.

6.5.2.3 Uncertainties and the need for clinical flexibility

For a number of the patient groups, the ICERs for several interventions compared to the previous element of the frontier are very similar. This means that the cost-effectiveness frontier is very flat, and plausible small changes to assumptions can result in interventions switching from being cost-effective to dominated or extended dominated. There is thus a high level of uncertainty in these patient groups regarding the choice of the 'best' device.

While exploratory, the probabilistic sensitivity analysis (PSA) results presented in Appendix 16 also indicate that the impact of parameter uncertainty is likely to be high. This is likely to be driven by the focus in our IPD analysis on fully capturing patient heterogeneity: by introducing a series of interaction effects, this necessarily reduces treatment effect precision. Our analysis does not suggest uncertainty regarding the overall efficacy of the devices, which is clearly demonstrated in the unadjusted network meta-analysis (see Section 4.2).

Finally, it is important to note that the cost-effectiveness results and the clinical effectiveness evidence concur, and there is no reason to treat ischaemic and non-ischaemic cardiomyopathy differently in terms of device therapy.

Hence, we recommend that guidance should be flexible, to allow clinicians to select the most appropriate device for a given patient in cases where the ICERs for two or more interventions are sufficiently similar.

6.5.2.4 Additional considerations

Despite having patient level data on over 12,000 individuals, it was not possible to answer all clinically relevant questions. The available evidence on these is presented below

- Atrial fibrillation: As noted in Section 2, these patients were excluded from most of the RCTs, and the resulting lack of data meant that we could not distinguish between patients with and without AF in our analysis. Only one of the trials in the IPD database included patients with permanent AF at baseline (RAFT⁸⁰). Results from RAFT showed no statistically significant difference between patients with permanent atrial fibrillation or flutter vs. those whom were in sinus rhythm or were atrially paced (p-value for interaction = 0.14 for primary endpoint of death or hospitalisation for heart failure). However the power of this analysis to detect any interaction effect is likely to have been limited by the number of patients in the permanent atrial fibrillation or flutter subgroup (n=229).
- Previous NICE guidance for ICD was predicated for some patients on patients having non-sustained VT on Holter monitoring and inducible VT on EP testing for patients with QRS duration <120ms or LVEF between 30-35%. Non-sustained VT on ECG was only collected in three of the smaller ICD trials (MUSTT, DEFINITE and MADIT) and EP testing in only one small ICD trial (MADIT). It would therefore be difficult to make evidence based statements stratified according to these tests
- Previous NICE guidance for CRT was predicated on the presence of mechanical dyssynchrony for patients with QRS 120-149ms. This appears to be based on the inclusion criteria for CARE-HF (the only study in which these data were collected). However, analysis of the IPD from CARE-HF shows that only ■ of patients in CARE-HF had QRS in the range 120-149ms. This

suggests that the favourable results in CARE-HF were driven by the wider QRS of patients in this trial (which was found to modify CRT efficacy in our analysis), rather than by the mechanical dyssynchrony criteria.

Also, the data from the clinical trials did not include the rarer ICD indications – hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, long QT Syndrome, etc., and so we were not able to assess which interventions should be used in these groups. Smaller trials and registries remain the best available information source on which to base treatment decisions in these patient groups.

7 Financial implications to the NHS and other parties

- The recommendations from the ABHI analysis presented in section 6.5.2 would lead to a widening of the eligibility criteria for an ICD or CRT device and consequently an increase in implant rates, but growth in uptake is likely to be gradual.
- Growth in implant rates should be viewed in the context that current rates are still below the minimum levels suggested under current guidance and the implant rates in other developed countries in Europe and North America.
- It is difficult to predict future implant rates for each device type because of unknowns relating to switching rates between types (e.g. ICD to CRT), and incomplete epidemiological data on the numbers of patients in each eligible group. It is therefore not feasible to present a full budget impact analysis.
- We present estimates of the annual cost of treatment under current and alternative scenarios. These represent the costs above and beyond those that would be incurred if patients remained on medical management alone.
- Depending on the choice of scenario and year of interest, the additional annual expenditure incurred by the NHS ranges from £41.6 million to £230.2 million.
- The majority of interventions were shown to be cost-effective in the groups where they are indicated. Hence, the cost of services displaced through the use of these technologies would be expected to be higher than the costs incurred (for example, hospitalisation rates would be reduced).

7.1 Introduction

The conclusions from the ABHI model described in section 6.5.2 would lead to an increase in implant rates, with the associated financial costs. However, experience with related technologies suggests that growth in implant rates is likely to be gradual rather than sudden. For example, uptake of pacemakers in England was still only 528 per million in 2010 – well below Heart Rhythm UK’s national target of 700 per million, even though access to these devices is relatively unrestricted.²¹ Furthermore, removal of the requirements for Holter monitoring, electrophysiology testing and echocardiography for dyssynchrony would mean that an increased implantation rate would be simpler and cheaper to implement than under the current recommendations.

Most importantly, the devices under consideration bring survival and symptomatic/quality of life benefits to patients in the proposed widened indications. We have shown them to be cost-effective. As current implantation rates do not yet reach even previously suggested minimum levels, we would argue that an increase in implantation rates to include the patients under discussion is clinically and humanistically desirable in terms of QALYs gained, and the cost of these benefits would not exceed willingness to pay thresholds.

The implications for switching rates (ICD to CRT, CRT-P to CRT-D, etc.) of such revised guidance are unknown. It is also unknown how many patients would be included who are currently treated with ICD but who technically lie outside of existing guidance (i.e. those with no history of MI). Furthermore, epidemiological data on the number of patients in each group is not as comprehensive as would ideally be required for a full budget impact analysis. Because of these unknowns, any attempt to predict revised implant rates is speculative. The following impact assessment is presented to assist in providing as credible an estimate as possible of the financial implications to the NHS, using the available evidence both from this submission and from real world NHS clinical practice. We will present ‘current’ and ‘alternative’ scenarios in terms of the split between CRT-P and CRT-D within CRT implant rates, and different projected increases in ICD implantation rates.

7.2 Implant rates arising from previous appraisals

The financial implications sections of previous independent academic submissions were brief and did not contain any replicable methodologies. As part of the previous review of ICDs, an estimated annual implant rate of 100 per million population was generated for budget impact purposes. This rate represented a doubling of the value derived during TA11.³³ The review associated with that appraisal quotes an audit of clinical records undertaken at an English tertiary hospital to determine the eligibility of patients for ICDs against the NICE guidance of the time. This study reported under-provision of ICD therapy in the UK, and found that the number of patients eligible for ICDs exceeded that predicted. The annual incidence of patients fulfilling national criteria was about 150 per million, with an additional 'prevalence' pool of about 41 per million. The authors calculated that applying the MADIT II criteria to determine eligibility for ICD would increase the number to 504 per million (new cases) and 311 per million (prevalent cases) per year. Thus, the targets for ICD arising from previous NICE appraisals potentially underestimate the size of the target population by a factor of between 10 and 25.

There was no implant rate estimate in the previous CRT appraisal. Subsequent extrapolation from prevalence studies estimated a required CRT implantation rate of 130/million/year, and this has been adopted as a target by the UK National Audit of Cardiac Rhythm Management Devices.²¹

We have estimated the financial implications of our proposed guidance in terms of changes to implant rates.

7.3 Input values for current budget impact assessment

7.3.1 UK population estimates

The UK National Statistics Database¹⁴³ was examined to derive the latest population size estimate for England and Wales. To this value, we have applied an assumed 1% annual growth rate to derive population estimates for the years 2012-2016 inclusive. The values used in the model are presented in Table 87.

Table 87: England and Wales population estimates (in millions) 2012-2016

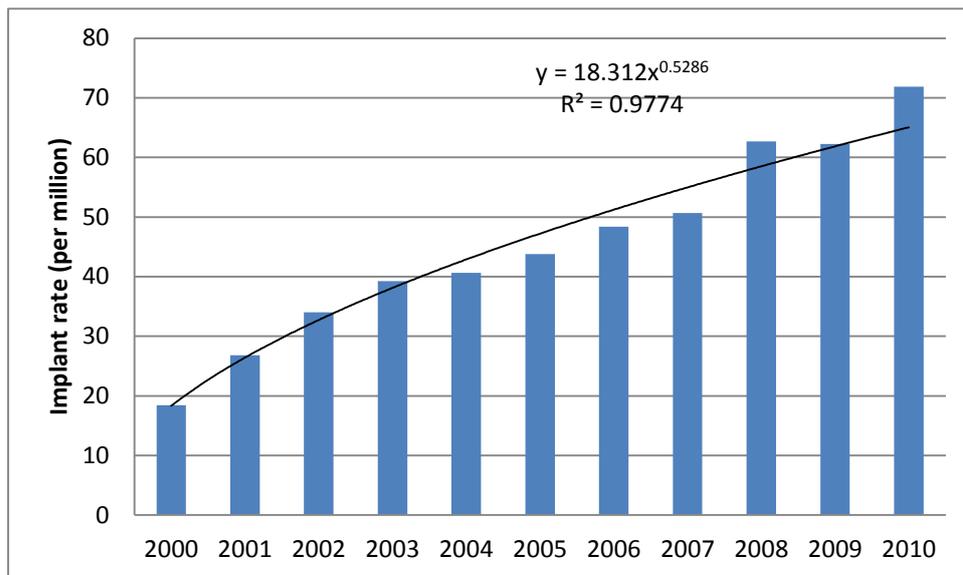
	2012	2013	2014	2015	2016
Value used	63.758	64.271	64.776	65.271	65.755

7.3.2 Implant rates used in ‘current scenario’

ICDs

The principal document we have drawn on is the latest National Device Survey by the CCAD research group, which contained implant rates for England and Wales from years 2000 to 2010 inclusive.²¹ A plot of the weighted average of the reported figures for England and Wales is presented in Figure 36, with a trend line.

Figure 36: England and Wales annual ICD implant rates (Data taken from Cunningham et al.)



The trend shows a slowing down in the change in implant rate over time. It is also noteworthy that the observed implant rates in all years are below the previous estimates derived by the independent evidence review group (discussed in Section 7.2 above). The fitted line was used to derive estimates of the expected ICD implant rates for 2012-2016 inclusive. The trend line is suggestive of a plateau effect being observed. Such an effect would arise due to patients who would historically have been offered an ICD device now being offered a CRT-D. This observation is further evidence that the conclusions of this submission are

aligned with routine clinical practice.

The predicted ICD implant rates used in the model, along with estimates of the number of implant procedures, are presented in Table 88.

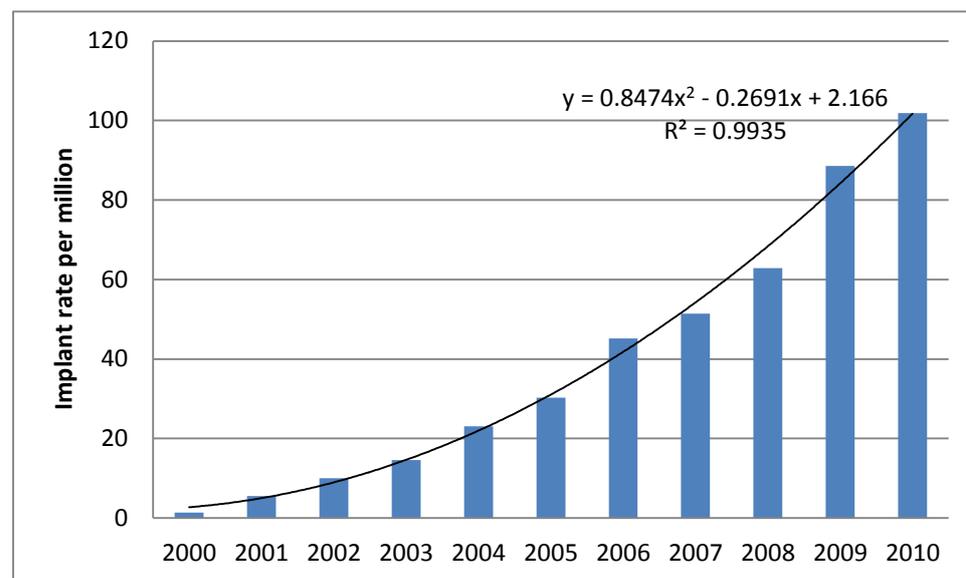
Table 88: Projected ICD implant rates (per million) and procedure counts

	2012	2013	2014	2015	2016
Implant rates	71.1	73.9	76.6	79.3	81.9
Procedure count	4,553	4,750	4,962	5,176	5,385

CRT

Cunningham *et al.*²¹ also report equivalent data for CRT implant rates; the corresponding plot of the weighted average values for England and Wales is presented in Figure 37 (with the best fitting trend line). In this case the trend is increasing.

Figure 37: England and Wales annual CRT implant rates (Data taken from Cunningham *et al.*)



Within the CCAD report it is not possible to assess the historical CRT-D/CRT-P case mix for new implants. Relevant information can, however, be derived from the UK Health Episode Statistics (HES) database for years 2009/10 and 2010/11.¹⁴⁴ The relevant data are presented in Table 89. The proportion of patients who were given a CRT-D device in 2010/11 is in line with device use splits for the UK and Western Europe.¹⁴⁵ The rapid growth in CRT-D usage in

recent years is a further indication of a potential switch from ICD to CRT-D usage.

Table 89: New implant counts (CRT-P and CRT-D) reproduced from the HES database

Code	Description	2009/10	2010/11
E07Z	Pace 3 - Biventricular and all congenital pacemaker Procedures - Resynchronisation Therapy	1,882	1,952
K59.6	Implantation of cardioverter defibrillator using three electrode leads	1,198	1,920
K61.7	Implantation of biventricular cardiac pacemaker system	61	71
TOTAL: CRT-P (E07Z)		1,882	1,952
TOTAL: CRT-D (K59.6, K61.7)		1,260	1,991
Proportion of implants CRT-D		40.1%	50.5%

In projecting forwards, we have therefore used the assumption that 50.5% of CRT patients receive a CRT-D and 49.5% receive a CRT-P device. We have also included a notional 'braking coefficient' on the projected implant rates of 2.5% per year to simulate a future plateau effect for CRT usage. The derived rates and the procedure counts are presented in Table 90.

Table 90: Projected CRT implant rates (per million) and procedure counts

	2012	2013	2014	2015	2016
Implant rates	141.9 ^a	161.4 ^b	179.5 ^c	199.1 ^d	219.1 ^e
Procedure count (CRT-D)	4,569	5,539	5,872	6,563	7,275
Procedure count (CRT-P)	4,478	5,135	5,756	6,433	7,131

a) Value excluding braking effect 141.9 per million; **b)** Value excluding braking effect 164.5 per million; **c)** Value excluding braking effect 188.8 per million; **d)** Value excluding braking effect 214.8 per million; **e)** Value excluding braking effect 242.5 per million

7.3.3 Implant rates used in 'alternative' scenarios

A large proportion of patients who would become eligible for a CRT-D under the potential new guidance lie within the current eligibility criteria for an ICD. Given the small difference in implant costs, the budget impact of the recommendations of this submission could be limited if CRT-D is given mainly to patients previously given ICD. However, it is likely that CRT-D use would increase at the expense of

ICD implant rates, because of the additional symptomatic benefits that CRT-D offers to patients with HF.

As an alternative to the 'current' scenario described above, we have assumed that as a result of the new guidance, CRT usage will continue on its current trajectory (see Table 91), but the CRT-D/CRT-P split will be 75%/25%. To reflect the greater use of ICDs in NYHA I/II patients we have assumed a range of multipliers to the projected current ICD implant rates (25% increase, 50% increase, 100% increase, 200% increase).

As the UK has failed to fully implement previous NICE guidance and is already lagging behind the value previously used to estimate budget impact in TA95 of 100 implant per million, the base value for these projections could be considered unduly low. The derived estimates are to be viewed as minimum bounds and not as targets to be regarded as ceiling rates.

The annual ICD implant rates used in the alternative scenarios are presented in Table 91.

Table 91: Implant rates (per million) used in all alternative scenarios

	2012	2013	2014	2015	2016
CRT (all scenarios)	141.9	161.4	179.5	199.1	219.1
- Of which CRT-P	35.5	40.4	44.9	49.8	54.8
- Of which CRT-D	106.4	121.0	134.6	149.3	164.3
ICD (scenario 1: 25% increase on current projections)	88.9	92.4	95.8	99.1	102.4
ICD (scenario 2: 50% increase on current projections)	106.7	110.9	114.9	119.0	122.9
ICD (scenario 3: 100% increase on current projections)	142.4	147.8	153.2	158.6	163.8
ICD (scenario 4: 200% increase on current projections)	213.3	221.1	229.8	237.9	245.7

7.3.4 Annual cost of treatment

An estimate of the 5 year (undiscounted) cost of treatment with the new intervention compared with the old one is a fundamental element of any financial impact analysis. In this instance, the relevant costs are all those that would be incurred *above and beyond what would be incurred if patients had remained on medical management*. Treatment and subgroup specific model outputs for the 48

patient groups discussed in Section 6.1 were weighted by the proportion of patients in each group, to generate the values for annual cost of treatment, conditional on being alive, presented in Table 92. Note that in patient groups where a given intervention is contraindicated (e.g. ICD in NYHA IV), these patients have not been included in the weighted average calculations. The increase in annual values is due to reoperations. The rates of growth for each device type are based on the parametric functions described in section 5.3.2. Hence, because CRT-D devices are expected to fail quicker than ICD or CRT-P the values will rise at a greater rate.

Table 92: Annual cost of treatment estimates used in the financial impact assessment

	2012	2013	2014	2015	2016
ICD	£15,710	£230	£441	£611	£735
CRT-P	£8,294	£80	£86	£88	£88
CRT-D	£19,042	£468	£852	£1,142	£1,327

7.3.5 Survival estimates

It is essential to know what proportions of patients who get each treatment survive to subsequent years. Weighted average model outputs were again used in the analysis: the values are presented in Table 93. Note that due to differences in device usage across NYHA classes (and in particular the assumption that CRT-P is used only in NYHA class III/IV and QRS duration ≥ 120 ms), direct comparisons of these survival estimates should not be made.

The values in this table are used to predict the proportion of the incident populations who are alive at subsequent years (and hence incur the costs presented in Table 92). For example, someone who gets an ICD will have a 92.9% chance of living one year, an 85.3% chance of living two years, and so on.

Table 93: Survival estimates used in the financial impact assessment

	Year 1	Year 2	Year 3	Year 4	Year 5
ICD	92.9%	85.3%	78.1%	71.2%	64.9%
CRT-P	86.9%	74.1%	62.7%	53.0%	44.7%
CRT-D	93.1%	85.8%	78.8%	72.1%	66.0%

7.4 Results

7.4.1 Scenario 1: 25% increase on current projections for ICD usage

The outputs from the model are presented in Table 94. The annual budgetary increase ranges from £41.6 million in year 1 to £69.9 million in year 5.

Table 94: Budget impact analysis: Scenario one

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£236,990,204	£267,092,765	£299,352,673	£336,036,417	£375,008,423
Total budget impact	£41,627,873	£47,176,815	£53,512,209	£60,893,306	£68,867,122

7.4.2 Scenario 2: 50% increase on current projections for ICD usage

The outputs from the model are presented in Table 95. The annual budgetary increase ranges from £59.4 million in year 1 to £91.9 million in year 5.

Table 95: Budget impact analysis: Scenario two

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£254,793,949	£285,988,507	£319,519,948	£357,617,274	£398,062,007
Total budget impact	£59,431,618	£66,072,557	£73,679,484	£82,474,163	£91,920,707

7.4.3 Scenario 3: 100% increase on current projections for ICD usage

The outputs from the model are presented in Table 96. The annual budgetary increase ranges from £95.0 million in year 1 to £138.0 million in year 5.

Table 96: Budget impact analysis: Scenario three

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£290,401,439	£323,779,992	£359,854,498	£400,778,988	£444,169,177
Total budget impact	£95,039,108	£103,864,042	£114,014,033	£125,635,877	£138,027,876

7.4.4 Scenario 4: 200% increase on current projections for ICD usage

The outputs from the model are presented in Table 97. The annual budgetary increase ranges from £166.3 million in year 1 to £230.2 million in year 5.

Table 97: Budget impact analysis: Scenario four

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario	£195,362,331	£219,915,950	£245,840,464	£275,143,111	£306,141,301
Alternative scenario	£361,616,418	£399,362,962	£440,523,597	£487,102,416	£536,383,515
Total budget impact	£166,254,087	£179,447,012	£194,683,133	£211,959,305	£230,242,215

7.4.5 Discussion of model outputs

Depending on the choice of scenario and year of interest, the additional annual expenditure incurred by the NHS ranges from £41.6 million to £230.2 million per year. Actual annual values will be somewhere between the derived values in each of the tables above. However, the key fact that needs to be considered

when interpreting these results is that the majority of interventions were shown to be cost-effective in the groups where they are indicated.

7.5 Implications to other interested stakeholders

In terms of implications to other parties, as noted by Fox *et al.*³⁴ in their 2007 assessment:

“The future development of CRT provision within the NHS is dependent upon both access to suitably trained cardiologists and associated clinical staff and the adequate provision of implantation centres and associated diagnostic infrastructure.

Clinical advisors have suggested that: (1) the current availability of cardiologists with the necessary skills to undertake CRT surgery is one to two per regional centre, this will increase to an additional one per district general hospital as further cardiologists are trained, and (2) the learning curve for CRT implantation is steep and training should be undertaken by senior and experienced implanters of conventional pacemakers and ICDs. Furthermore, resources will be needed for associated clinical staff, technicians and the related diagnostic infrastructure including properly equipped cardiac catheter laboratories.”

We believe the views expressed in this statement are still relevant.

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**Association of British Healthcare
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**NATIONAL INSTITUTE FOR HEALTH AND
CLINICAL EXCELLENCE**

Multiple Technology Appraisal

**Implantable cardioverter defibrillators for
the treatment of arrhythmias and cardiac
resynchronisation therapy for the treatment
of heart failure (review of TA95 and TA120)**

Appendices

6th July 2012

Appendix 1: Search strategies used to identify RCTs

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and
Ovid MEDLINE(R) <1948 to Present>

Search run on 27/06/2011

- 1 (CRT or "cardiac resynchron\$ therap\$").tw. (6517)
- 2 resynchron\$ therap\$.tw. (2829)
- 3 BVP.tw. (170)
- 4 Cardiac Resynchronization Therapy/ (228)
- 5 (biventricular adj10 pac\$).tw. (1261)
- 6 (biventricular adj10 stimulat\$).tw. (157)
- 7 ((cardiac or heart) adj10 resynch\$).tw. (3034)
- 8 (coronary adj10 resynch\$).tw. (131)
- 9 (atriobiventricular adj10 pac\$).tw. (14)
- 10 (atrio biventricular adj10 pac\$).tw. (23)
- 11 CRT-P.tw. (133)
- 12 CRT-D.tw. (176)
- 13 cardioversion.tw. (4098)
- 14 cardioverter.tw. (6545)
- 15 Defibrillators, Implantable/ (8786)
- 16 (internal adj3 (defibrillat\$ or cardioverter)).tw. (422)
- 17 (implant adj3 (cardioverter or defibrillat\$)).tw. (122)
- 18 (cardiac adj3 defibrillat\$).tw. (1061)
- 19 ((implant or internal or cardiac) and defib\$).tw. (7618)
- 20 icd.tw. (14797)
- 21 or/1-20 (35301)
- 22 Intraventricular conduction delay\$.tw. (271)
- 23 Dilated cardiomyopathy.tw. (10812)
- 24 (Sudden death adj3 cardiac).tw. (801)
- 25 ((prolonged or wide) adj2 QRS).tw. (1056)
- 26 (Premature ventricular adj1 (complex\$ or contraction)).tw. (794)
- 27 ((Reduced or low) adj ejection fraction).tw. (1045)
- 28 ((impaired or dysfunction or function) adj3 (left ventric\$ or LVEF or LV)).tw. (37111)
- 29 (ventricular adj1 (tachycardia or fibrillation)).tw. (25008)
- 30 arrhythmi\$.tw. (57496)
- 31 heart failure.tw. (85570)
- 32 ((cardiac or ventricular or intraventricular) adj5 asynchron\$).tw. (444)
- 33 ((cardiac or ventricular or intraventricular) adj5 dyssynchron\$).tw. (882)

34 cardiac arrest.tw. (16215)
 35 tachycardia, ventricular/ (8877)
 36 Arrhythmias, Cardiac/ (47995)
 37 Heart Failure/ (71586)
 38 Death, Sudden, Cardiac/ (9017)
 39 Ventricular Dysfunction, Left/ or Bundle-Branch Block/ (23476)
 40 Bundle Branch Block.tw. (6055)
 41 Ventricular Fibrillation/ (13640)
 42 Heart Arrest/ (19743)
 43 Myocardial Infarction/ (126739)
 44 or/22-43 (368895)
 45 Randomized controlled trials as Topic/ (73673)
 46 Randomized controlled trial/ (309567)
 47 Random allocation/ (71762)
 48 Double blind method/ (110773)
 49 Single blind method/ (15106)
 50 Clinical trial/ (463846)
 51 exp Clinical Trials as Topic/ (242485)
 52 clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial,
 phase iv/ or multicenter study/ (558228)
 53 or/45-52 (851498)
 54 randomized controlled trial.pt. (309567)
 55 controlled clinical trial.pt. (82654)
 56 random allocation.sh. (71762)
 57 double blind method.sh. (110773)
 58 single blind method.sh. (15106)
 59 (clin\$ adj25 trial\$).tw. (200910)
 60 ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj25 (blind\$ or mask\$ or dummy\$)).tw. (114910)
 61 Placebos/ (29766)
 62 Placebo\$.tw. (133939)
 63 Random\$.tw. (553900)
 64 or/54-63 (914706)
 65 53 or 64 (1220129)
 66 Case report.tw. (168393)
 67 Letter/ (733158)
 68 Historical article/ (275454)
 69 or/66-68 (1167008)
 70 65 not 69 (1192243)
 71 21 and 44 and 70 (3760)
 72 animals/ not (animals/ and humans/) (3520949)
 73 71 not 72 (3508)
 74 limit 73 to english language (3198)

75 limit 74 to yr="1990 -Current" (3152)

Database: Embase<1988 to 2011 Week 25>

Search run on 27/06/2011

- 1 (CRT or "cardiac resynchron\$ therap\$").tw. (9071)
- 2 resynchron\$ therap\$.tw. (4112)
- 3 BVP.tw. (178)
- 4 cardiac resynchronization therapy/ (5525)
- 5 (biventricular adj10 pac\$).tw. (1670)
- 6 (biventricular adj10 stimulat\$).tw. (219)
- 7 ((cardiac or heart) adj10 resynch\$).tw. (4377)
- 8 (coronary adj10 resynch\$).tw. (167)
- 9 (atrio biventricular adj10 pac\$).tw. (30)
- 10 (atriobiventricular adj10 pac\$).tw. (20)
- 11 CRT-P.tw. (242)
- 12 CRT-D.tw. (485)
- 13 cardioversion.tw. (4285)
- 14 cardioverter.tw. (7839)
- 15 (internal adj3 (defibrillat\$ or cardioverter)).tw. (442)
- 16 (implant\$ adj3 (cardioverter or defibrillat\$)).tw. (9516)
- 17 (cardiac adj3 defibrillat\$).tw. (1115)
- 18 ((implant or internal or cardiac) and defib\$).tw. (8844)
- 19 icd.tw. (20125)
- 20 *defibrillator/ (6658)
- 21 or/1-20 (44411)
- 22 *Heart arrest/ (10051)
- 23 *myocardial infarction/ (48787)
- 24 *Death,-Sudden,-Cardiac/ (8275)
- 25 cardiac arrest.tw. (15652)
- 26 Intraventricular conduction delay\$.tw. (280)
- 27 Dilated cardiomyopathy.tw. (12299)
- 28 (sudden death adj3 cardiac).tw. (818)
- 29 ((prolonged or wide) adj2 QRS).tw. (1190)
- 30 (Premature ventricular adj1 (complex\$ or contraction)).tw. (699)
- 31 ((Reduced or low) adj ejection fraction).tw. (1302)
- 32 ((impaired or dysfunction or function) adj3 (left ventric\$ or LVEF or LV)).tw. (39565)
- 33 (ventricular adj1 (tachycardia or fibrillation)).tw. (22091)
- 34 arrhythmi\$.tw. (52667)
- 35 *congestive cardiomyopathy/ (5894)
- 36 *heart muscle conduction system/ (1786)
- 37 *heart arrhythmia/ (18228)

38 *heart bundle branch block/ (712)
 39 *heart failure/ (39054)
 40 *congestive heart failure/ (17950)
 41 heart failure.tw. (96051)
 42 ((cardiac or ventricular or intraventricular) adj5 asynchron\$).tw. (464)
 43 ((cardiac or ventricular or intraventricular) adj5 dyssynchron\$).tw. (1299)
 44 *Bundle-Branch Block/ (712)
 45 Bundle Branch Block.tw. (4682)
 46 *heartventricletachycardia/ (8113)
 47 *syncope/ (5496)
 48 *heartventricle fibrillation/ (5098)
 49 or/22-48 (273295)
 50 Clinical trial/ (758285)
 51 Randomized controlled trial/ (265459)
 52 Randomization/ (49808)
 53 Single blind procedure/ (13620)
 54 Double blind procedure/ (90508)
 55 Crossover procedure/ (29846)
 56 Placebo/ (146356)
 57 Rct.tw. (6934)
 58 random*.tw. (588686)
 59 (clinical trial\$ or controlled clinical trial\$ or major clinical stud\$ or controlled stud\$).tw. (219539)
 60 (clinical adj25 trial\$).tw. (213401)
 61 ((single\$ or double\$ or treble\$ or triple\$) and (blind\$ or mask\$)).tw. (117874)
 62 Placebo\$.tw. (137596)
 63 Prospective study/ (157946)
 64 or/50-63 (1381558)
 65 Case study/ (10159)
 66 Abstract report/ or letter/ (611863)
 67 or/65-66 (621895)
 68 64 not 67 (1352204)
 69 21 and 49 and 68 (4664)
 70 limit 69 to english language (4204)
 71 animal/ not (animal/ and human/) (526120)
 72 animal experiment/ (1040422)
 73 71 or 72 (1559640)
 74 70 not 73 (3995)
 75 conference.so. (435795)
 76 74 not 75 (3512)
 77 limit 76 to yr="1990 -Current" (3499)

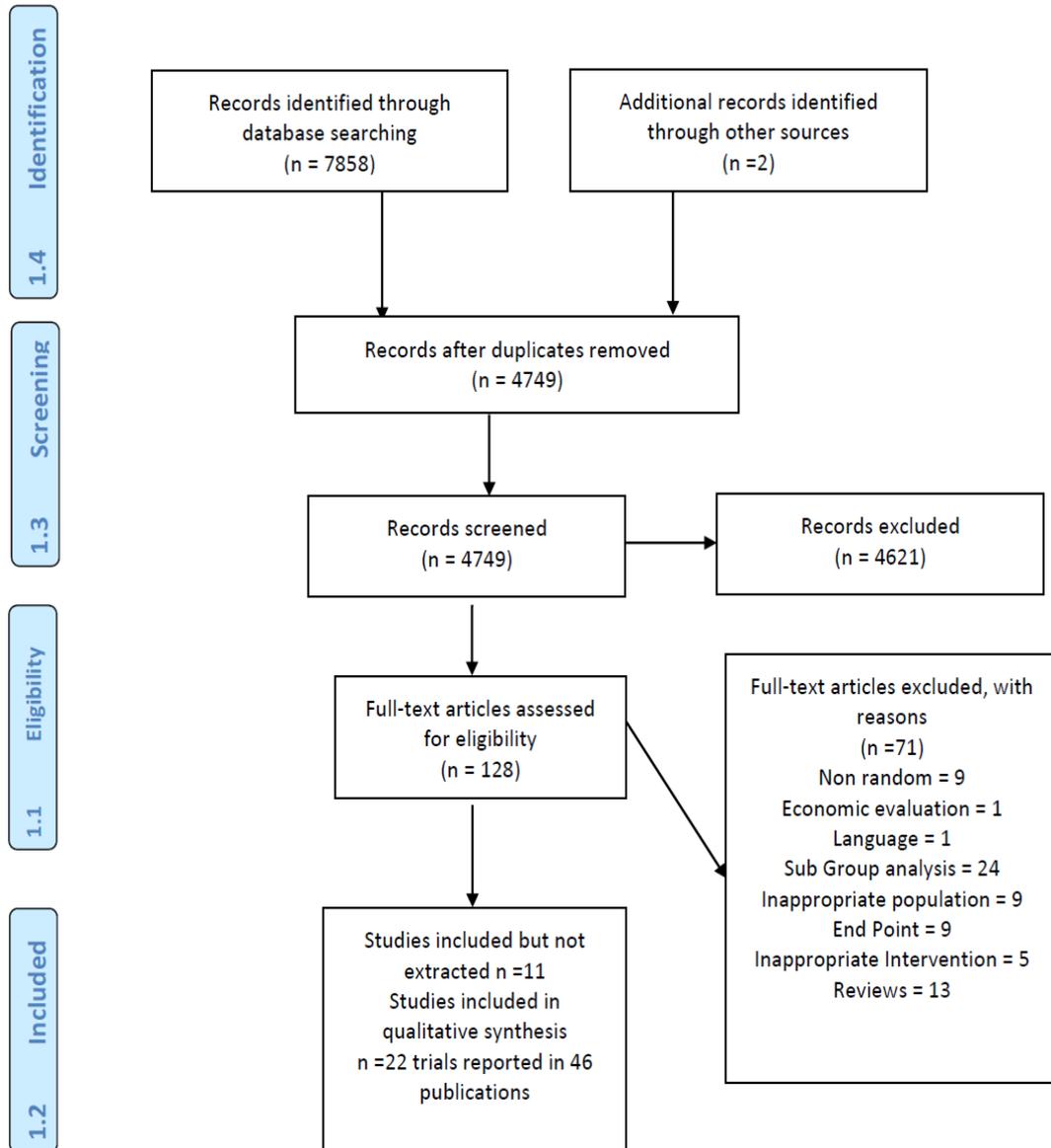
Database: Cochrane

Search run on: 28/06/2011

#1	(CRT or cardiac resynchron* therap*):ti,ab,kw in Clinical Trials	647
#2	(resynchron* therap*):ti,ab,kw in Clinical Trials	204
#3	(BVP):ti,ab,kw in Clinical Trials	14
#4	MeSH descriptor Cardiac Resynchronization Therapy, this term only	4
#5	(biventricular NEAR pac*):ti,ab,kw in Clinical Trials	108
#6	(biventricular NEAR stimulat*):ti,ab,kw in Clinical Trials	16
#7	((cardiac or heart) NEAR resynch*):ti,ab,kw in Clinical Trials	205
#8	(coronary NEAR resynch*):ti,ab,kw in Clinical Trials	3
#9	(atrioventricular NEAR pac*):ti,ab,kw in Clinical Trials	3
#10	(atrio biventricular NEAR pac*):ti,ab,kw in Clinical Trials	11
#11	(CRT-P):ti,ab,kw in Clinical Trials	23
#12	(CRT -D):ti,ab,kw in Clinical Trials	58
#13	(cardioversion):ti,ab,kw in Clinical Trials	546
#14	(cardioverter):ti,ab,kw in Clinical Trials	470
#15	MeSH descriptor Defibrillators, Implantable, this term only	734
#16	(internal NEAR (defibrillat* or cardioverterter)):ti,ab,kw in Clinical Trials	19
#17	(implant NEAR (cardioverter OR defibrillat*)):ti,ab,kw in Clinical Trials	119
#18	(cardiac NEAR defibrillat*):ti,ab,kw in Clinical Trials	283
#19	((implant OR internal OR cardiac) AND defib*):ti,ab,kw in Clinical Trials	709
#20	(icd):ti,ab,kw in Clinical Trials	780
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#22	(intraventricular conduction delay):ti,ab,kw in Clinical Trials	31
#23	(Dilated cardiomyopathy):ti,ab,kw in Clinical Trials	551
#24	(Sudden death NEAR cardiac):ti,ab,kw in Clinical Trials	641
#25	((prolonged or wide) NEAR QRS):ti,ab,kw in Clinical Trials	84
#26	(Premature ventricular NEAR (complex* or contraction)):ti,ab,kw in Clinical Trials	415
#27	((Reduced or low) NEAR ejection fraction):ti,ab,kw in Clinical Trials	446

#28	((impaired or dysfunction or function) NEAR (left ventric* or LVEF or LV)):ti,ab,kw in Clinical Trials	4865
#29	(ventricular NEAR (tachycardia or fibrillation)):ti,ab,kw in Clinical Trials	1673
#30	(heart failure):ti,ab,kw in Clinical Trials	8459
#31	((cardiac or ventricular or intraventricular) NEAR asynchron*):ti,ab,kw in Clinical Trials	25
#32	((cardiac or ventricular or intraventricular) NEAR dyssynchron*):ti,ab,kw in Clinical Trials	56
#33	MeSH descriptor Arrhythmias, Cardiac, this term only	1604
#34	MeSH descriptor Heart Failure, this term only	4620
#35	MeSH descriptor Ventricular Dysfunction, Left, this term only	1412
#36	(Bundle Branch Block):ti,ab,kw in Clinical Trials	178
#37	(arrhythmi*):ti,ab,kw in Clinical Trials	5106
#38	(cardiac arrest):ti,ab,kw in Clinical Trials	990
#39	MeSH descriptor Heart Arrest, this term only	533
#40	MeSH descriptor Death, Sudden, Cardiac explode all trees	452
#41	MeSH descriptor Bundle-Branch Block explode all trees	79
#42	MeSH descriptor Ventricular Fibrillation explode all trees	425
#43	MeSH descriptor Myocardial Infarction explode all trees	7646
#44	(#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43)	23964
#45	(#21 AND #44), from 1990 to 2011	1418
#46	(#45)	1207

Appendix 2: Prisma Flow Diagram



Appendix 3: Assessment of risk of bias

All included studies were critically appraised following the criteria specified by NICE. This assessment requires the evaluation of individual components that affect risk of bias. This method is described in the Cochrane Handbook for Systematic Reviews and the Centre for Reviews and Dissemination guidance. In line with this method, the following items were appraised:

Description of randomisation:

A method of randomisation will be considered adequate when any pattern of allocation is equally likely. Examples of acceptable methods of randomisation include:

- The use of a computer random number generator
- Referring to a random number table

The description of randomisation will be regarded as unclear if there is insufficient information about the sequence generation process. For example, a study described as randomised but no method of randomisation is described.

Description of allocation concealment:

An adequate method of allocation concealment ensures patients and investigators are unaware of the forthcoming assignment. Examples of appropriate methods of allocation concealment include the following:

- Central allocation: telephone, pharmacy-controlled
- Sequentially numbered, opaque, sealed envelopes
- Sequentially numbered drug containers of identical appearance

Inadequate methods of allocation concealment include:

- the use of open random allocation schedule: list of random numbers
- use of non-opaque or not sequentially numbered envelopes
- allocation by alternation, date of birth

If there is insufficient information to assess the method of allocation concealment this will be regarded as unclear.

Blinding of participants, investigators and outcome assessors:

Criteria for an adequate method of blinding will be based on the following:

- Blinding of patients and investigators is ensured and unlikely that the blinding could have been broken.
- Either patients or investigators were not blinded but the outcome assessment was blinded (outcome adjudicated by a blinded events committee).

The following will be regarded as inadequate method of blinding:

- No blinding or incomplete blinding
- Study described as double blind but likely that blinding could have been broken

Method of blinding will be regarded as unclear if there is insufficient information to assess blinding. For example, a study described as double-blind but no description of blinding is provided.

Description of patients' baseline characteristics- whether the groups were similar at the outset of the study in terms of prognostic factors:

Adequate reporting should include a detailed description of the main prognostic factors of patients at baseline per treatment group and report any unbalances between the groups.

Inadequate description of patient's baseline characteristics will include: no description or insufficient information of patient's baseline characteristics or details provided for the whole group of patients in the study rather than per treatment arms.

Intention-to-treat analysis

Very often, patients enrolled in a randomised trial do not receive the study treatment to which they were randomised or are withdrawn from the study. An intention-to-treat (ITT) analysis includes data on all trial patients and analyses them according to the intervention to which they were randomised.

While it is possible to analyse data of patients according to the intervention groups they were allocated to, it is not always possible to measure outcome data

on all the patients due to withdrawals and drop-outs. For this reason a true ITT analysis cannot be performed without making assumptions about missing outcome data.

It is common for authors to report an ITT analysis even though some outcome data are missing.

An ITT analysis will be regarded as adequate if there is a statement confirming that the analysis was based on ITT or if it is clear from the text that data from patients were analysed according to the intervention group they were randomised. As regards whether appropriate methods were used to account for missing data, we will highlight where there is a high proportion of missing outcomes or large difference between groups.

Table 1: Assessment of risk of bias of included studies

Study reference	Reporting of randomization	Reporting of allocation concealment	Reporting of blind treatment assignment/ blind outcome assessment	Description of pts. baseline characteristics/ group balance	Analysis based on ITT
AMIOVIRT	Unclear	Unclear	Adequate	Adequate	Adequate
CARE-HF	Adequate	Adequate	Adequate	Adequate	Adequate
CAT	Unclear	Adequate	Unclear	Adequate	Unclear
COMPANION	Unclear	Unclear	Adequate	Adequate	Adequate
Contak-CD	Unclear	Unclear	Unclear	Adequate	Unclear
DEFINITE	Unclear	Unclear	Adequate	Adequate	Adequate
MADIT	Unclear	Unclear	Unclear	Adequate	Adequate
MADIT-CRT	Unclear	Adequate	Adequate	Adequate	Adequate
MADIT II	Unclear	Adequate	Unclear	Adequate	Adequate
MIRACLE	Unclear	Adequate	Adequate	Adequate	Adequate
MIRACLE-ICD	Adequate	Adequate	Adequate	Adequate	Adequate
MIRACLE-ICD II	Adequate	Adequate	Adequate	Adequate	Adequate
MUSTIC	Unclear	Unclear	Inadequate	Adequate	Adequate
Piccirillo et al	Unclear	Unclear	Unclear	Adequate	Unclear
Pinter et al	Unclear	Unclear	Adequate	Adequate	Unclear
RAFT	Unclear	Adequate	Adequate	Adequate	Adequate
RESPOND	Adequate	Adequate	Unclear	Adequate	Adequate
RETHINQ	Adequate	Adequate	Adequate	Adequate	Adequate
REVERSE	Unclear	Unclear	Adequate	Adequate	Adequate
RHYTHM ICD	Unclear	Unclear	Unclear	unclear	Unclear
SCD- HeFT	Unclear	Unclear	Adequate	Adequate	Adequate
Vector	unclear	Unclear	Unclear	unclear	unclear

Appendix 4: List of secondary prevention trials

AVID

A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. The New England journal of medicine 1997;337:1576-83.

Causes of death in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. Journal of the American College of Cardiology 1999 Nov 1;34(5):1552-9.

Antiarrhythmics Versus Implantable Defibrillators (AVID)--rationale, design, and methods. American Journal of Cardiology 1995 Mar 1;75(7):470-5.

CIDS

Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-302.

Connolly SJ, Gent M, Roberts RS, Dorian P, Green MS, Klein GJ, et al. Canadian implantable defibrillator study (CIDS): Study design and organization. American Journal of Cardiology 1993;72(16):103F-8F.

MAVERIC

Lau EW, Griffith MJ, Pathmanathan RK, Ng GA, Clune MM, Cooper J, et al. The Midlands Trial of Empirical Amiodarone versus Electrophysiology-guided Interventions and Implantable Cardioverter-defibrillators (MAVERIC): a multi-centre prospective randomised clinical trial on the secondary prevention of sudden cardiac death. Europace : European pacing, arrhythmias , and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias , and cardiac cellular electrophysiology of the European Society of Cardiology 2004;6:257-66.

CASH

Siebels J, Kuck K-H. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). American Heart Journal 1994;127(4 II SUPPL.):1139-44

Siebels J, Cappato R, Ruppel R, Schneider MAE, Kuck KH, Kalmar P, et al. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). American Journal

of Cardiology 1993;72(16):109F-13F.

Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation 2000 Aug 15;102(7):748-54.

Wever et al

Wever EF, Hauer RN, van Capelle FL, Tijssen JG, Crijns HJ, Algra A, et al. Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in postinfarct sudden death survivors. Circulation 1995 Apr 15;91(8):2195-203.

Wever EFD, Ramanna H, Hauer RNW, Robles de Medina EO. Cardioverter-defibrillator implantation: Better first-choice strategy for postinfarction cardiac arrest survivors. Cardiology Review 1996;13(5):28-33.

Appendix 5: Reported adverse events

Table 2- Adverse events reported in the AMIOVERT trial (n, % unless otherwise stated)

Event	Occurrences
<i>ICD arm</i>	
Received amiodarone for the following reasons:	
Atrial fibrillation	8 (15.69)
Frequent appropriate defibrillator therapies requiring amiodarone	1 (1.96)
Other reasons	2 (3.92)
Underwent cardiac transplantation (reason not reported)	1 (1.96)
<i>OMT arm</i>	
Adverse events after initiation of therapy	
These patients had their drug discontinued because of adverse events ¹	25 (48.08)
Adverse events after 26.1 (16.9) months of entry the trial	
An ICD was inserted in 8 patients for the following reasons:	
Near- syncope	2 (3.85)
Cardiac arrest	2 (3.85)
Amiodarone intolerance	4 (7.69)
Underwent cardiac transplantation (reason not reported)	2 (3.85)

n = patients in the group reporting an adverse event 1-Full details of the particular adverse event experienced by the 25 patients were not provided.

Table 3- Adverse events reported in the CARE-HF trial (n, % unless otherwise stated)

Event	Occurrences
<i>OMT arm</i>	
Device related death	
Septicemia after receiving a device	1 (0.25)
Other adverse events	
Worsening heart failure	263 (65.10)
Atrial arrhythmias/ ectopy	41(10.15)
<i>CRT-P arm</i>	
Device related death	
Death from Heart failure aggravated by lead displacement	1 (0.24)
Most common device or procedure related adverse events	
lead displacement	24 (5.87)
coronary- sinus dissection	10 (2.44)
pocket erosion	8 (1.96)
pneumothorax	6 (1.47)
device related infection	3 (0.73)
Other adverse events	
Worsening heart failure	191(46.69)
Atrial arrhythmias/ ectopy	64 (15.65)

NB: The frequency of respiratory tract infections, hypotension, falls or syncope, acute coronary syndromes, renal dysfunction, ventricular arrhythmias or ectopy, and neurologic events were similar in the two groups (OMT vs. CRT-P).

Table 4- Adverse events reported in the CAT trial (n, % unless otherwise stated)

Event	Occurrences
<i>ICD arm</i>	
Complications within 30 days of device implantation	
Device dislocation	1
Bleeding	1
Electrode dislocation revised by surgery	2
Complications during long term follow up (24 months)	
10 complications occurred in 7 (14%) patients	
Electrode dislocation & sensing isolation	7
Infections	2
Perforation	1
<i>OMT arm</i>	
Complications were only reported for the ICD arm	

Table 5- Adverse events reported in the COMPANION trial (n, % unless otherwise stated)

Event	Occurrences
<i>CRT-D arm</i>	
Moderate or severe adverse event related to the implantation procedure	
Moderate or severe adverse events related to the implantation procedure occurred in 8 % of patients including the following	
Coronary venous dissection	0.5%
Coronary venous perforation	0.8%
Coronary venous tamponade	0.3%
<i>CRT-P arm</i>	
Moderate or severe adverse event related to the implantation procedure	
Moderate or severe adverse event related to the implantation procedure occurred in 10% of patients including the following:	
Coronary venous dissection	0.3%
Coronary venous perforation	1.10%
Coronary venous tamponade	0.5%
<i>OMT arm</i>	
Details of individual adverse events were not reported. However, the author reported that a total of 61% of the patients in this arm experienced moderate to severe adverse event from any cause.	

NB: in the CRT-D arm a total of 69% patients experienced moderate to severe adverse events from any cause.

However, full details of these were not provided. In the CRT-P arm a total of 66% of patients experienced moderate or severe adverse event from any cause. However, full details were again not provided.

Table 6- Adverse events reported in the CONTAK-CD trial (n/N)

Event	Occurrences
Adverse events during implantation	
Placement of coronary venous lead failure	66/567 ¹
Other adverse event (within the 30-day post-implant recovery period)	
Death due to pump failure	5/501 ²
Death due to pulseless electrical activity resulting from defibrillation threshold	1/501 ²
Death due to incessant ventricular tachycardia	1/501 ²
Death due to cardiac cause	1/501 ²
Death from unknown cause	1/501 ²

1- total number patients with an implant attempt. 2- successfully implanted patients. n = number of patients in the arm reporting an adverse event

Table 7- Adverse events reported in the DEFINITE trial (n, % unless otherwise stated)

Event	Occurrences
<i>ICD arm</i>	
Complications during the implantation of the ICD 3 (1.3%)	
Haemothorax	1 (0.43%)
Pneumothorax	1 (0.43%)
Cardiac tamponade	1 (0.43%)
Complications during the long term follow up phase 10 (4.4%)	
Lead dislodgement or fractures	6 (2.62%)
Venous thrombosis	3 (1.31%)
Infection	1 (0.43%)
ICD upgrades	13 (5.68%)
Development of Sinus-node dysfunction requiring dual chamber ICDs	2 (0.87%)
NYHA class III/IV heart failure and prolonged QRS Interval requiring biventricular device	11 (4.80%)
<i>OMT arm</i>	
Received ICDs due to syncope or heart failure and prolong QRS interval	23 (10.04)

Table 8- Adverse events reported in the MADIT trial (n, % unless otherwise stated)

Event	Occurrences
<i>ICD arm</i>	
The total number of patients with adverse events was 19 (20%)	
Syncope	1 (1.05%)
Sinus bradycardia	3 (3.16%)
Pulmonary embolism	1 (1.05%)
Atrial fibrillation	4 (4.21%)
Pneumothorax	2 (2.10%)
Bleeding	1 (1.05%)
Venous thrombosis	1 (1.05%)
Surgical infection	2 (2.10%)
Problems with defibrillator lead	7(7.37%)
Malfunction of defibrillator generator	3 (3.16%)
<i>OMT arm</i>	
The total number of patients with adverse events was 12 (12%)	
Hypotension	1 (0.99%)
Syncope	5 (4.95%)
Hypothyroidism	1 (0.99%)
Sinus bradycardia	3 (2.97%)
Pulmonary fibrosis	3 (2.97%)
Pulmonary embolism	1 (0.99%)
Malfunction of defibrillator generator	2 (1.98%)

Table 9- Adverse events reported in the MADIT II trial (n, % unless otherwise stated)

Event	Occurrences
<i>ICD arm</i>	
Device related adverse events	
Lead related problems requiring surgical intervention	13 (1.8 %)
Non-fatal infection requiring surgical intervention	5 (0.7 %)
Non-Device related adverse events	
Worsening heart failure requiring Hospitalization	148 (19.9%)
<i>OMT arm</i>	
Worsening heart failure requiring Hospitalization	73 (14.90%)

Table 10- Adverse events reported in the MADIT-CRT trial (n, % unless otherwise stated)

Event	Occurrences
<i>CRT-D arm</i>	
The total number of patients with adverse events was 19 (20%)	
Adverse event during hospitalisation after device implantation	
Death due to pulmonary embolus documented on autopsy	0.09%
Adverse event within 30 days of device implantation	
Pneumothorax	1.7%
Infection	1.1%
Pocket hematoma requiring evacuation	3.3%
Left ventricular coronary-vein reposition	4%
Adverse event during CRT-D implantation	
Coronary venous dissection with pericardial effusion	0.5%
<i>ICD arm</i>	
Adverse event within 30 days of device implantation	
Pneumothorax	0.8%
Infection	0.7%
Pocket hematoma requiring evacuation	2.50%

NB: during long term follow up after first 30 days in the CRT-D arm, serious device related adverse events occurred with a frequency of 4.5 per 100 device months and in the ICD arm serious device related adverse events occurred with a frequency of 5.2 per 100 device months

Table 11- Adverse events reported in the MIRACLE trial (n, % unless otherwise stated)

Event	Occurrences
<i>CRT-P arm</i>	
Adverse event during Implantation procedure	
Complete heart block requiring permanent cardiac pacing	2 (0.35)
Progressive hypotension	1 (0.18)
Asystole needing cardiopulmonary resuscitation	1 (0.18)
Coronary sinus dissection	23 (4.03)
Coronary vein or coronary sinus perforation	12 (2.10)
Adverse event after implantation	
Left ventricular lead reposition	20 (3.79)
Left ventricular lead replacement	10 (1.89)
Pacemaker related infection requiring explanation	7 (1.33)

NB: There was no significant difference in the frequency of adverse event unrelated to the device or heart failure between the two treatment groups

Table 12- Adverse events reported in the MIRACLE-ICD trial (n, % unless otherwise stated)

Event	Occurrences
<i>CRT-D arm</i>	
From implant to hospital discharge	
Left ventricular lead related	37 (23%)
Coronary sinus dissection	15 (9.4%)
Cardiac perforations	4 (2.5%)
Heart failure decompensation	6 (3.8%)
Heart block	3 (1.9%)
Muscle stimulation	4 (2.5%)
Pericardial effusion	2 (1.3%)
Pericarditis	1 (0.6%)
Ventricular tachycardia/ventricular fibrillation	5 (3.1%)
Haemothorax/pneumothorax	3 (1.9%)
Elevated pacing/loss of capture	7 (4.4%)
Post discharge in non-randomised CRT systems implanted (n=10)	
Left ventricular lead related	3 (10.7%)
ICD systems related	0
Procedure related	3 (10.7%)
Heart failure decompensation	7 (25.0%)
Other	15 (53.6%)
Post-discharge in non-randomised unsuccessful CRT systems implant patients (n=50)	
Procedure related	1 (2.9%)
Heart failure decompensation	19 (54.3%)
Other	15 (42.9%)
Post-discharge in randomised CRT-ON patients (n=187)	
Left ventricular lead related	21 (11.4%)
ICD systems related	9 (4.9%)
Procedure related	10 (5.4%)
Heart failure decompensation	63 (34.2%)
Other	81 (44.0%)
<i>ICD arm (CRT-OFF)</i>	
Post-discharge in randomized/ successfully implanted patients (n=182)	
Left ventricular lead related	14 (7.5%)
ICD systems related	14 (7.5%)
Procedure related	13 (7.0%)
Heart failure decompensation	71 (38.2%)
Other	74 (39.8%)

Table 13- Adverse events reported in the MADIT-ICD-II trial (n, % unless otherwise stated)

Event	Occurrences
<i>CRT-D arm</i>	
Among the 210 patients undergoing a CRT-D implant attempt, 46 (22%) patients experienced a total of 56 complications from the time of implant to hospital discharge <i>which include the following</i>	
Complications during implant attempt	
Left ventricular lead related	19 (34%)
Coronary sinus dissections	3 (5.3%)
Cardiac perforations	3 (5.35%)
Lead dislodgement	5 (8.9%)
23 patients failed their initial attempt; 4 eventually receiving a CRT-D system	
Complications from hospital discharge to end of randomization period	
66 (35%) of 191 patients with successful CRT-D implant, experienced 109 complications which include the following:	
Left ventricular lead related	19(17%)
Lead dislodgements	11(10.09%)
Cardiac perforations	1 (0.92%)
Diaphragmatic muscle stimulation	3 (2.75%)
Elevated pacing thresholds	4 (3.67%)

Table 14- Adverse events reported in the MUSTIC trial (n, % unless otherwise stated)

Event	Occurrences
Uncorrectable loss of left ventricular pacing efficacy and did not complete the two crossover periods.	2
Inactive pacing	
Severe decompensation leading to a premature switch to active pacing	1
Decompensation due to atrial fibrillation	1
Active pacing	
Sudden death	1
Decompensation due to rapidly progressive aortic stenosis	1
Death from acute myocardial infarction a few hours after a premature switch to active pacing because of severe decompensation	1
Sudden death after switching from inactive to active	1

Table 15- Adverse events reported in Picorillo et al. (n, % unless otherwise stated)

Event	Occurrences
Major complications following implantation	0
Of the 15 patients randomised to the ICD group 2 (13.3%) were hospitalised due to worsening of heart failure	

Table 16- Adverse events reported in Pinter et al. (n, % unless otherwise stated)

Event	Occurrences
Of the 90 attempted implants, 75 (83.3%) were successful	
Acute procedural related complications included:	
Haematoma	1(1.11%)
Right ventricular lead failure requiring replacement	1(1.11%)
Device related complications in successfully implanted patients	
Of the 75 successful implants, 2 patients (2.6%) were not randomised due to device-related technical difficulties (double sensing)	
<i>CRT-ON</i>	
late Left ventricular capture failure	1(2.78%)
death due to cardiac cause	1(2.78%)
<i>CRT-OFF</i>	
Worsening congestive heart failure	1(2.78%)
Death from cardiac cause	1(2.78%)

Table 17- Adverse events reported in the RAFT trial (n, % unless otherwise stated)

Event	Occurrences
<i>CRT-D arm</i>	
Of the 894 patients in the CRT-D group, 888 (99.3%) underwent device implantation. Reasons for non-implantation included 4 cases in which the patient died and 2 cases in which the patient or physician declined to participate.	
Device or implantation related complications (first 30 days)	
There were 118 device or implantation related complications among 888 patients receiving CRT-D, including:	
Device pocket haematoma requiring intervention	14 (1.6%)
Haemothorax/pneumothorax	11 (1.2%)
Device pocket infection requiring intervention	21 (2.4%)
Lead dislodgement requiring intervention	61 (6.9%)
Device pocket problems requiring revision	4 (0.5%)
Coronary sinus dissection	11 (1.2%)
<i>ICD arm</i>	
Of the 904 patients in the ICD group, 899 (99.4%) underwent device implantation. Reasons for non-implantation included 4 cases in which the patient or physician declined to participate and 1 case in which there was a lack of venous access.	
Adverse event within 24hours after device implantation	
Death from worsening heart failure	8 (0.9%)
Device or implantation related complications (first 30 days)	
There were 61 device or implantation related complications among 899 patients in the ICD arm. These included:	
Haemothorax/pneumothorax	8 (0.9%)
Device pocket haematoma requiring intervention	11 (1.2%)
Device pocket infection requiring intervention	16 (1.8%)
Lead dislodgement requiring intervention	20 (2.2%)
Device pocket problems requiring revision	1 (0.1%)

Table 18- Adverse events reported in the RESPOND trial. (n, % unless otherwise stated)

Event	Occurrences
Adverse events not reported	

Table 19- Adverse events reported in the RETHINQ trial (n, % unless otherwise stated)

Event	Occurrences
<i>Implant attempt patients</i>	
Deep vein thrombosis	3 (1.70)
Pneumothorax	2 (1.20)
Pericarditis	2 (1.20)
Coronary sinus perforation	1 (0.60)
Lead dislodgement	13(7.60)
Infection	6 (3.50)
bleeding/ haematoma	2 (1.20)
loss of pacemaker lead capture	2 (1.20)
Phrenic-nerve stimulation	3 (1.70)
----- <i>CRT arm</i>	
There were 24 heart-failure events requiring intravenous therapy in 14 patients (16.1%)	
----- <i>ICD arm</i>	
There were 41 heart failure events requiring intravenous therapy in 19 patients (22.3%)	

Table 20- Adverse events reported in the REVERSE trial (n, % unless otherwise stated)

Event	Occurrences
During or just before implantation	
There were 26 procedure or system-related complications among the 642 patients who underwent an implant attempt:	
Adverse drug reaction	4(15.38)
Pneumothorax	4(15.38)
Atrial fibrillation or flutter	4(15.38)
Coronary sinus dissection	3(11.54)
Pulmonary Oedema	2(7.69)
Ventricular Fibrillation	2(7.69)
Complete heart block	2(7.69)
Cardiac Tamponade	1(3.85)
Pericardial effusion	1(3.85)
Electromechanical dissociation	1(3.85)
Hypotension	1(3.85)
Increased defibrillation threshold	1(3.85)
Procedure or system related adverse event after implantation	
After implantation and during the 12-month follow-up, 101 of the 621 successfully implanted patients experienced a total of 138 procedure or system-related complications (postoperative procedure or system-related complication rate was 16%). Of these the most common postimplant complications were:	
Left ventricular lead dislodgement	41(29.71)
Right ventricular lead dislodgement	15(10.87)
Right atrial lead dislodgement	10(7.25)
Diaphragmatic muscle stimulation	14(10.14)
Atrial fibrillation or flutter	8(5.80)
Implant site haematoma	5(3.62)
Hypotension	4(2.90)
Pericardial effusion	4(2.90)
System related adverse event during 12 months of follow up	
Among the 621 successfully implanted patients during the first 12 months there was one CRT therapy-related complication in which cardiac failure was resolved by turning CRT off.	
There were 66 left ventricular lead complications among 59 patients (left ventricular lead related complications rate was 10%) which required reoperation in 48 patients (8% of successfully implanted patients). The most common events in the 66 left ventricular lead related complications were:	
Left ventricular lead dislodgement	41(62.12)
Diaphragmatic muscle stimulation	14(21.21)
Subclavian vein thrombosis	3(4.55)

Table 21- Adverse events reported in the RHYTHM-ICD trial (n, % unless otherwise stated)

Event	Occurrences
A total of 97 adverse events were reported in 70 patients, of which 29 were complications and 68 were observations	
Complications¹	
Coronary sinus perforation/dissection	2
Diaphragmatic/Phrenic nerve stimulation	3
Lead dislodgement or migration	9
Bleeding/hematoma	6
Blood clot/thrombosis	1
High defibrillation/cardioversion requirements	2
Infection	1
Noise on EGM post shock (non-SJM RV lead)	1
Pneumothorax	2
Retained foreign body (surgical sponge)	1
Elevated pacing threshold- LV lead	1
Observations²	
Asystolic episode during LV lead placement	1
Bleeding/haematoma	10
Blood clot/thrombosis	2
Coronary sinus perforation/dissection	6
Diaphragmatic/phrenic nerve stimulation-LV lead	10
Diaphragmatic/phrenic nerve stimulation-RV lead	2
Heart block at implant	2
High defibrillation/cardioversion requirements	1
Hypotension requiring ventilator support	1
Inappropriate therapy for SVT	10
Infection	3
Possible pulmonary embolism	1
T-Wave sensing	2
Pocket inflammation/seroma	1

1- defined as adverse events that require invasive intervention; 2- defined as adverse events that can be managed without invasive intervention

Table 22- Adverse events reported in the SCD-HeFT trial (n, % unless otherwise stated)

Event	Occurrences
<i>ICD arm</i>	
Clinically significant complications ¹ at the time of implantation	41 (5)
Clinically significant post-operative complications ¹	75 (9)
<i>Amiodarone and placebo arms</i>	
The only complications observed in the amiodarone group, as compared with the placebo group were increased tremor (4%) and increased hypothyroidism (6%)	

1- Clinical events requiring surgical correction, hospitalisation or new and otherwise unanticipated drug therapy.

Appendix 6: Multiple imputation approach (All-cause mortality)

Multiple imputations were created to impute values for the following variables (numbers in brackets denote number of instances in which values were missing): age (1); gender (1); NYHA (1); QRS (1); LVEF (1); Ischemia (1) and LBBB (229).

The imputation was carried out in the Amelia package¹. Five imputed data sets were created. The approach used assumes that the complete (unobserved) data set has a multivariate normal distribution and that data are missing at random. Draws from the estimated complete data multivariate normal distribution are made using a combination of an expectation-maximisation algorithm and bootstrapping.

A description of the variables included in the imputation process is provided as Table 23.

Table 23: Variables included in imputation process

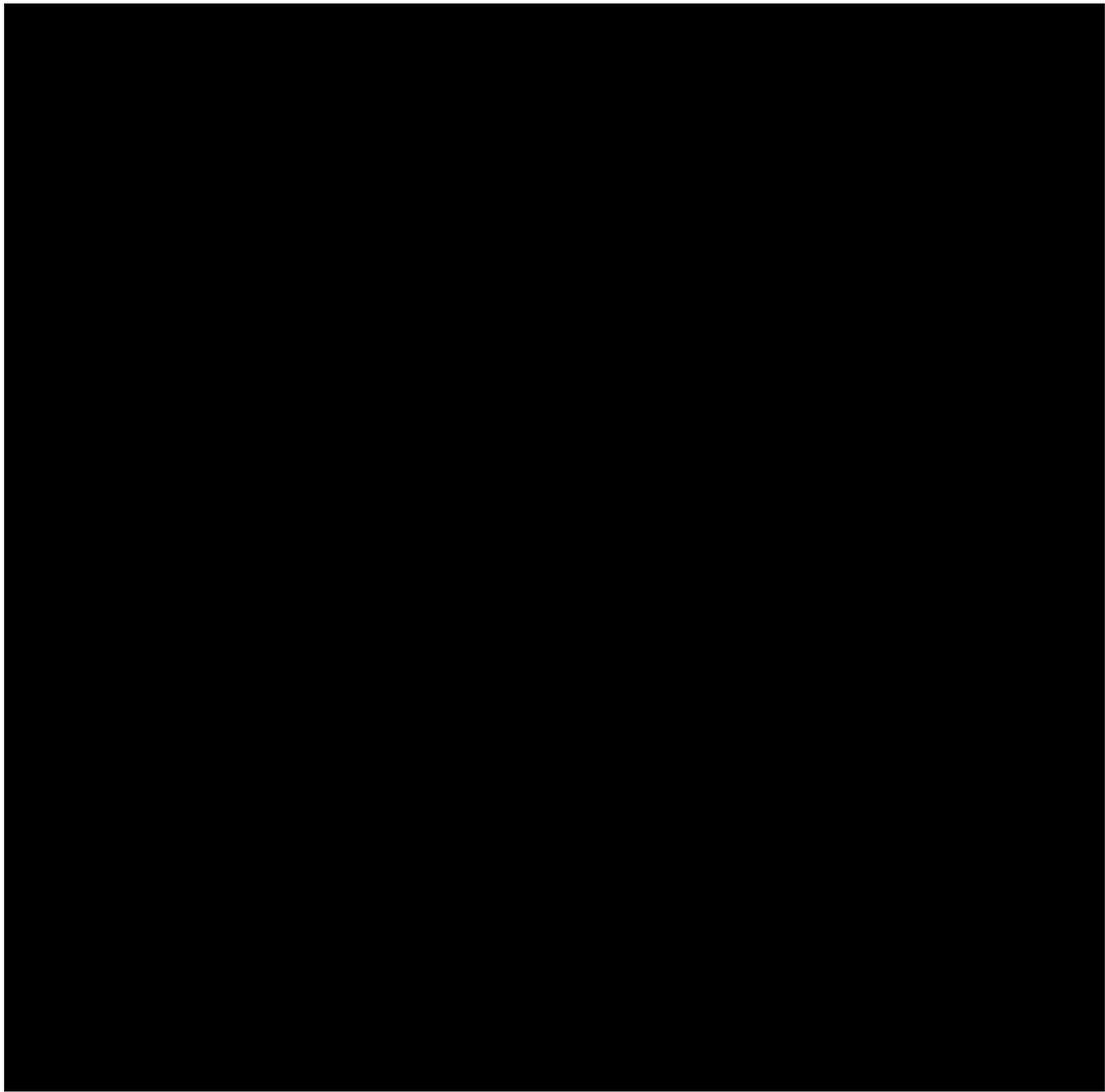
Variables included in analysis and imputation	Variables included in imputation only ^a	Variables included in analysis only
Time to death or loss to follow-up	Randomisation date	Device type – conditional upon study this should not be related to outcomes due to randomisation
Whether death or loss to follow-up	Weight	
Gender	Height	Study – the model did not converge when STUDY dummy variables were included, presumably due to the collinearity of the 'study' and other independent variables.
Age	History of MI	
NYHA	History of diabetes	
QRS	History of stroke	
LVEF	Systolic blood pressure	
Ischemia	6 minute hall walk	
LBBB	Receiving diuretics at baseline	
US	Receiving ACEI/ARB at baseline	
	Receiving beta-blockers at baseline	
	Receiving statins at baseline	
	RBBB	
	Prior ICD	

a) the following variables were collected in the data shell but not included in the imputations algorithm

¹ <http://cran.r-project.org/web/packages/Amelia/vignettes/amelia.pdf>

(with reasons): Patient ID (not predictive); Date of implant (highly correlated with date of randomisation); Diuretic name and dose/cause of death/creatinine (data not clean); Diastolic Blood Pressure (highly correlated with systolic blood pressure); Prior CRT (no patients were recorded to have had a prior CRT); History of spontaneous VT or VF/History of spontaneous, sustained VT/History of VF (data not thought to be consistently recorded across studies); Cross-over (would have to be treated as survival variable in which case too highly correlated with follow-up); Date of heart failure diagnosis/history of atrial tachycardia/receiving allopurinol at baseline/cholesterol/haemoglobin/lymphocytes/uric acid/date of last hospitalisation/brain natriuretic peptide/history of atrioventricular node ablation/history of ventricular flutter/history of atrial fibrillation/history of atrial flutter/sodium (all had very high levels of missingness [REDACTED] and were therefore excluded).

The graphs below display the predicted and observed values for QRS and LVEF, the only continuous covariables with a substantive number of missing values. The black lines depict the distribution of observed values. The red lines depict the distribution of imputed values. The graphs suggest that the imputation algorithm is imputing reasonable values for these variables.



Appendix 7: Explanation for absence of covariate adjusted random effects analysis (All-cause mortality)

Two alternative approaches to running the network meta-analysis were considered:

1. Stratified Cox proportional hazards model using all IPD (approach followed)
2. Two-stage approach (alternative approach considered) – this would have involved fitting individual Cox proportional hazards regressions to each trial. These could then have been used to generate trial specific hazard ratios for each covariable pattern (patient profile). These hazard ratios could then have been synthesised using a standard network meta-analysis approach for aggregate data.

Theoretically both approaches could be run as random effects analyses. However, for approach (1) this is not thought to be possible using standard frequentist software (e.g. R, SAS). It would be possible to run this analysis as a random effects model using Bayesian software (e.g. WinBUGS) however this would be computationally expensive. The exact run time is not predictable but would be expected to run to days or weeks for a database of this size. A previous analysis recorded run times of 41 seconds for 1,000 iterations on a database of 42 patients with 17 distinct event times (<http://www.mrc-bsu.cam.ac.uk/bugs/documentation/exampVol1/node29.htm>) whereas our database includes over 12,638 patients and 1,700 distinct event times). In addition, the benchmark analysis was not stratified.

Despite the potential to run a random effects version of option (2) easily, a number of problems with this approach were identified. The requirement to run separate regressions for each trial would have greatly reduced the power of the analysis to detect treatment effect modifiers. In addition, where treatment effect modifiers differed across analyses of different trials, difficult judgement calls regarding the final covariable set would have been required. The approach would also involve fitting a large number of parameters to the data set, reducing precision. Finally, this approach would not have generated a single estimate of

treatment effect modification, making the resulting models difficult to clinically validate. We concluded the advantage of approach (1) were sufficient to offset the disadvantage of not having a random effect version of the model.

Appendix 8 – Further detail regarding covariable-adjusted IPD network meta-analysis model

Equations (1) and (2) describe the difference between the model fitted without and with covariables as treatment effect modifiers.

- Equation 1 – unadjusted. This model is the stratified Cox PH model unadjusted for treatment effect modifiers. This model contains only dummy variables for each of the devices (CRT-P, CRT-D and ICD) and takes the following form:
 - $\lambda_{ij} = \lambda_{oj}(t)\exp(\beta_{CRT-P}D_{CRT-P\ ij} + \beta_{CRT-D}D_{CRT-D\ ij} + \beta_{ICD}D_{ICD\ ij})$
 - Where λ_{ij} is the hazard for the *ith* patient in the *jth* trial, the β 's are the treatment coefficients expressing the efficacy of the devices relative to optimal pharmacological therapy (OPT) and the *D*'s are the device specific dummy variables which take the value 1 if patient *i* in trial *j* was randomised to that device.
- Equation 2 – adjusted. This model is the stratified Cox PH model adjusted for treatment effect modifiers. This model contains dummy variables for each of the devices (CRT-P, CRT-D and ICD), covariable main effects and device by covariable interactions and takes the following form (assuming one covariable, though the formula is easily generalised to multiple covariables):
 - $\lambda_{ij} = \lambda_{oj}(t)\exp(\beta_{cov}X_{covij} + \beta_{CRT-P}D_{CRT-P\ ij} + \beta_{CRT-D}D_{CRT-D\ ij} + \beta_{ICD}D_{ICD\ ij} + \beta_{inter.CRT-P}D_{CRT-P\ ij}X_{covij} + \beta_{inter.CRT-D}D_{CRT-D\ ij}X_{covij} + \beta_{inter.ICD}D_{ICD\ ij}X_{covij})$
 - Where X_{covij} and β_{cov} are the covariable and coefficient on the covariable respectively and $\beta_{inter.DEV}$ is the coefficient on the device by covariable interaction.

Selection of covariables for inclusion in the final preferred model was based on the following exploratory analyses:

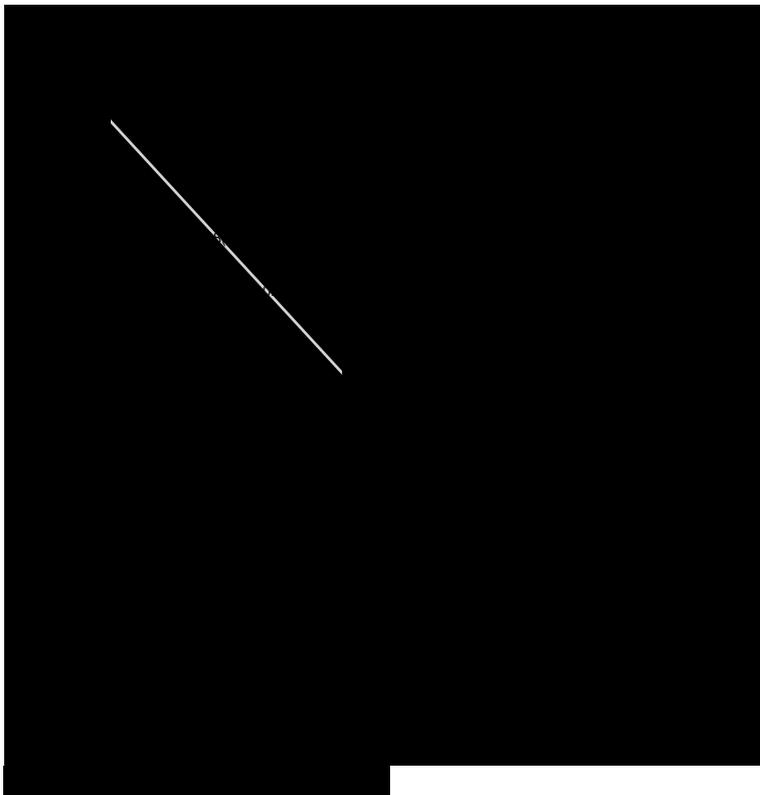
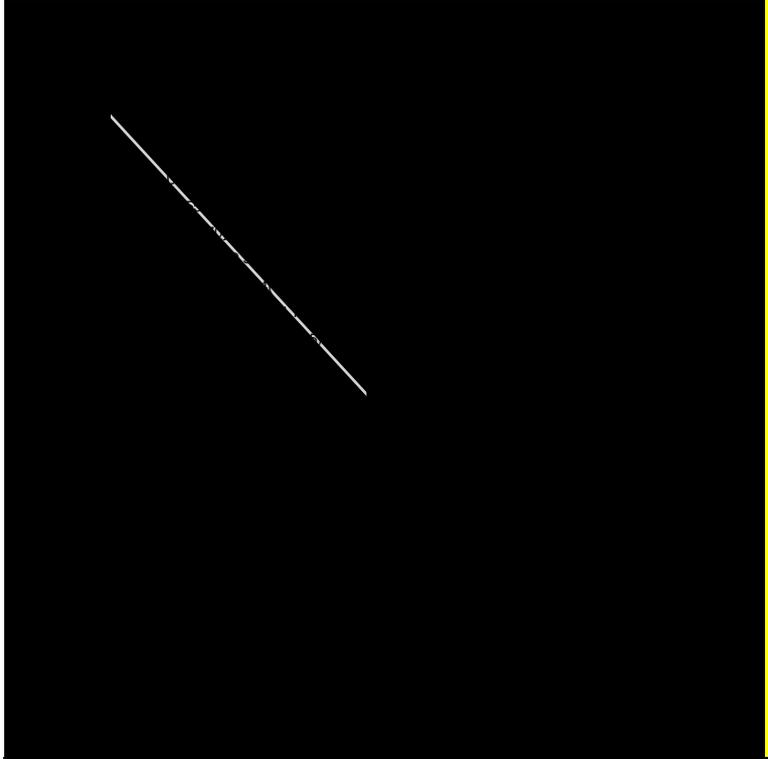
1. A review of univariate analyses - This involved including each covariable individually as a treatment effect modifier for all devices and reviewing

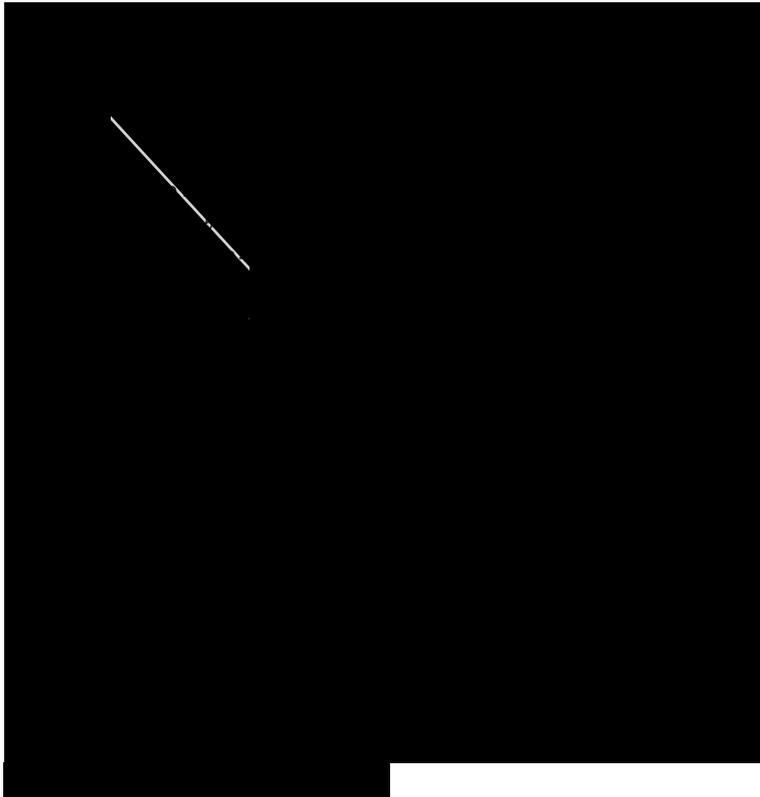
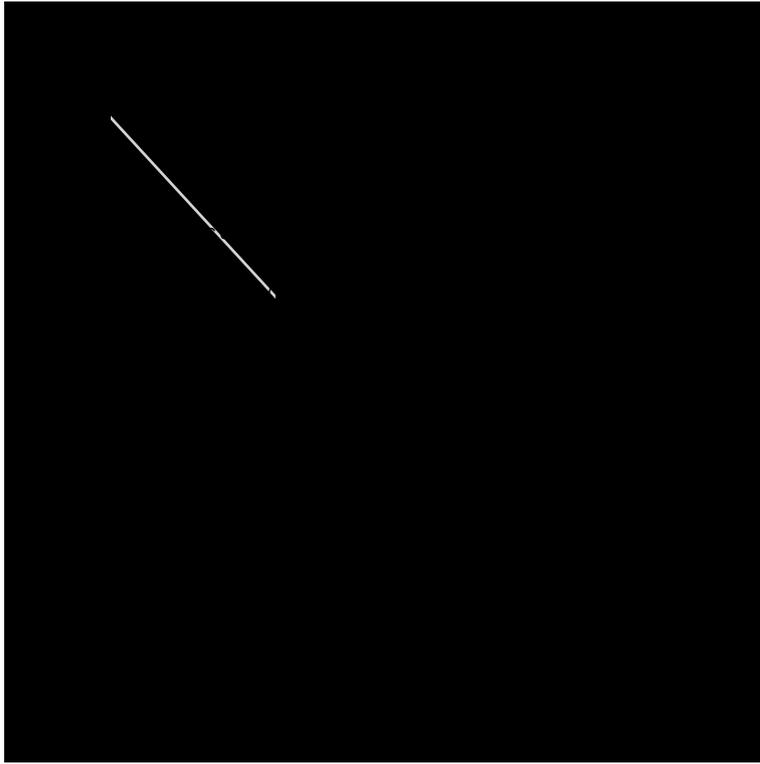
the results for statistical significance and clinically meaningful trends.

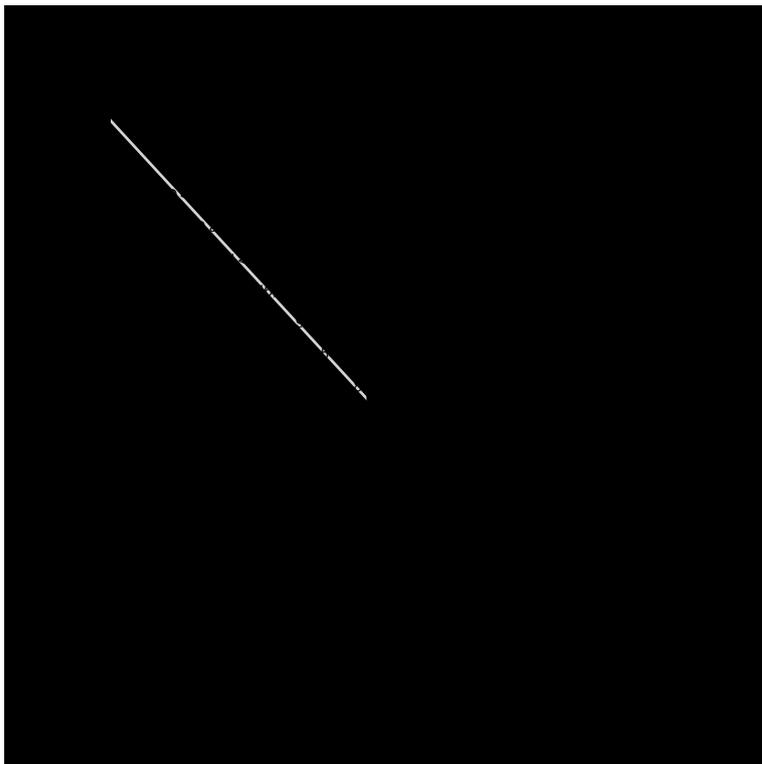
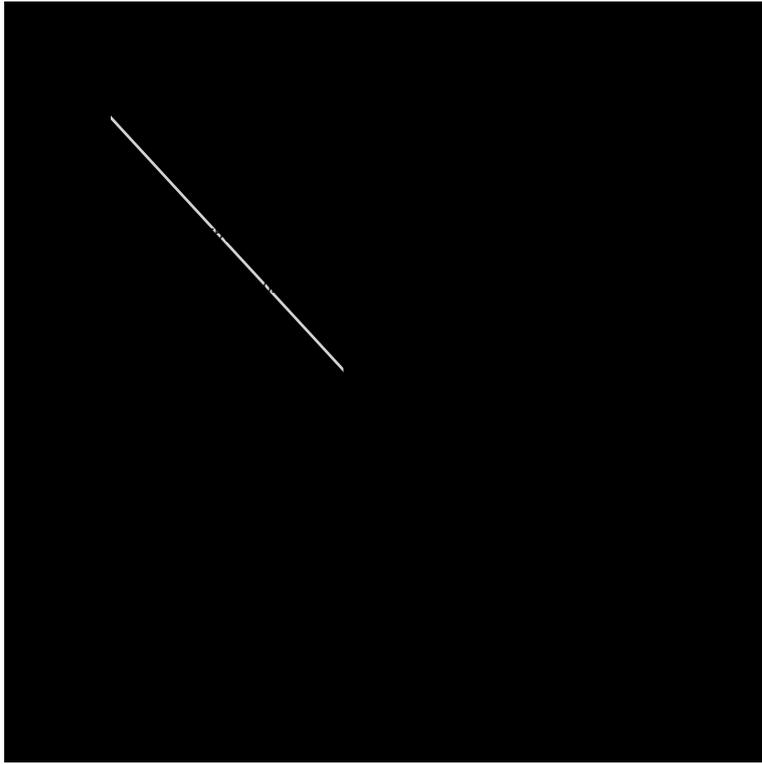
2. Multivariate analyses - a stepwise algorithm was used to select covariables for retention. A forward and backward selection algorithm based on Akaike's Information Criterion (AIC) with 2 degrees of freedom for the penalty was used. The stepwise procedure was run in two ways: once with treatment effect modifiers forced for all device treatment effects or none. The second analysis was more flexible and allowed the treatment effect modifiers to vary by device. This approach was thought to be clinically plausible as the devices act on different causes of mortality. The model was set up so that device by covariable interaction effects could only be included if the main covariable effects were included. The treatment main effects were forced in all models.
3. Clinical knowledge – These intermediary analyses were reviewed by two clinicians in order to assess their plausibility.

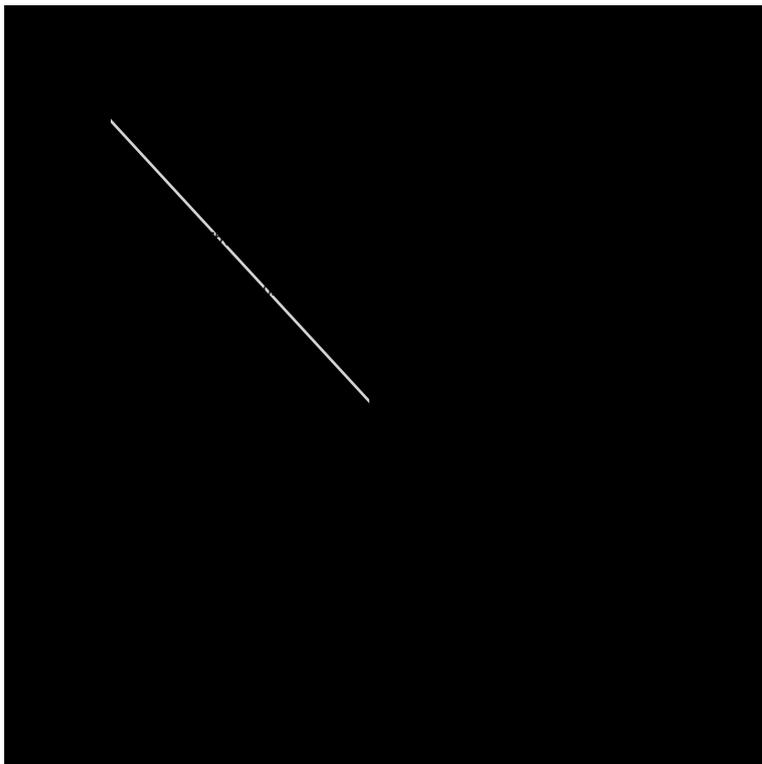
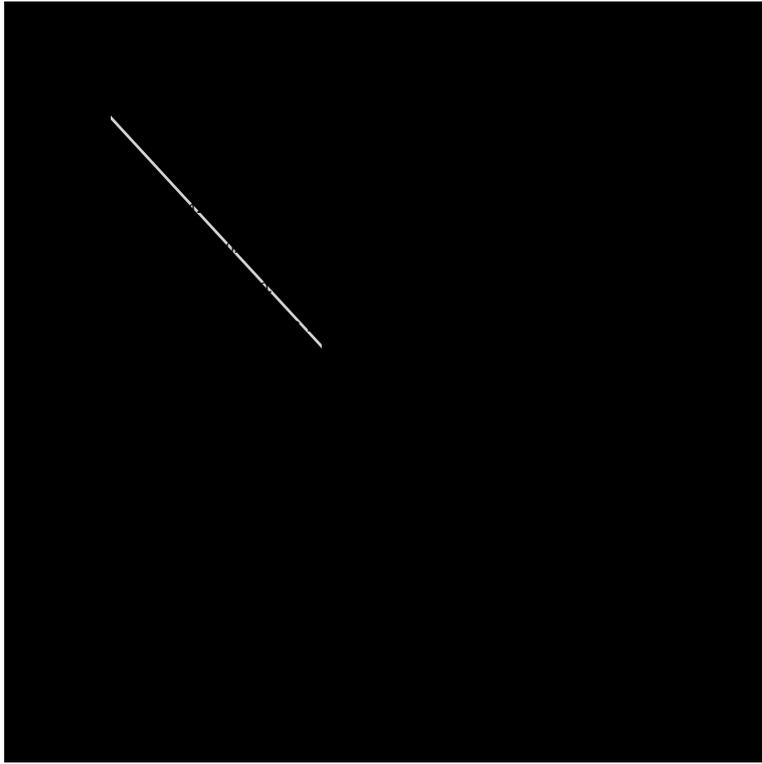
Appendix 9 – Graphical presentation of univariate exploratory analyses (All-cause mortality)

Note: p-values rounded to three decimal places.









**Appendix 10 – Parameters used in sensitivity analysis
examining inclusion of NYHA 4 as a treatment
effect modifier (all-cause mortality)**

Variable ^a	Hazard ratio	P-value
ICD	■	■
CRT-P	■	■
CRT-D	■	■
QRS<120	■	■
QRS>=120	■	■
LBBB	■	■
AGE>=60	■	■
GENDER=M	■	■
NYHA4	■	■
ICD*QRS<120	■	■
ICD*QRS>=120	■	■
ICD*LBBB	■	■
ICD*GENDER=M	■	■
ICD*AGE>=60	■	■
ICD*NYHA4	■	■
CRTP*QRS>=120	■	■
CRTP*LBBB	■	■
CRTP*GENDER=M	■	■
CRTP*AGE>=60	■	■
CRTP*NYHA4	■	■
CRTD*QRS>=120	■	■
CRTD*LBBB	■	■
CRTD*GENDER=M	■	■
CRTD*AGE>=60	■	■
CRTD*NYHA4	■	■

Appendix 11: LOS approach to modelling all-cause hospitalisation

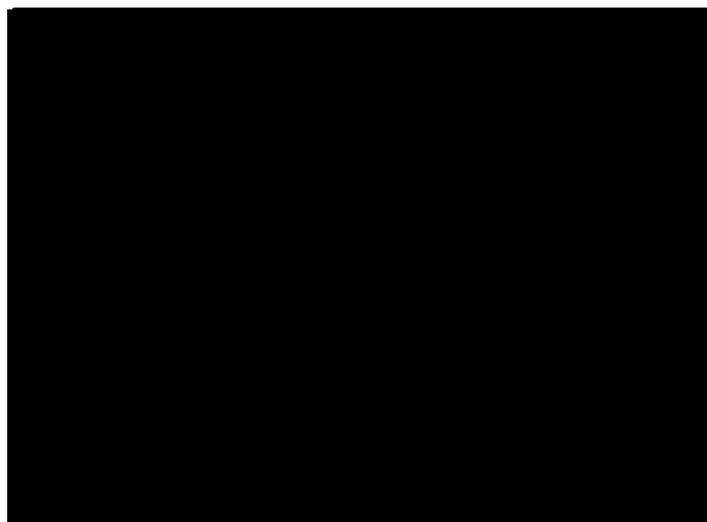
Estimation of baseline rate

A similar process to that described in section 4.3 for expected number of events was performed, with the negative binomial model again selected. The same variables were considered as predictors. The final model was again selected using a stepwise approach ($P=0.05$), and the covariates are presented in Table 24. The plot of observed compared to predicted proportions is presented in Figure 1.

Table 24: NBRM used to predict baseline monthly length of stay (days, OPT)

Covariable	B Coefficient	Std. error	Z score	e^{β}
NYHA = III	████	████	████	████
NYHA=IV	████	████	████	████
Non-North American region	████	████	████	████
Age	████	████	████	████
Constant	████	████	████	████

Figure 1: Comparison of observed vs. fitted baseline length of stay (days, OPT)



The derived monthly values for individuals who are NYHA I/II, III or IV are █████ days, respectively. Since the analyses are to be used in a UK clinical context, the non-North American binary variable was set to 1 in all

calculations. The starting age was again assumed to be 66.

The predicted days per month hospitalised for all NYHA classes are small, and so careful consideration as to the appropriateness of these results is required. On the basis of information in the latest NHS schedule of reference costs, the mean length of stay is 3.03 days for all elective procedures and 5.65 days for all non-elective procedures. Restricting the calculation to cardiovascular related procedures, the two values are 2.96 and 4.67 days respectively. Within this category further restriction to heart failure related hospitalisation (currency code EB03) yields weighted average LOS estimates of 6.28 and 7.56 days respectively. Thus, regardless of which category is used, average hospital stays for procedures are short. For the purposes of the current analysis we have used the data for all cardiovascular related admissions in our costing protocols.

Given the low probabilities of being hospitalised in any given month and the expected length of stay for an event, the expected number of days in hospital per month will be very low. The derived values are therefore in line with what would be expected in routine practice.

Estimation of treatment effect on hospital stay

The process for estimating the impact of treatment on the number of days per month spent in hospital was identical to that described for the number of events per month. The preferred model was again the NBRM and the final covariates used, again after removal of all redundant parameters, are presented in Table 25. The comments relating to the modelling of number of events per month are equally relevant here and will not be repeated. In particular, the assumptions made relating to the use of alternative values are assumed to hold for length of stay. Interactions between ischaemic aetiology and treatment option were again included as potential covariates. The derived treatment effects are presented in Table 26

Table 25: Negative binomial model used to predict the impact of treatment on days per month hospitalised

Covariable	β Coefficient	Std. error	Z score	e^{β}
Device = ICD	████	████	████	████
Device = CRT-D	████	████	████	████
Device = CRT-D and ischaemic	████	████	████	████
Device = CRT-P and ischaemic	████	████	████	████
Device = CRT-P and NYHA = IV	████	████	████	████

Table 26: Treatment effects on all cause hospitalisation (days per month)

	NYHA I/II	NYHA III	NYHA IV
<i>Non-ischaemic aetiology</i>			
ICD	████	████	████████████
CRT-P	████████████	████	████
CRT-D	████	████	████
<i>Ischaemicaetiology</i>			
ICD	████	████	████████████
CRT-P	████████████	████	████
CRT-D	████	████	████

* IPD analysis counter-intuitive since both treatment options involve common element (CRT). Hence CRT-D value used for both options.

The final values used in the model for this sensitivity analysis are presented in Table 27 to Table 29.

Table 27: All-cause hospitalisation (ICD, days per month)

	NYHA I/II	NYHA III	NYHA IV
Ischaemic aetiology	████	████	N/A
Non-ischaemic aetiology	████	████	N/A

Table 28: All-cause hospitalisation (CRT-P, days per month)

	NYHA I/II	NYHA III	NYHA IV
Ischaemic aetiology	N/A	■	■
Non-ischaemic aetiology	N/A	■	■

Table 29: All-cause hospitalisation (CRT-D, days per month)

	NYHA I/II	NYHA III	NYHA IV
Ischaemic aetiology	■	■	■
Non-ischaemic aetiology	■	■	■

Appendix 12: Justification for method used to model HRQoL

In addition to Poisson and negative binomial models, zero inflated versions of the two models were also considered, given the very high proportion of patients reporting a value 1 (and hence a change from unity of 0%). Overall, the Zero Inflated Negative Binomial (ZINB) model was the option that best fitted the data on the basis of formal statistical tests (BIC, AIC, Vuong) and assessment of goodness of fit.

The clinical parameters assessed for potential impact on baseline utility were NYHA class, LVEF, ischaemic aetiology, QRS duration and gender. Additional variables considered were geographical location (US, non-US) and baseline age. At the time of analysis stepwise variable selection was not available in combination with ZINB, and so model selection was made via a series of likelihood ratio tests. LVEF was the only variable removed from the full model.

However, close inspection of the final model, in particular the “always zero” component, raised considerable concern. Across the whole data set there were only █ patients with NYHA IV, and only four of these reported a utility score of 1 (i.e. a decrement of zero). Hence, the ZINB model was extremely unstable and appeared not to have converged despite running for 5,000 iterations. The lack of convergence would have meant that a probabilistic sensitivity analysis would not have been possible, as a Cholesky decomposition matrix could not be constructed. The derived results from the model were also counter-intuitive in that patients with a very wide QRS were predicted to have a better HRQoL than patients who had a narrower QRS. Overall, despite being technically the most appropriate model, the ZINB model was not used in the final analysis, and instead the second best fit – a negative binomial model – was used.

APPENDIX 13: Cost-effectiveness frontiers for all patient groups

In order to provide the committee with the greatest amount of information, we have produced and presented the information in Table 11 and Table 12 (main report section 6.1) as cost-effectiveness frontiers. For convenience, these are grouped by LBBB status and NYHA class. Note that all discussion in relation to the patient count in each group is also applicable to the interpretation of these plots.

No LBBB, NYHA I

Figure 2: Cost-effectiveness frontier (NYHA I, QRS<120ms, non-ischemic, no LBBB)

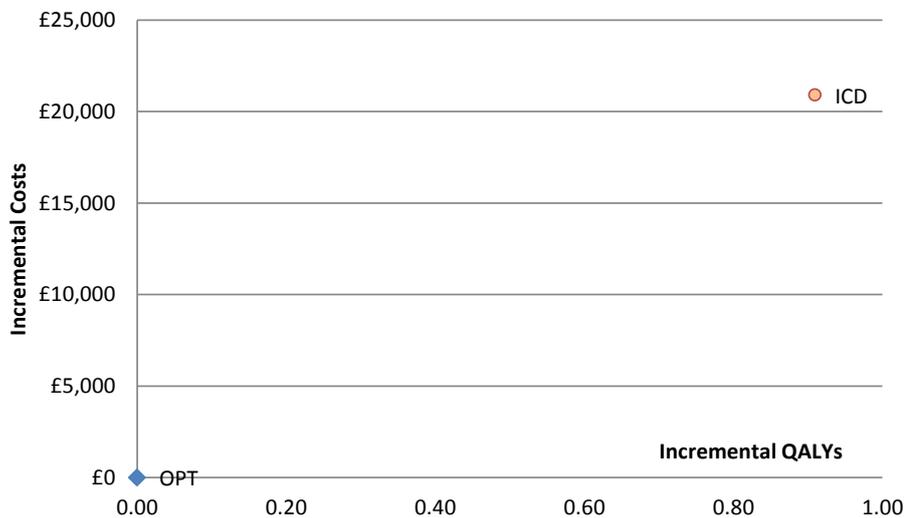


Figure 3: Cost-effectiveness frontier (NYHA I, QRS≥120ms, ≤149ms, non-ischemic, no LBBB)

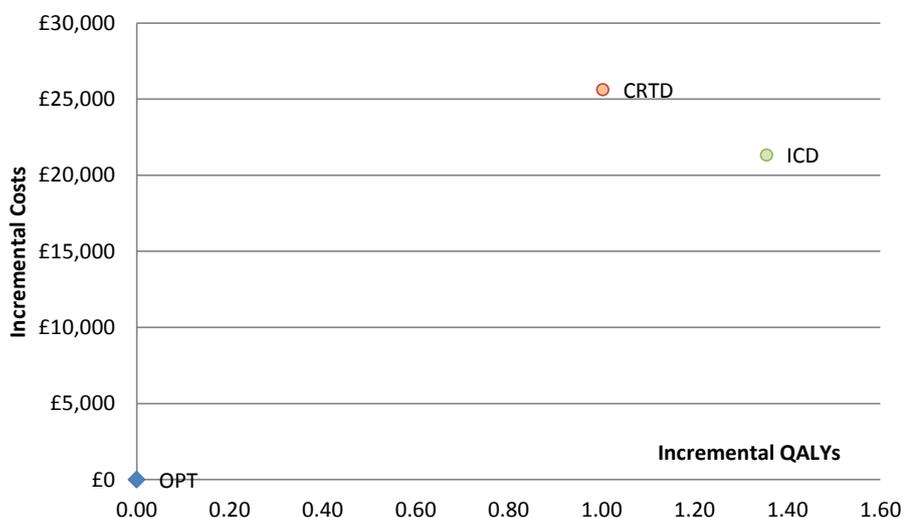


Figure 4: Cost-effectiveness frontier (NYHA I, QRS \geq 150ms non-ischemic, no LBBB)

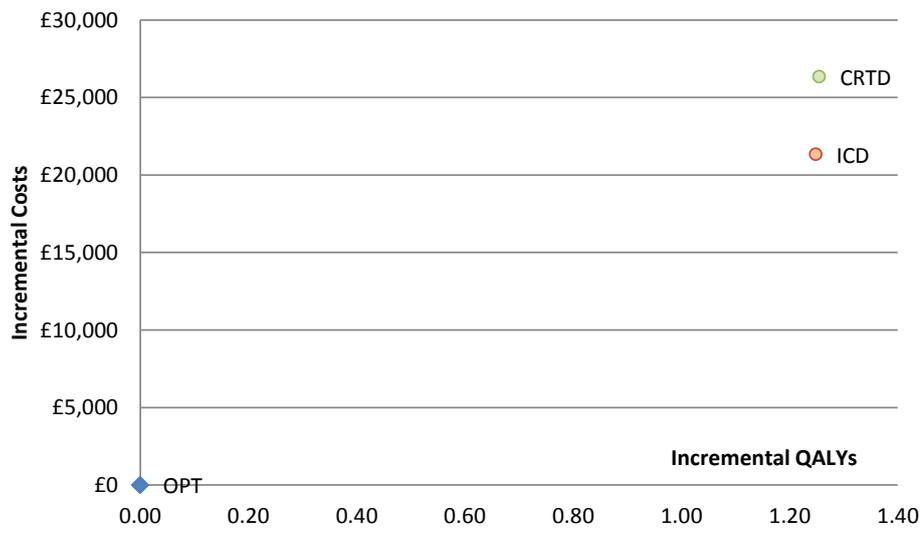


Figure 5: Cost-effectiveness frontier (NYHA I, QRS<120ms, ischemic, no LBBB)

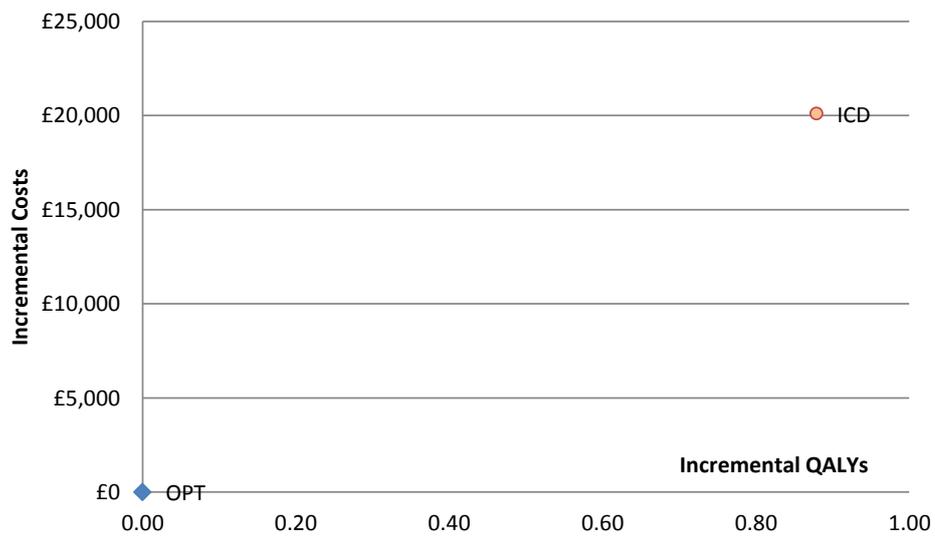


Figure 6: Cost-effectiveness frontier (NYHA I, QRS \geq 120ms, \leq 149ms, ischemic, no LBBB)

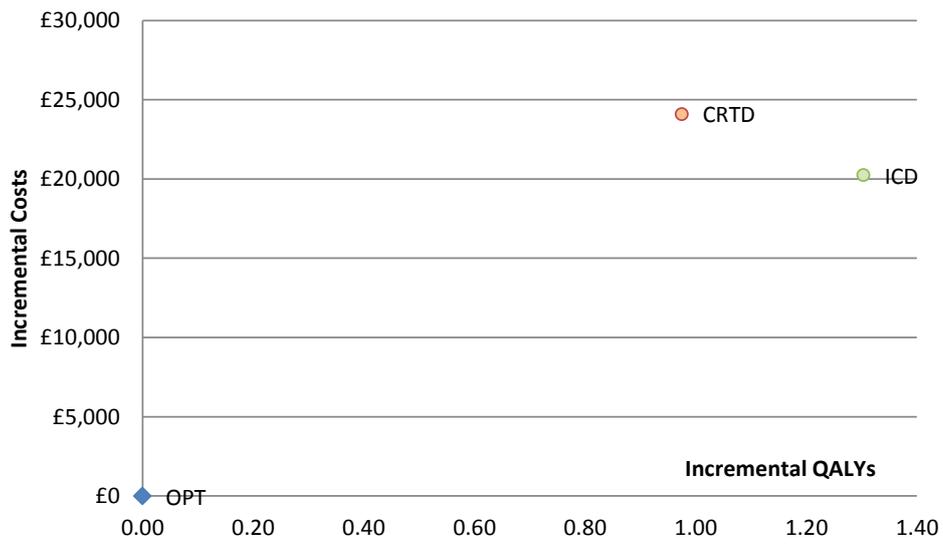
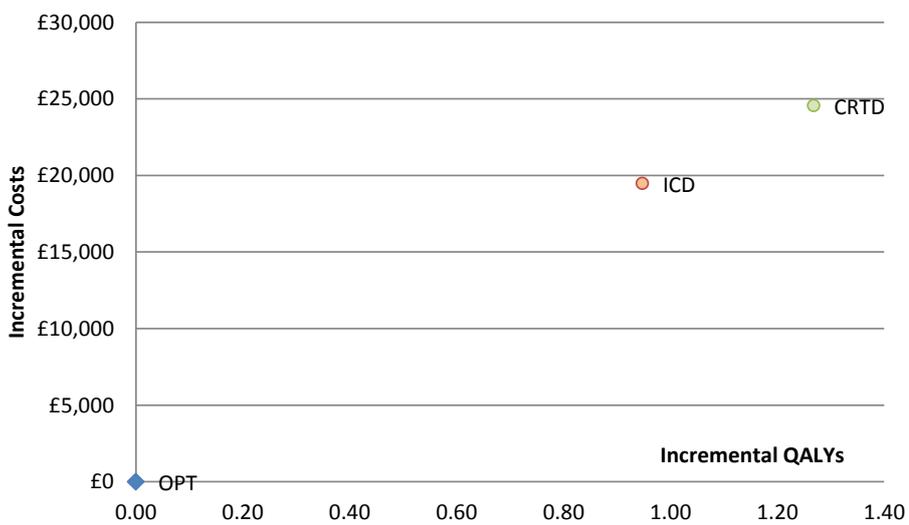


Figure 7: Cost-effectiveness frontier (NYHA I, QRS \geq 150ms ischemic, no LBBB)



No LBBB, NYHA II

Figure 8: Cost-effectiveness frontier (NYHA II, QRS<120ms, non-ischemic, no LBBB)

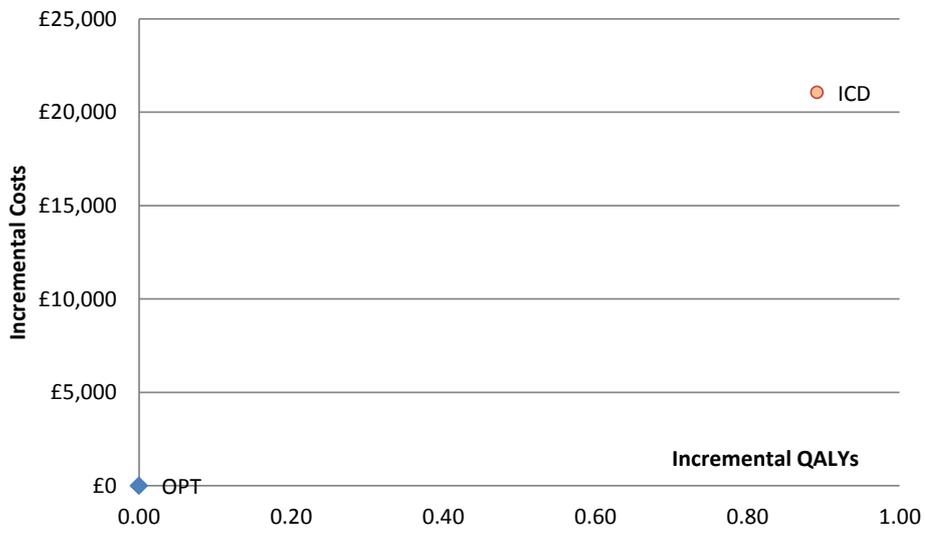


Figure 9: Cost-effectiveness frontier (NYHA II, QRS≥120ms, ≤149ms, non-ischemic, no LBBB)

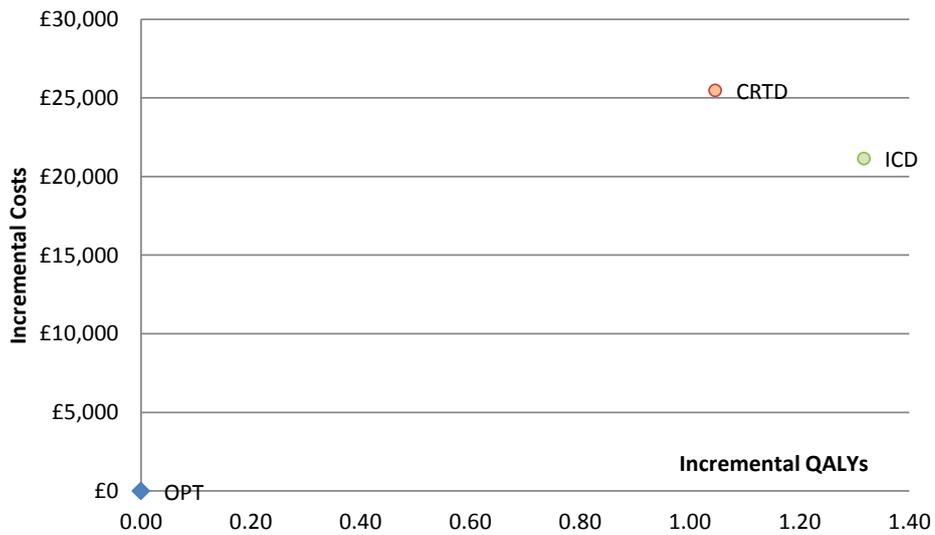


Figure 10: Cost-effectiveness frontier (NYHA II, QRS \geq 150ms non-ischemic, no LBBB)

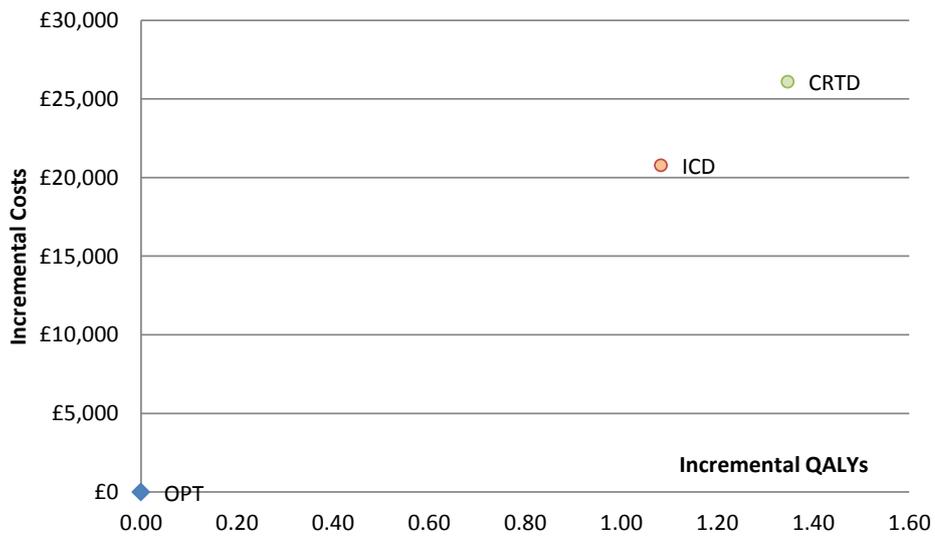


Figure 11: Cost-effectiveness frontier (NYHA II, QRS<120ms, ischemic, no LBBB)

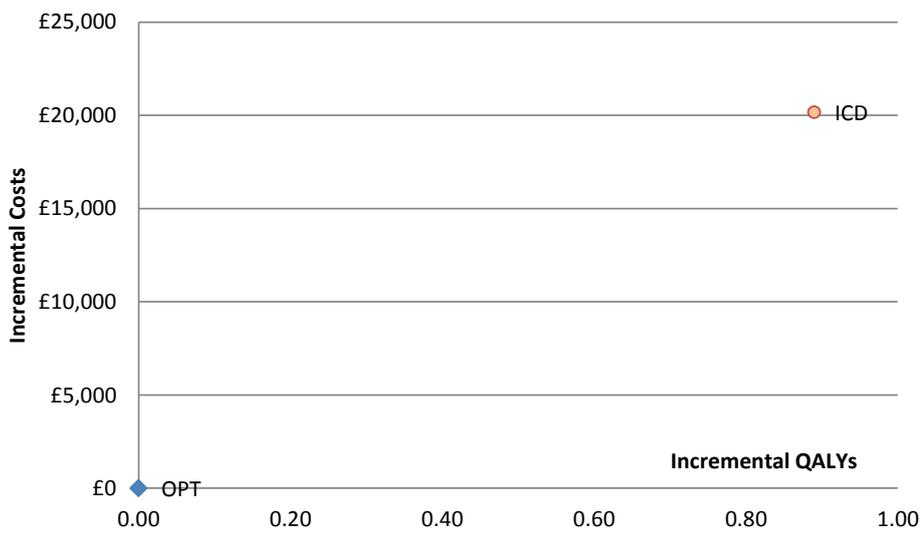


Figure 12: Cost-effectiveness frontier (NYHA II, QRS \geq 120ms, \leq 149ms, ischemic, no LBBB)

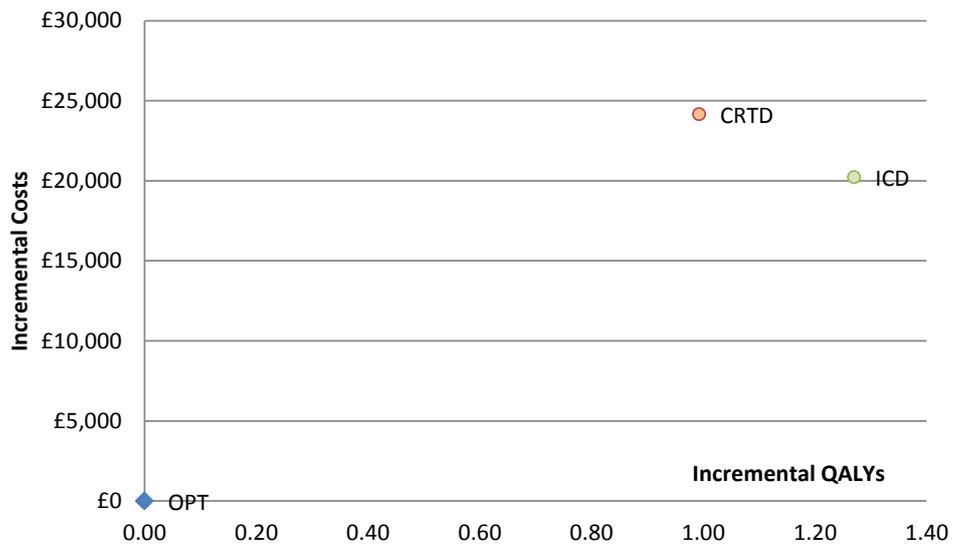
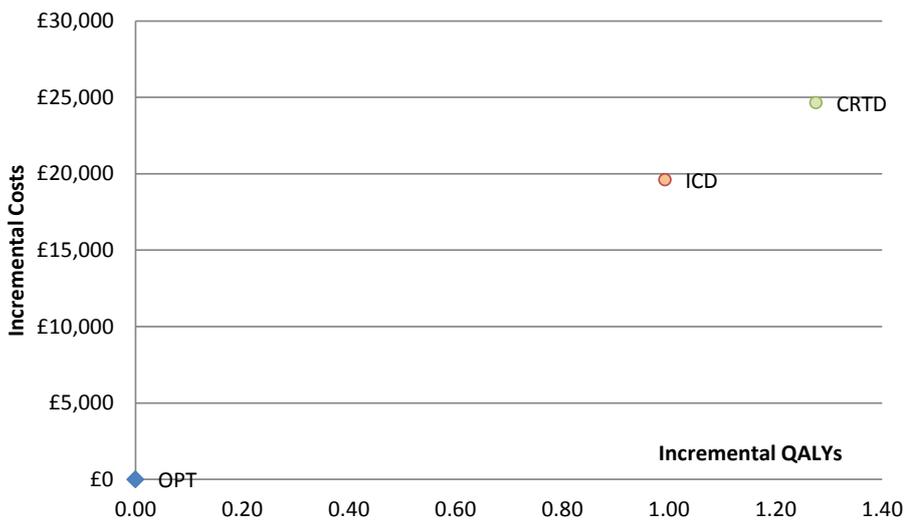


Figure 13: Cost-effectiveness frontier (NYHA II, QRS \geq 150ms ischemic, no LBBB)



No LBBB, NYHA III

Figure 14: Cost-effectiveness frontier (NYHA III, QRS<120ms, non-ischemic, no LBBB)

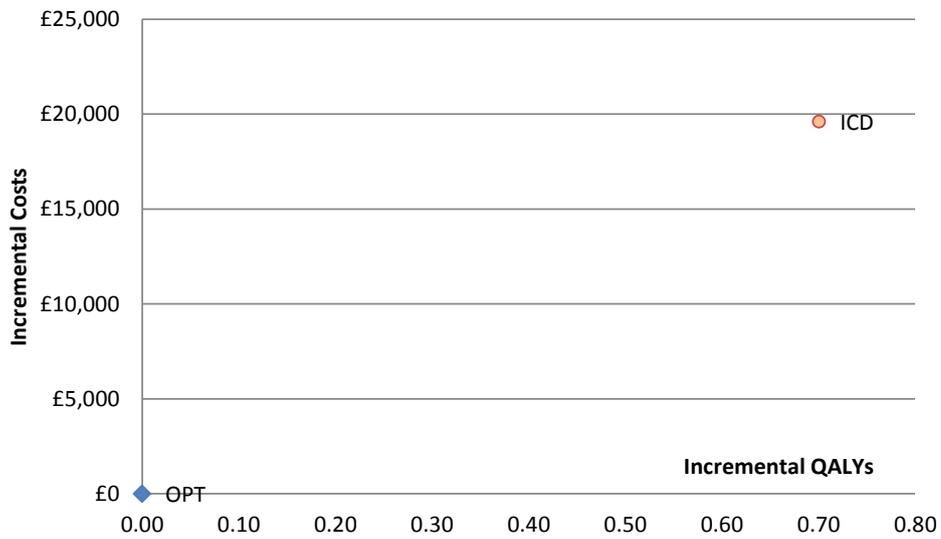


Figure 15: Cost-effectiveness frontier (NYHA III, QRS≥120ms, ≤149ms, non-ischemic, no LBBB)

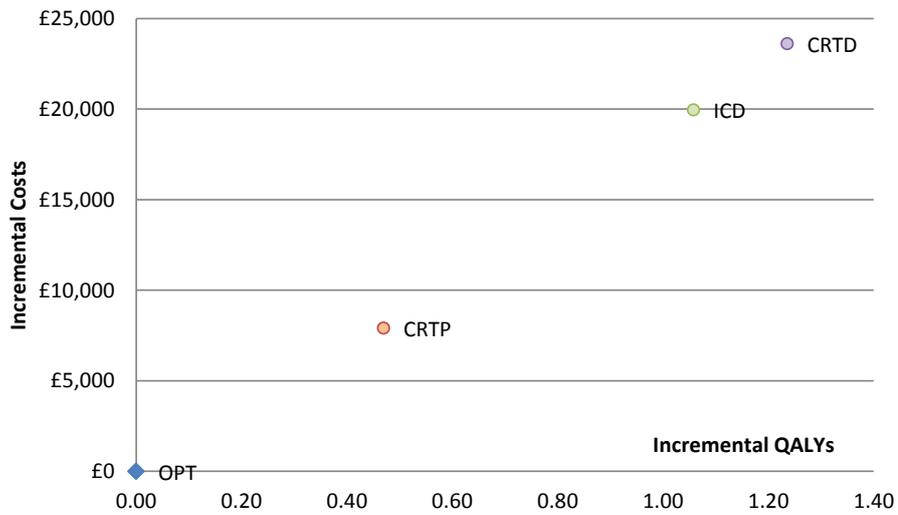


Figure 16: Cost-effectiveness frontier (NYHA III, QRS \geq 150ms non-ischemic, no LBBB)



Figure 17: Cost-effectiveness frontier (NYHA III, QRS<120ms, ischemic, no LBBB)

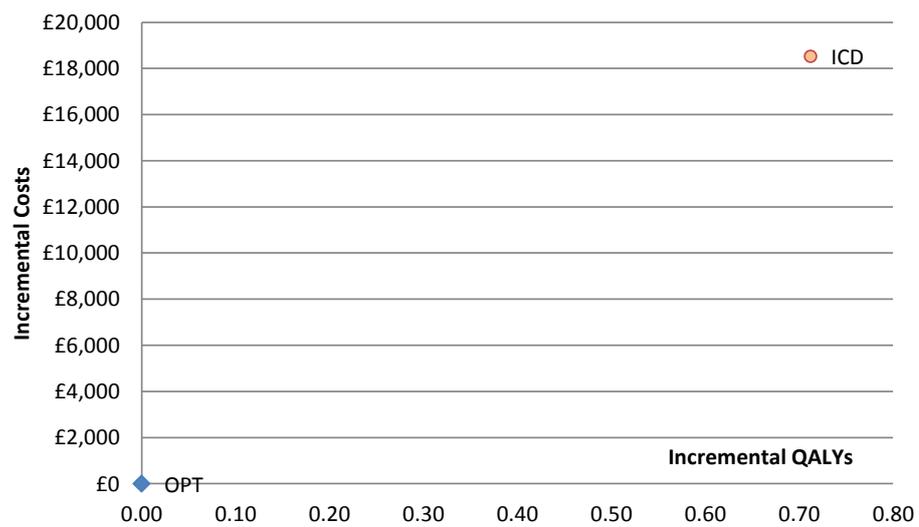


Figure 18: Cost-effectiveness frontier (NYHA III, QRS \geq 120ms, \leq 149ms, ischemic, no LBBB)

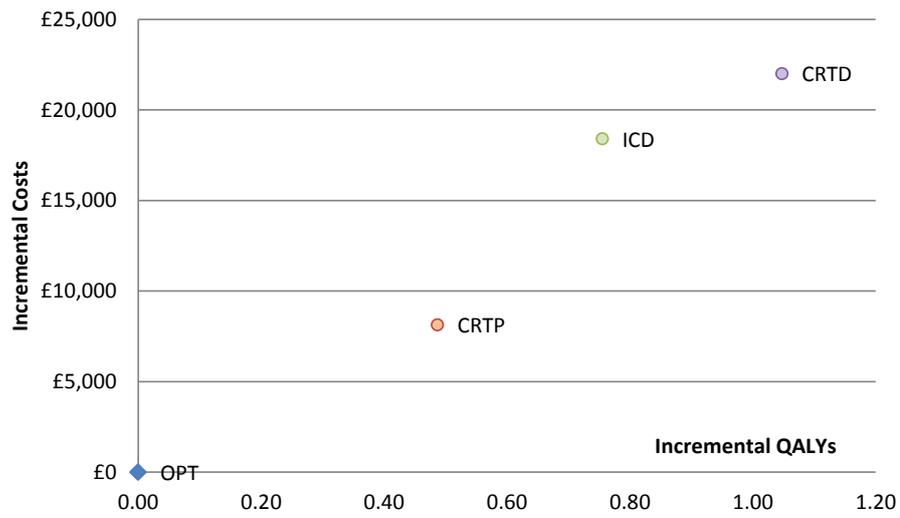
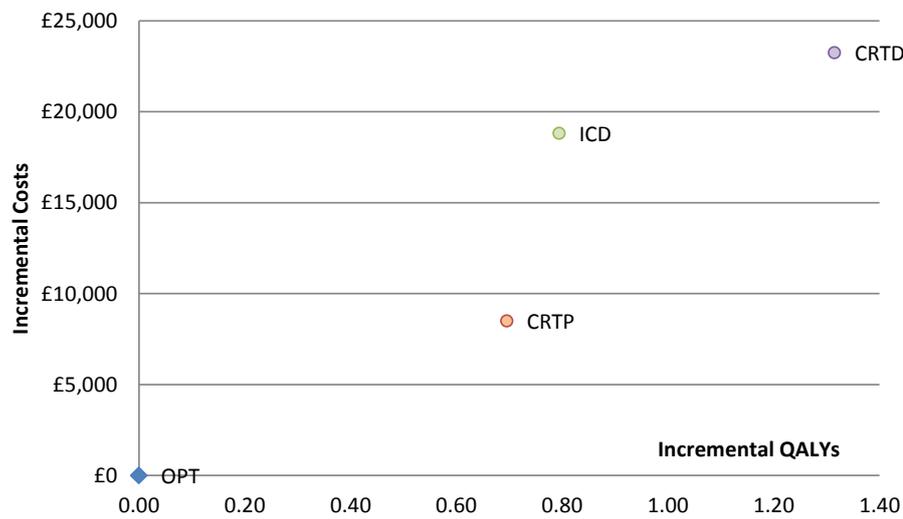


Figure 19: Cost-effectiveness frontier (NYHA III, QRS \geq 150ms ischemic, no LBBB)



No LBBB, NYHA IV

Figure 20: Cost-effectiveness frontier (NYHA IV, QRS \geq 120ms, \leq 149ms, non-ischemic, no LBBB)

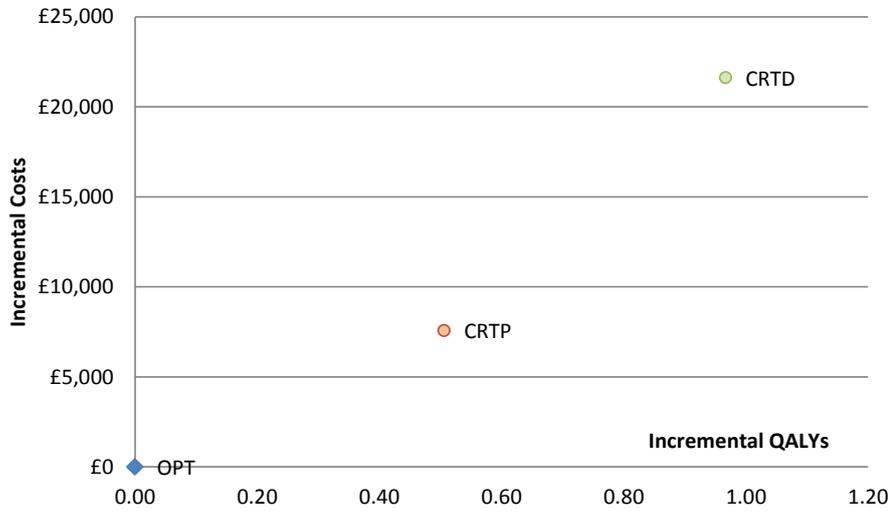


Figure 21: Cost-effectiveness frontier (NYHA IV, QRS \geq 150ms non-ischemic, no LBBB)

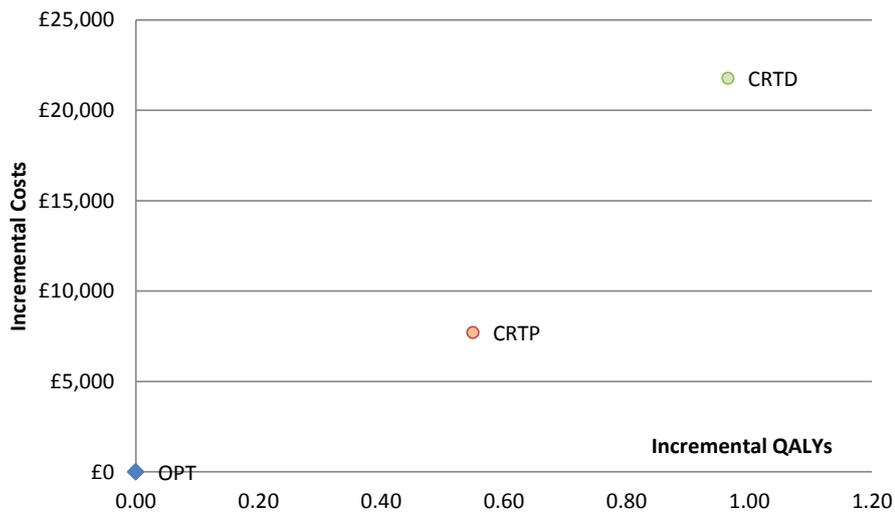


Figure 22: Cost-effectiveness frontier (NYHA IV, QRS \geq 120ms, \leq 149ms, ischemic, no LBBB)

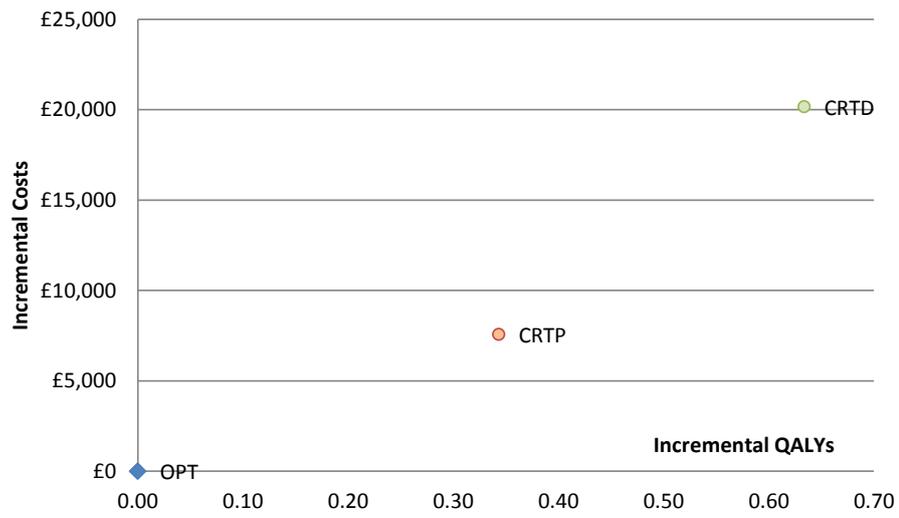
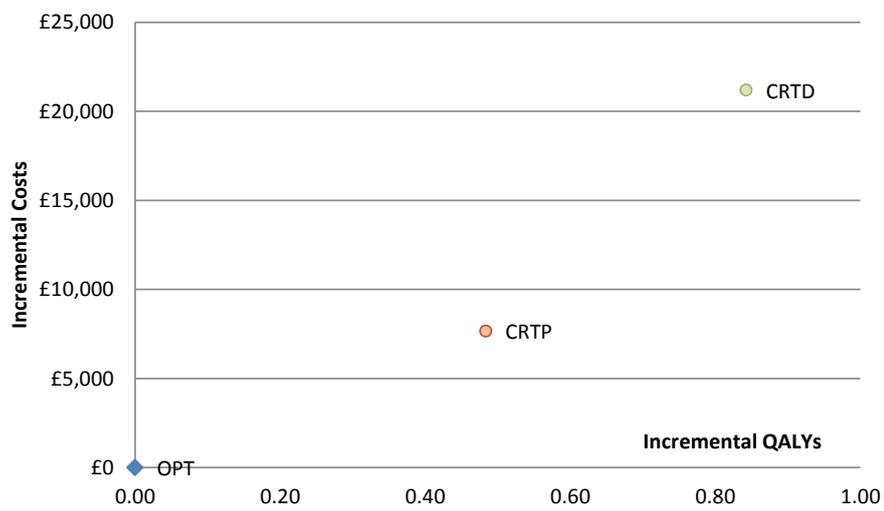


Figure 23: Cost-effectiveness frontier (NYHA I, QRS \geq 150ms ischemic, no LBBB)



LBBB, NYHA I

Figure 24: Cost-effectiveness frontier (NYHA I, QRS \geq 120ms, \leq 149ms, non-ischemic LBBB)

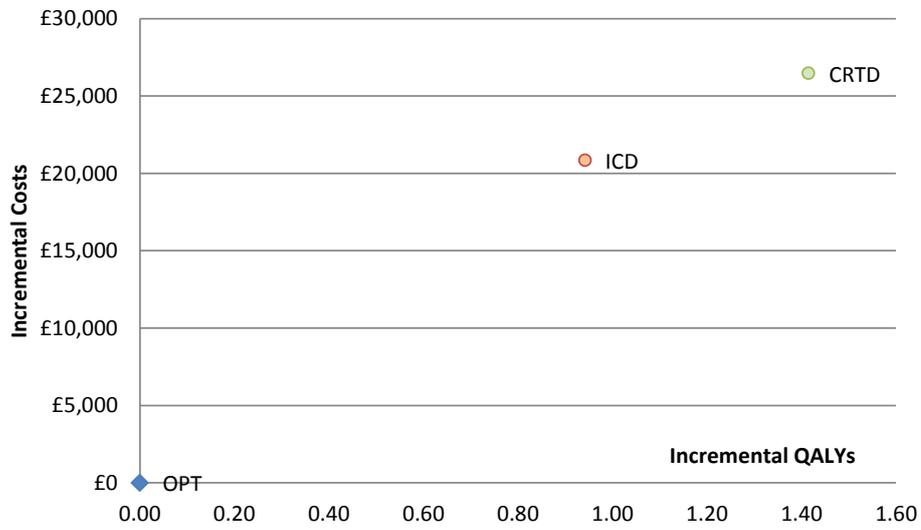


Figure 25: Cost-effectiveness frontier (NYHA I, QRS \geq 150ms non-ischemic, LBBB)

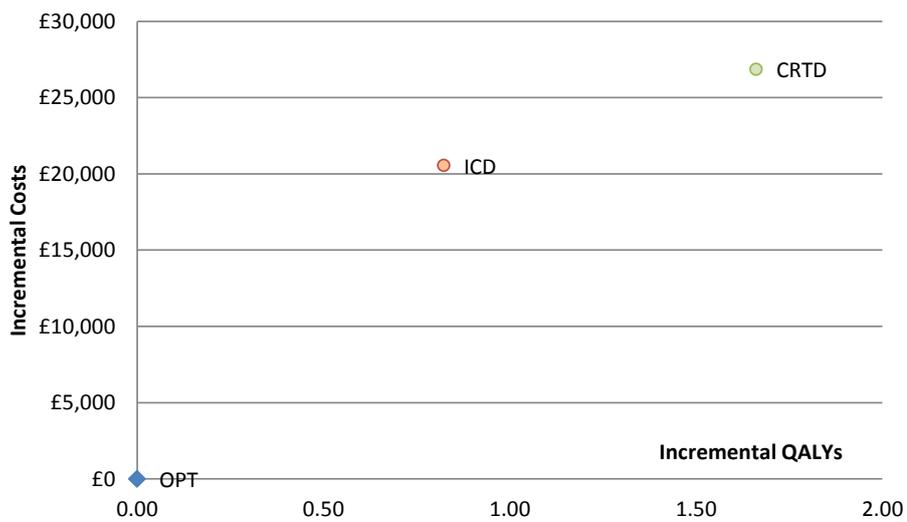


Figure 26: Cost-effectiveness frontier (NYHA I, QRS \geq 120ms, \leq 149ms, ischemic, LBBB)

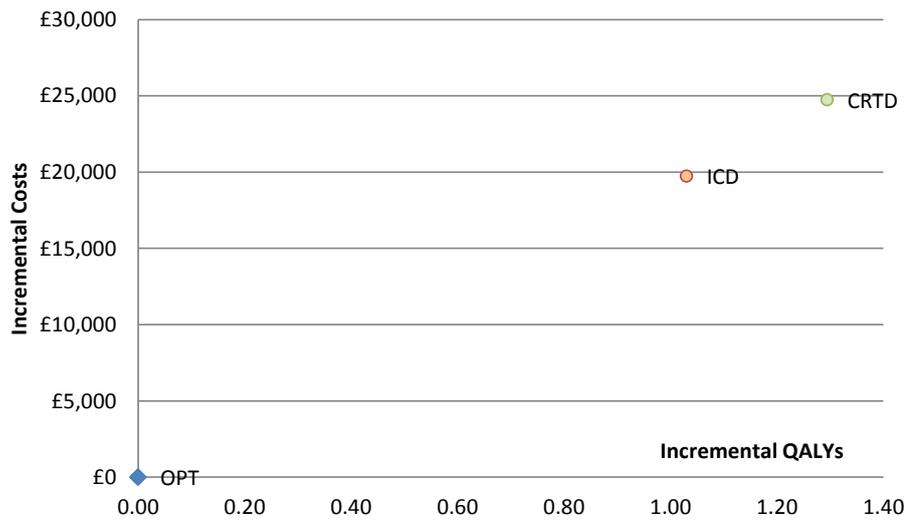
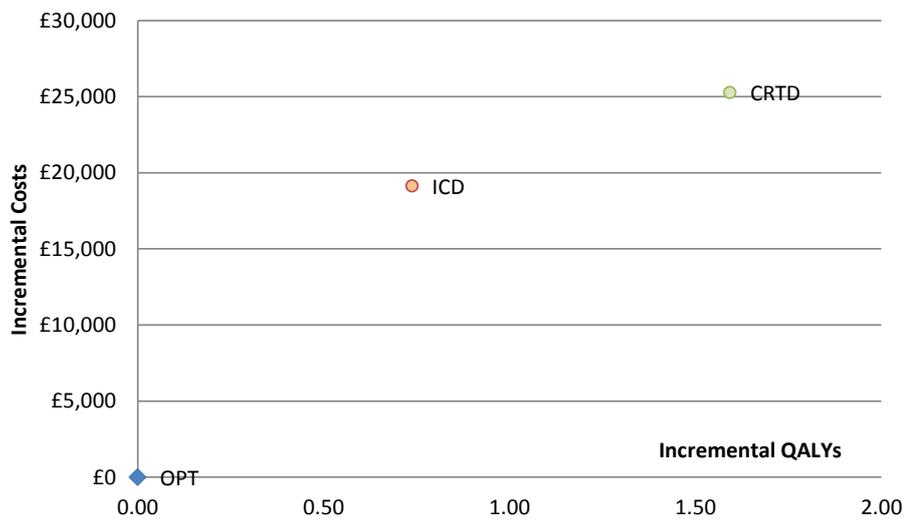


Figure 27: Cost-effectiveness frontier (NYHA I, QRS \geq 150ms ischemic, LBBB)



LBBB, NYHA II

Figure 28: Cost-effectiveness frontier (NYHA II, $QRS \geq 120ms, \leq 149ms$, non-ischemic LBBB)

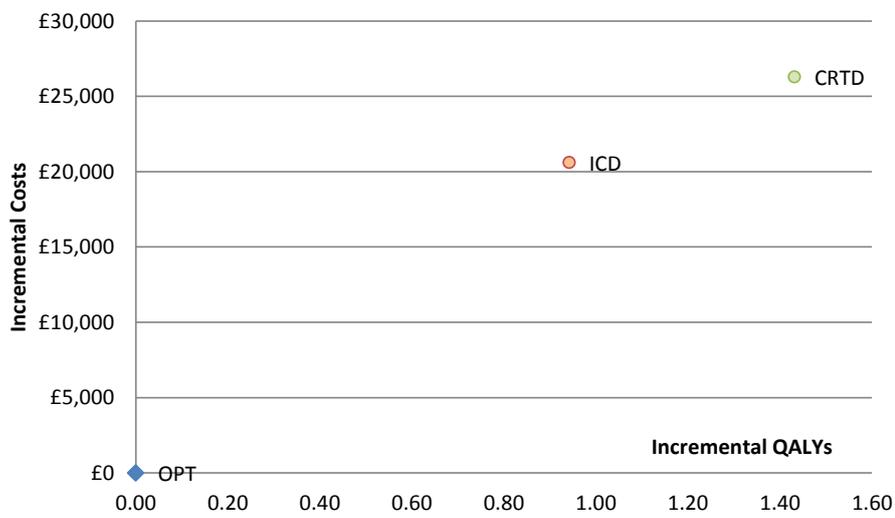


Figure 29: Cost-effectiveness frontier (NYHA II, $QRS \geq 150ms$ non-ischemic, LBBB)

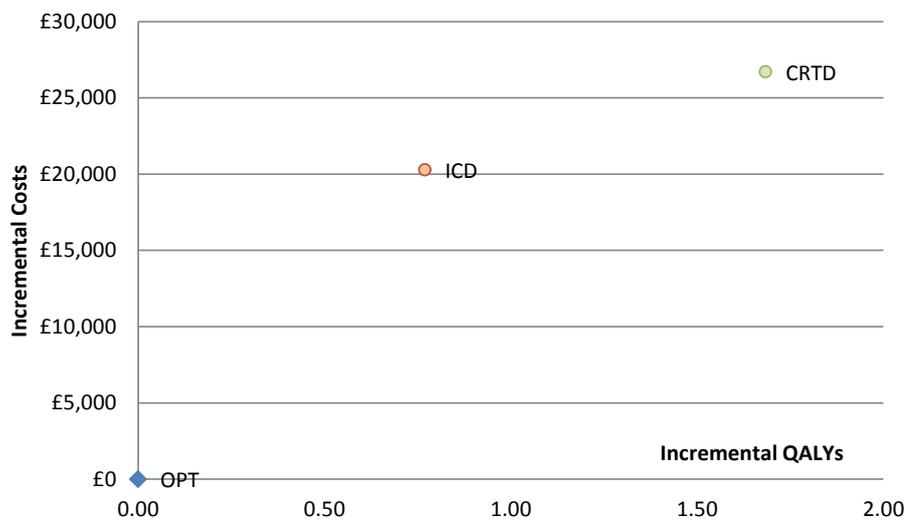


Figure 30: Cost-effectiveness frontier (NYHA II, QRS \geq 120ms, \leq 149ms, ischemic, LBBB)

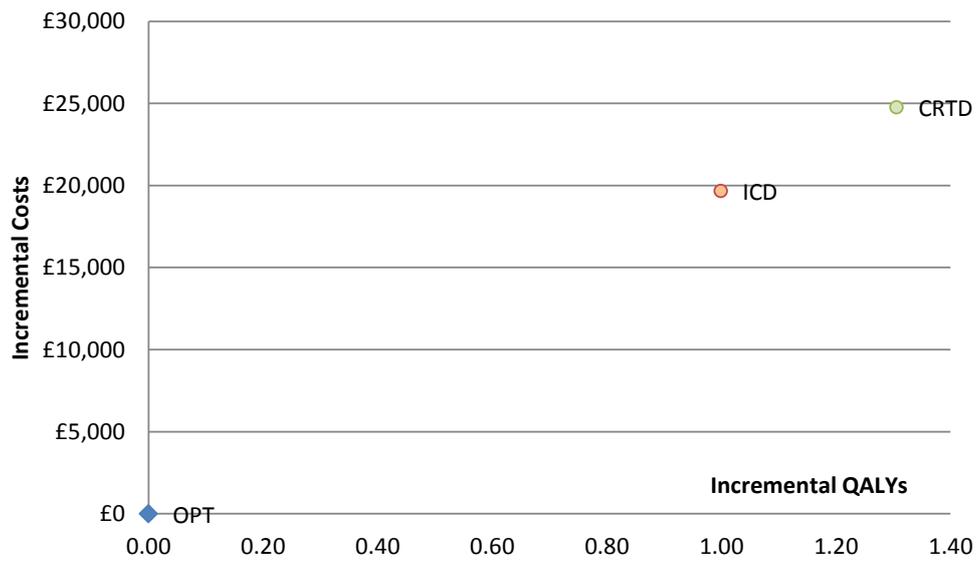
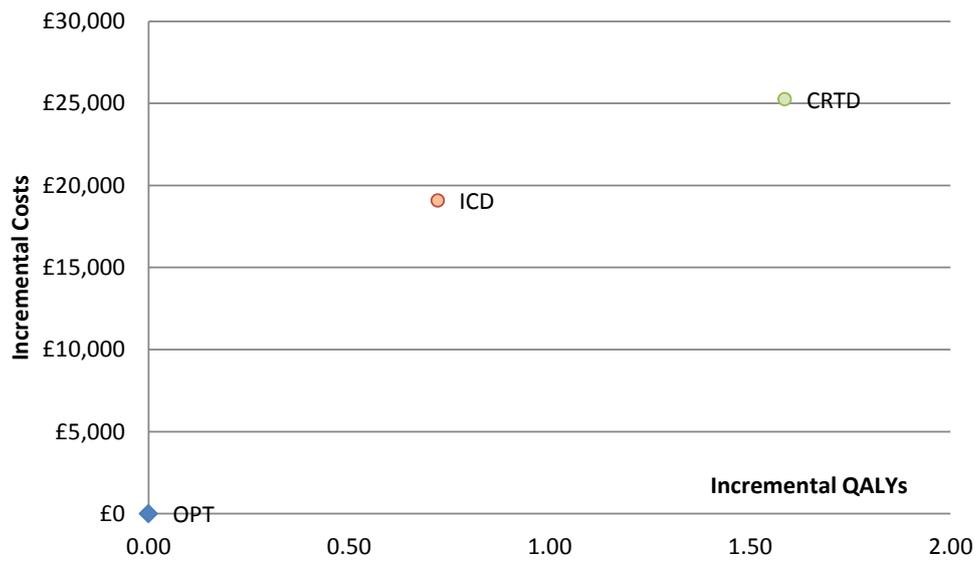


Figure 31: Cost-effectiveness frontier (NYHA II, QRS \geq 150ms ischemic, LBBB)



LBBB, NYHA III

Figure 32: Cost-effectiveness frontier (NYHA III, QRS \geq 120ms, \leq 149ms, non-ischemic LBBB)

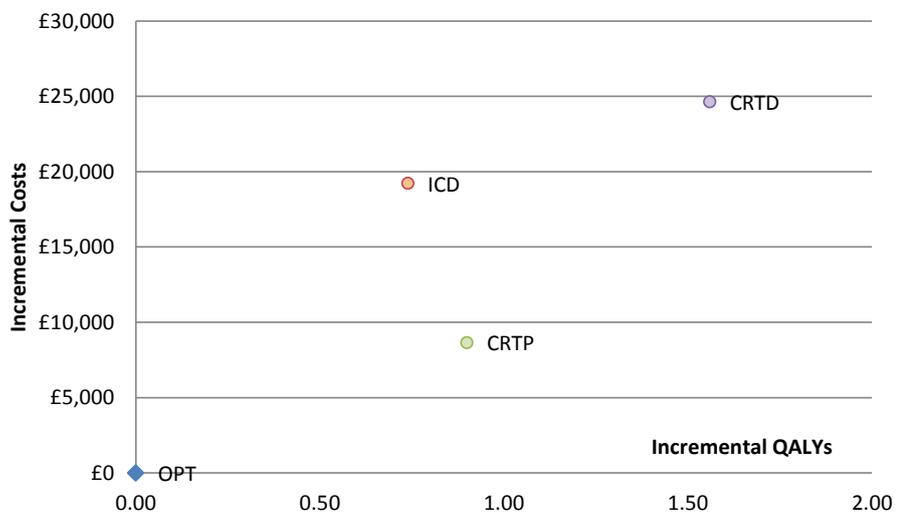


Figure 33: Cost-effectiveness frontier (NYHA III, QRS \geq 150ms non-ischemic, LBBB)

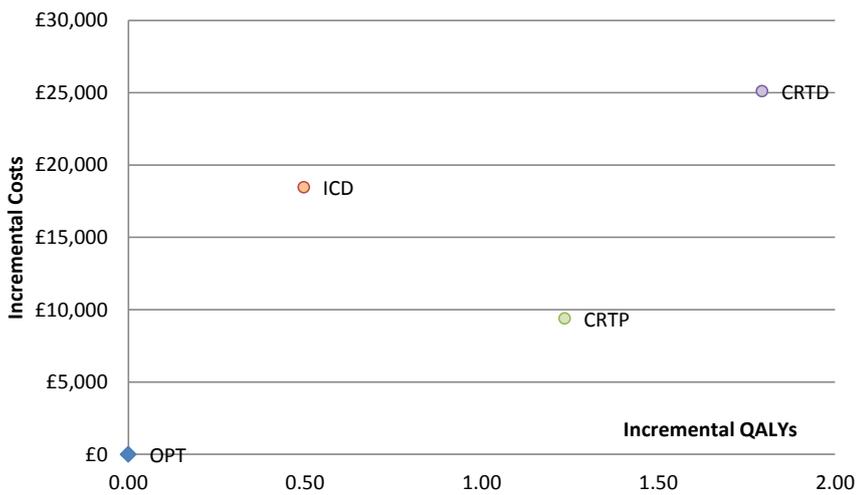


Figure 34: Cost-effectiveness frontier (NYHA III, QRS \geq 120ms, \leq 149ms, ischemic, LBBB)

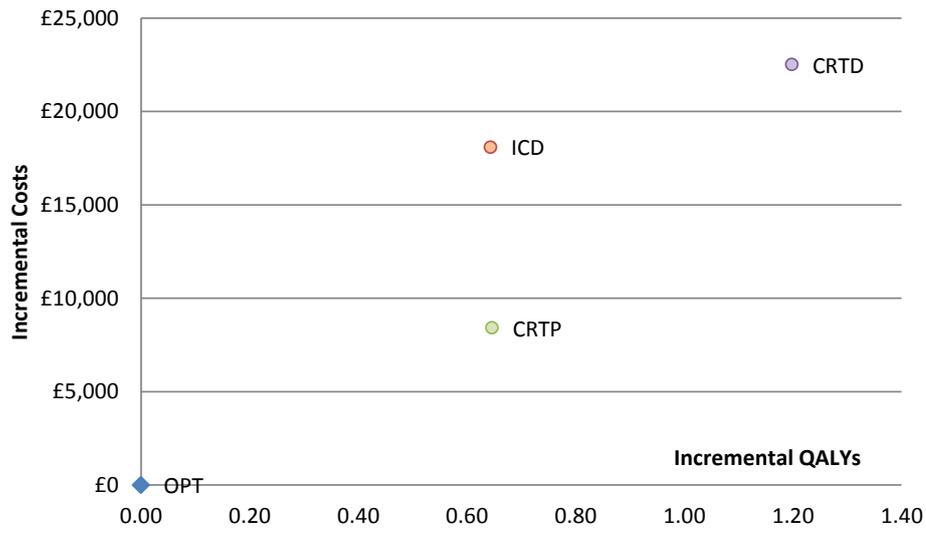
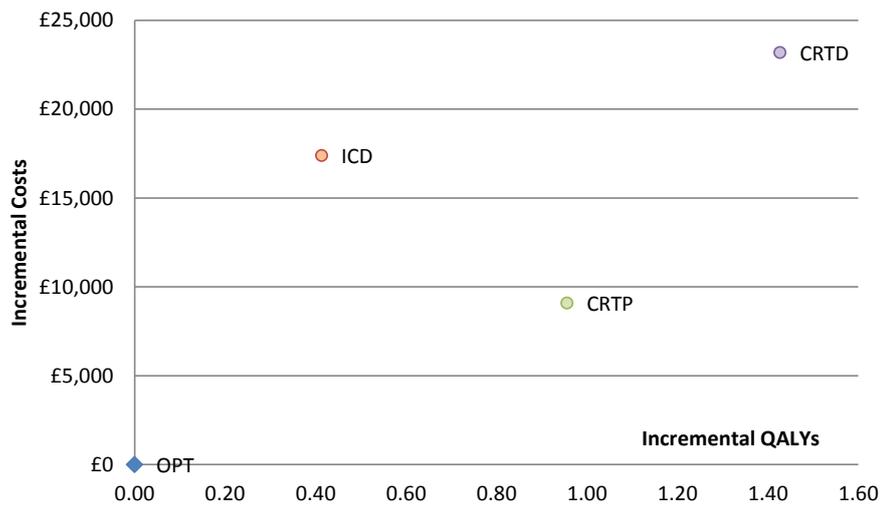


Figure 35: Cost-effectiveness frontier (NYHA III, QRS \geq 150ms ischemic, LBBB)



LBBB, NYHA IV

Figure 36: Cost-effectiveness frontier (NYHA IV, $QRS \geq 120ms, \leq 149ms$, non-ischemic LBBB)

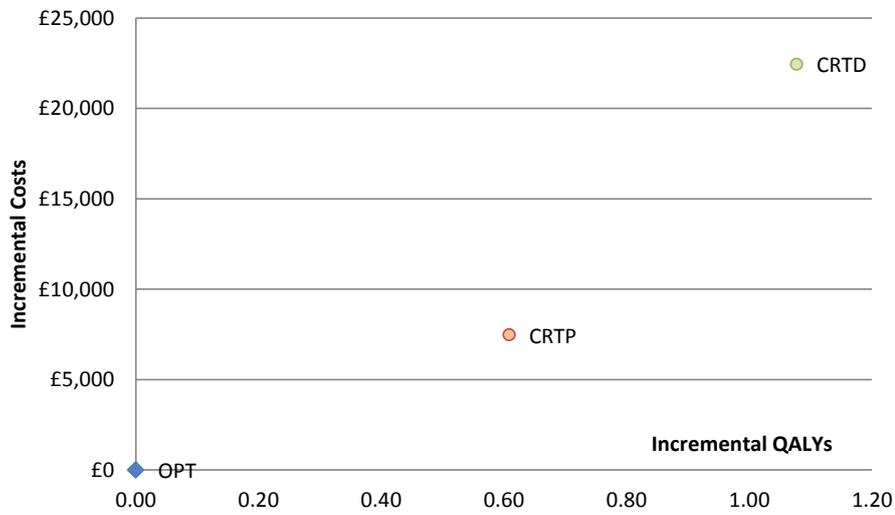


Figure 37: Cost-effectiveness frontier (NYHA IV, $QRS \geq 150ms$ non-ischemic, LBBB)

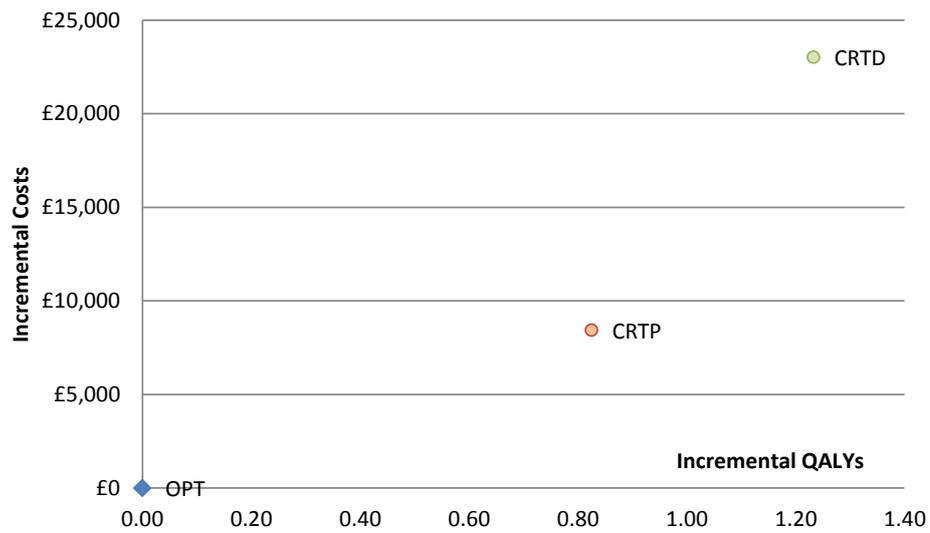


Figure 38: Cost-effectiveness frontier (NYHA IV, QRS \geq 120ms, \leq 149ms, ischemic, LBBB)

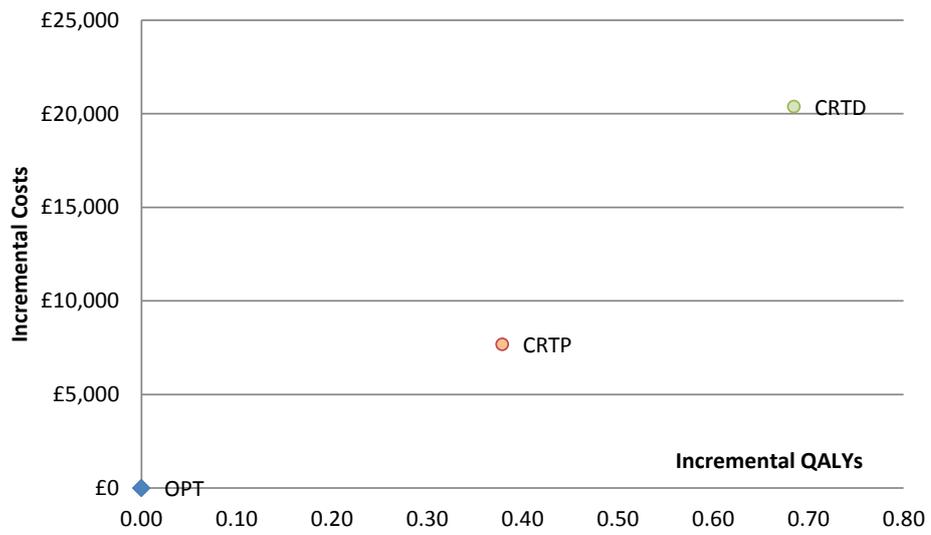
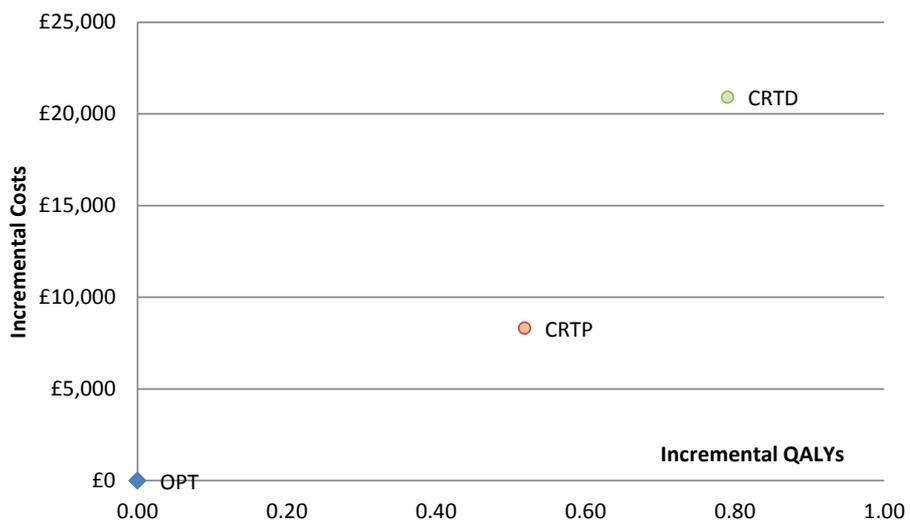


Figure 39: Cost-effectiveness frontier (NYHA IV, QRS \geq 150ms ischemic, LBBB)



APPENDIX 14: Cost-effectiveness frontiers for all NYHA III patient groups (excluding CRT-P)

Figure 40: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥ 120 ms, ≤ 149 ms, non-ischemic)

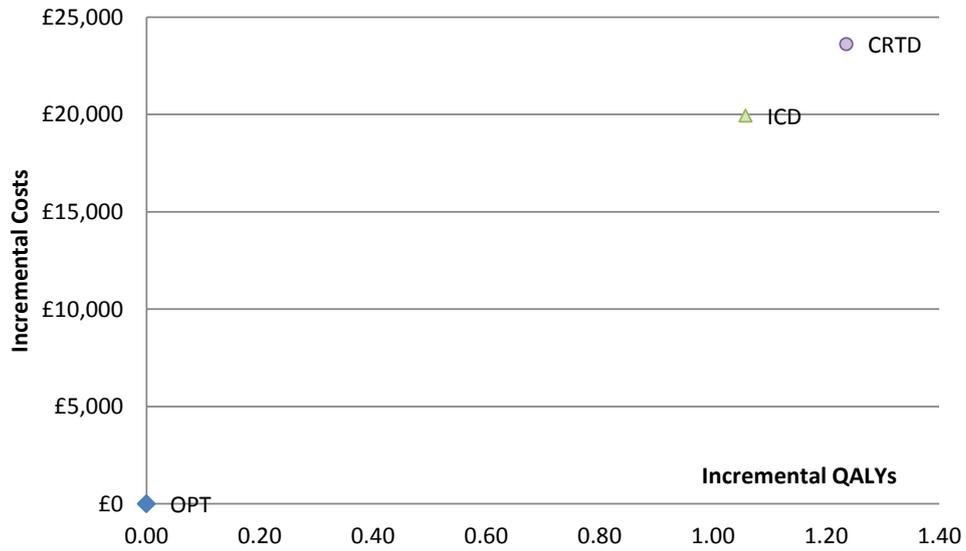


Figure 41: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥ 150 ms, non-ischemic)

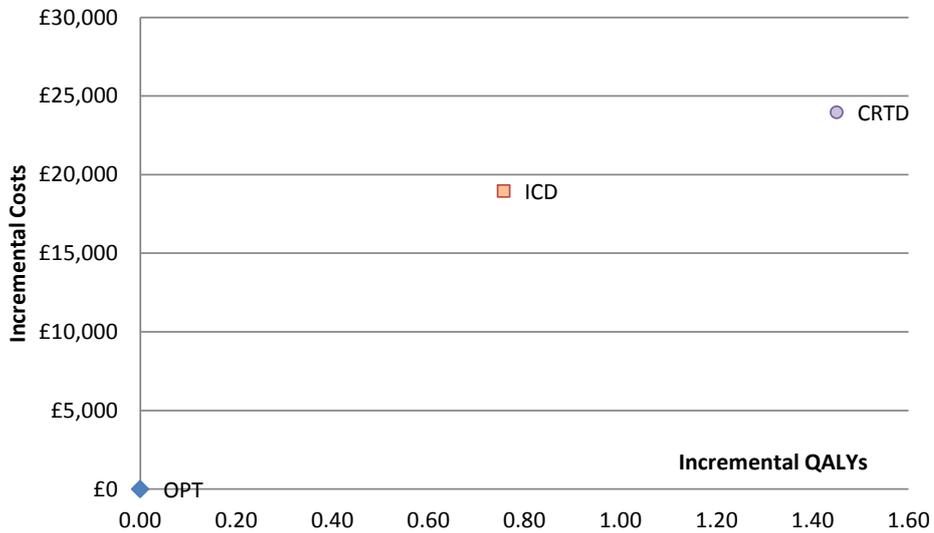


Figure 42: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥ 120 ms, ≤ 149 ms, ischemic)

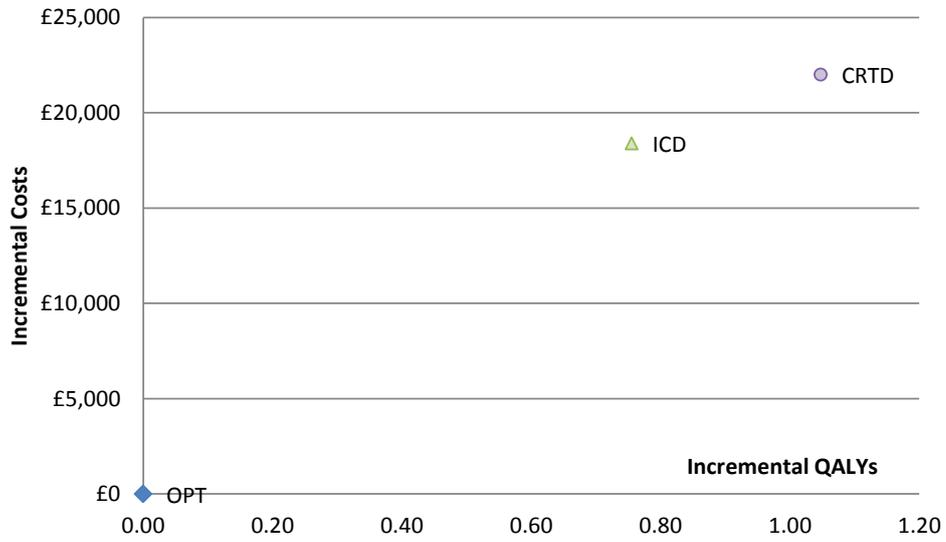


Figure 43: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥ 150 ms, Ischemic)

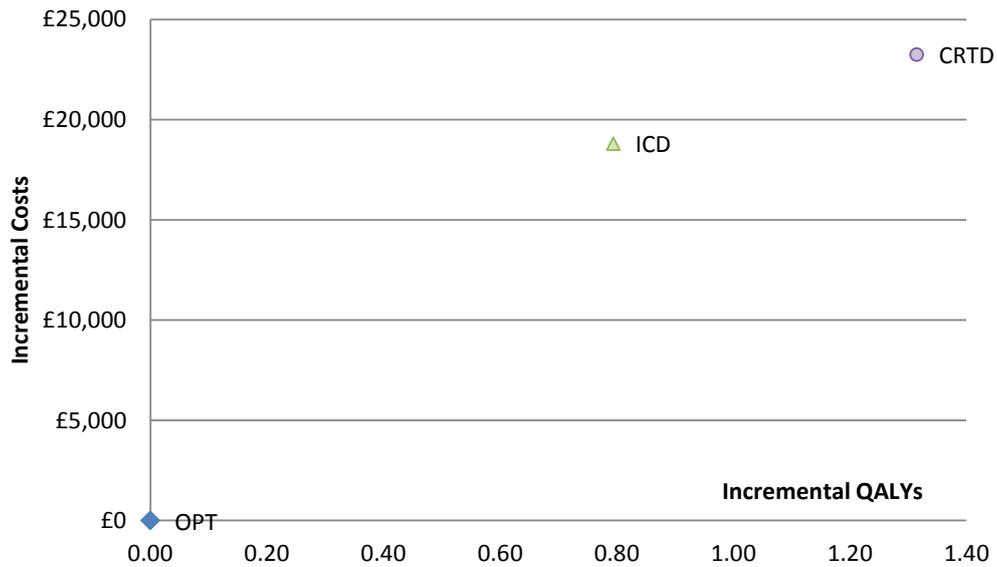


Figure 44: Cost-effectiveness frontier excluding CRT-P (LBBB, QRS ≥ 120 ms, ≤ 149 ms, non-ischemic)

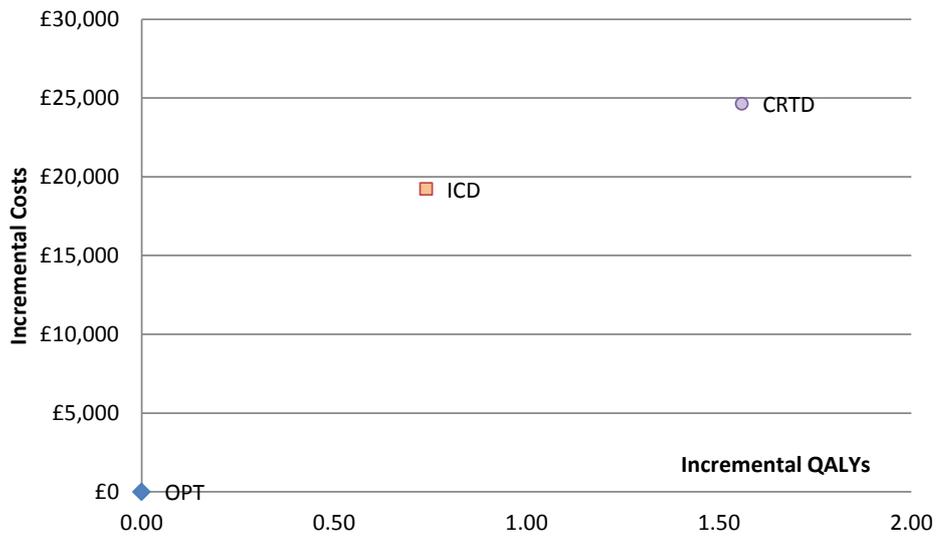


Figure 45: Cost-effectiveness frontier excluding CRT-P (LBBB, QRS ≥ 150 ms, non-ischemic)

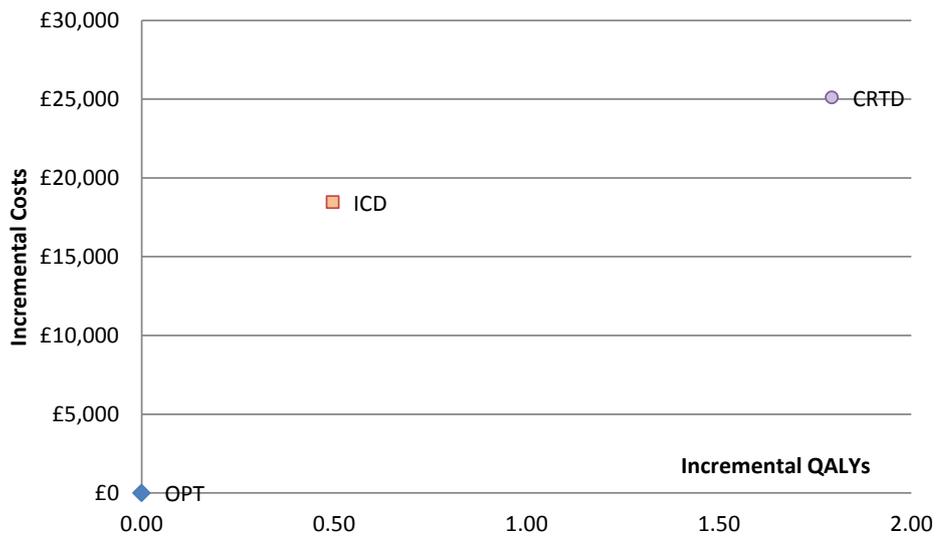


Figure 46: Cost-effectiveness frontier excluding CRT-P (LBBB, QRS ≥ 120 ms, ≤ 149 ms, ischemic)

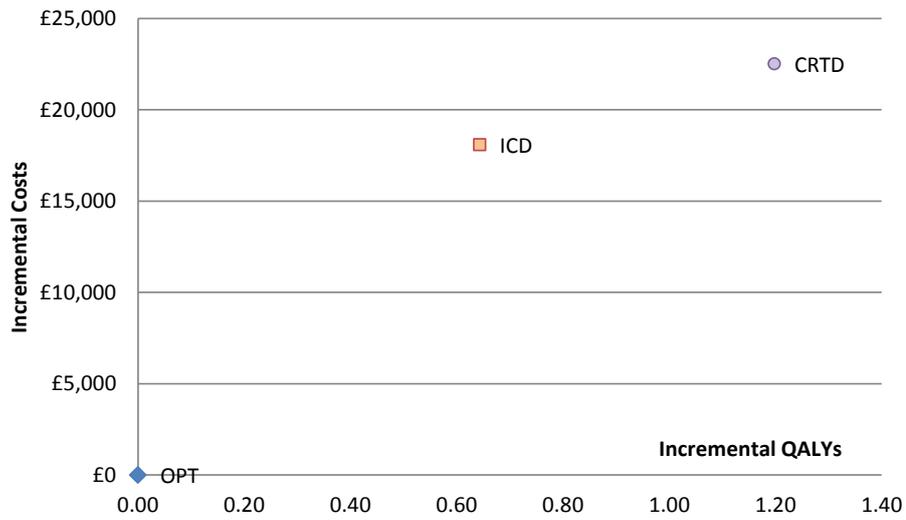
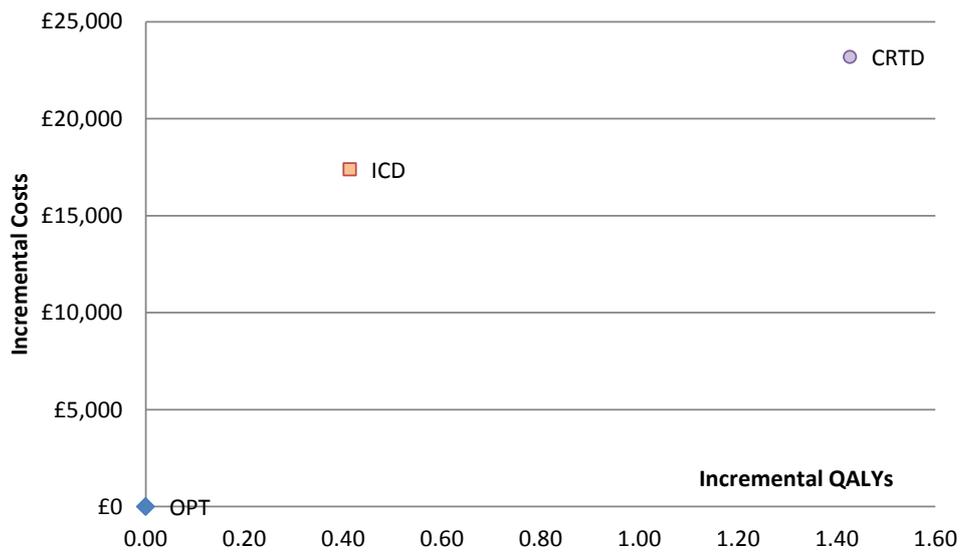


Figure 47: Cost-effectiveness frontier excluding CRT-P (No LBBB, QRS ≥ 150 ms, Ischemic)



APPENDIX 15: Additional deterministic sensitivity analyses

Use of length of stay as opposed to event counts to model hospitalisations

As noted in section 4.7, we evaluated the impact of all-cause hospitalisation using a length of stay as well as a count per month approach. The impact of running the model using the LOS method is presented in Table 30 and Table 31. In general, the effect on the ICERs was very modest.

Table 30: Deterministic sensitivity analysis – LOS approach to modelling all cause hospitalisation (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,148	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,030	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,371	£1,201,871	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,076	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,878	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,123	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,840	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,460	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,534	£30,333	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,938	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,370	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£20,140	£20,344	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,681	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	Ext Dominated	£18,759	£33,621
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£16,258	£21,006
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,748	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£15,653	Ext Dominated	£24,875
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,425	£25,778
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£12,960	£37,818	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£8,698	£41,991	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£11,737	£51,506	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£6,631	£46,232	N/A

Table 31: Deterministic sensitivity analysis – LOS approach to modelling all cause hospitalisation (no LBBB)

NYHA Class	Etiology	QRS Duration	1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,030	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,166	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,452	£21,734	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,598	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,658	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,879	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,840	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,751	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£15,856	£20,109
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,662	£22,966
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,655	£25,546
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£9,838	£29,884
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£11,159	£39,589	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£10,114	£44,980	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£11,560	£49,124	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£10,305	£55,748	N/A

Increase in period of mortality treatment effect

As noted in section 3.9, long term evidence supports the possibility that the benefits of treatment in terms of reduction in all-cause mortality last longer than we have included in the base case. We have therefore explored the impact of maintaining the treatment effect for 10 years instead of 7.5 years on the cost-effectiveness of all devices. The results are presented in Table 32 and Table 33.

As expected, the impact of the change is more pronounced in patients with NYHA I/II heart failure than in those with NYHA III/IV heart failure. Increasing the period of treatment benefit has, in general, reduced all ICERs, but the changes are fairly modest. Hence, the model is insensitive to increases in this parameter.

Table 32: Deterministic sensitivity analysis – mortality treatment effect maintained for ten years (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,902	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,644	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£17,000	£1,675,069	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,851	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,504	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,215	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,668	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,079	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,206	£25,787	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,722	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,008	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	£19,853	£21,764	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£28,008	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	Ext Dominated	£18,916	£29,969
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£13,025	£23,330
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,152	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£19,572	Ext Dominated	£24,252
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£14,254	£24,904
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£17,254	£30,154	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£16,227	£33,282	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£24,335	£43,180	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£18,008	£37,297	N/A

Table 33: Deterministic sensitivity analysis – mortality treatment effect maintained for ten years (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,880	N/A
I	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,087	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,143	£23,231	N/A
I	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,558	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,509	N/A
II	Non-Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,812	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,786	£20,336	N/A
II	Ischemic	>=150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,708	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,328	£22,716
III	Non-Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£9,596	£26,118
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£15,331	Ext Dominated	£24,846
III	Ischemic	>=150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,284	£28,874
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£14,622	£31,134	N/A
IV	Non-Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£11,988	£34,614	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£22,314	£41,379	N/A
IV	Ischemic	>=150ms	OPT	CRTD	CRTD	N/A	Referent	£17,687	£45,925	N/A

Decrease in period of mortality treatment effect

In order to test the impact of a more negative assumption surrounding the duration of all-cause mortality treatment effect, we set the starting point for the tapering off effect to 5 years (base case 7.5 years). The impact of this alternative assumption on the cost-effectiveness of all devices is presented in Table 34 and Table 35.

Overall, truncating the period of treatment efficacy below that observed in long term studies results in an increase in the cost-effectiveness ratios. It is interesting that the model is not only robust to increases in this parameter but also to decreases, since the highest meaningful ICER generated for patients with NYHA I/II heart failure remains below £30,000 per QALY gained. Hence, when the model is executed using overly conservative assumptions, the cost-effectiveness of all interventions is marginal.

Table 34: Deterministic sensitivity analysis – truncation of all-cause mortality treatment effect period (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,136	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,902	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£19,478	£844,105	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,608	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,264	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,349	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£26,977	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£18,264	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,792	£29,017	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,468	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,797	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,919	£24,221	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£31,354	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	Ext Dominated	£20,968	£24,844
III	Non-Ischemic	>150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£13,540	£25,841
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£28,160	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	CRTD	Referent	£19,871	Ext Dominated	£25,730
III	Ischemic	>150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£14,635	£27,049
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£17,489	£31,552	N/A
IV	Non-Ischemic	>150ms	OPT	CRTD	CRTD	N/A	Referent	£16,472	£35,069	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£24,462	£44,264	N/A
IV	Ischemic	>150ms	OPT	CRTD	CRTD	N/A	Referent	£18,205	£38,865	N/A

Table 35: Deterministic sensitivity analysis – truncation of all-cause mortality treatment effect period (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,506	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,469	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£21,205	£25,920	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,439	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,059	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,094	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£21,869	£22,598	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,578	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£12,872	£25,399
III	Non-Ischemic	>150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£10,098	£29,662
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£15,670	£26,687
III	Ischemic	>150ms	OPT	ICD	CRTD	CRTD	Referent	Dominated	£11,632	£31,590
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£14,889	£33,237	N/A
IV	Non-Ischemic	>150ms	OPT	CRTD	CRTD	N/A	Referent	£12,251	£37,430	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTD	CRTD	N/A	Referent	£22,429	£42,482	N/A
IV	Ischemic	>150ms	OPT	CRTD	CRTD	N/A	Referent	£17,831	£47,651	N/A

Decrease in HRQoL treatment effect period

Despite evidence derived using the long term MLWHF data in our trial database, and the EQ-5D analysis presented in Cleland *et al.*, we have modelled the assumption that the HRQoL treatment effects begin to recede after the average follow up period in the CARE-HF study (circa 2.5 years). The impact of this alternative approach on the cost-effectiveness ratios is presented in Table 36 and Table 37.

HRQoL benefits are greatest in NYHA III/IV patients receiving CRT treatment. In these groups, the truncation of the benefit period has resulted in modest increases in all ICERs. The impact in patients with NYHA I/II heart failure is modest, regardless of treatment option. Hence, the model is robust to changes in this parameter.

Table 36: Deterministic sensitivity analysis – truncation of HRQoL treatment effect period (no LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,068	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,753	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£17,115	£591,782	N/A
I	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,014	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,568	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,361	N/A
II	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£23,722	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,073	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	£19,223	£19,931	N/A
II	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£22,788	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,967	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,315	N/A
III	Non-Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£27,972	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£18,426	£19,141	£28,285
III	Non-Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,985	£24,879
III	Ischemic	<120ms	OPT	ICD	N/A	N/A	Referent	£25,992	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£17,734	Ext Dominated	£25,134
III	Ischemic	>150ms	OPT	CRTP	ICD	CRTD	Referent	£12,531	Ext Dominated	£26,218
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£15,638	£31,086	N/A
IV	Non-Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,637	£34,510	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,795	£44,145	N/A
IV	Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£16,469	£38,478	N/A

Table 37: Deterministic sensitivity analysis – truncation of HRQoL treatment effect period (with LBBB)

NYHA Class	Etiology	QRS Duration	C-E Sequence				ICERs			
			1st	2nd	3rd	4th	1st	2nd	3rd	4th
I	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,703	N/A
I	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,164	N/A
I	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
I	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,120	N/A
I	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,866	N/A
II	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,362	N/A
II	Non-Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,858	N/A
II	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
II	Ischemic	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,954	N/A
II	Ischemic	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£15,912	N/A
III	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Non-Ischemic	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,161	£24,453
III	Non-Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£7,914	£28,432
III	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
III	Ischemic	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£13,684	Ext Dominated	£25,940
III	Ischemic	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,937	£30,556
IV	Non-Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Non-Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£12,882	£32,519	N/A
IV	Non-Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£10,602	£36,439	N/A
IV	Ischemic	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A
IV	Ischemic	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£20,856	£42,290	N/A
IV	Ischemic	>150ms	OPT	CRTP	CRTD	N/A	Referent	£16,433	£47,256	N/A

APPENDIX 16: Indicative probabilistic sensitivity analyses

As noted in the main text, for reasons of computational complexity we have executed the probabilistic sensitivity analysis for eight patient profiles. Due to the effects of non-decision variables, comparison of these results with those generated for the pooled patient profiles is highly challenging. Nonetheless, these analyses highlight that the deterministic and probabilistic results are broadly aligned (allowing for Monte Carlo error in all calculations).

Male, 65 years old, NYHA II, Ischemic etiology, QRS \geq 150ms, LVEF between 20 and 25%, no LBBB

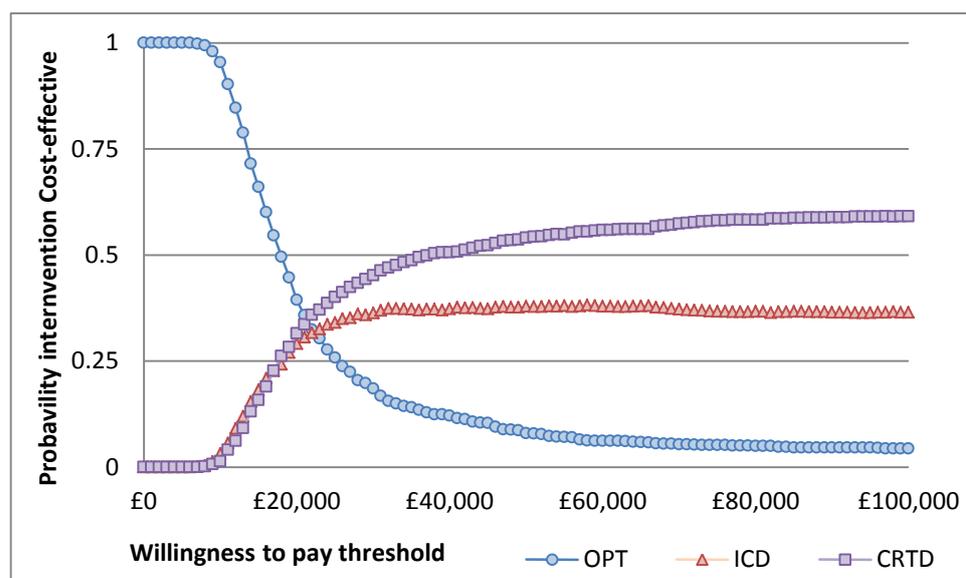
Table 38: Deterministic cost-effectiveness results for sample pt. #1

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£20,613	0.92	Extended Dominated
CRT-D	+£27,336	1.28	£21,330

Table 39: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #1

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£21,627 (£13,875, £32,277)	0.91 (-0.51, 2.22)	Extended Dominated
CRT-D	+£28,349 (£18,503, £42,817)	1.20 (-0.51, 2.73)	£23,604

Figure 48: Cost-effectiveness acceptability curves for sample pt. #1



Female, 65 years old, NYHA II, Ischemic etiology, QRS \geq 150ms, LVEF between 20 and 25%, no LBBB

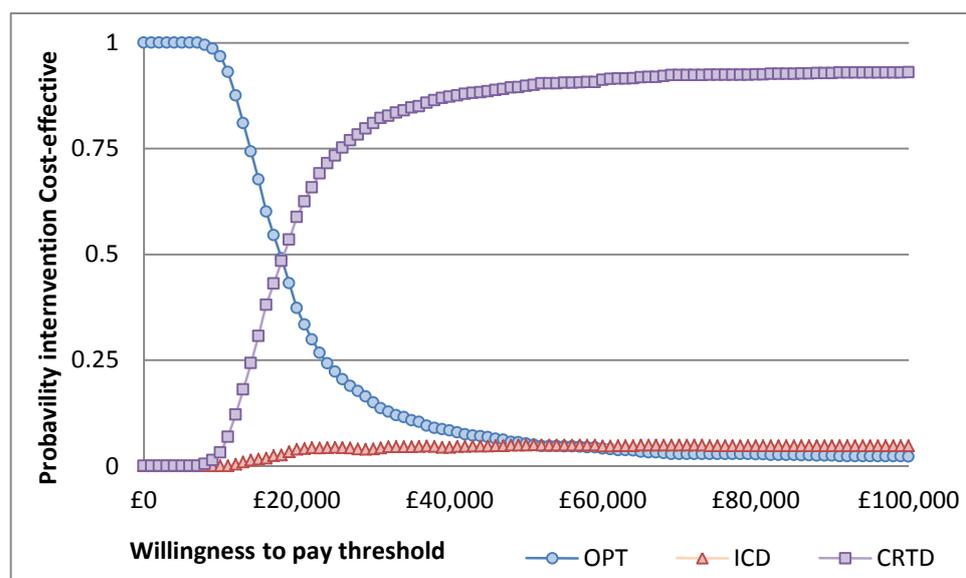
Table 40: Deterministic cost-effectiveness results for sample pt. #2

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	£19,736	0.23	Extended Dominated
CRT-D	£29,170	1.76	£16,565

Table 41: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #2

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	£20,640 (£13,032, £30,556)	0.21 (-1.12, 1.43)	Extended Dominated
CRT-D	£30,319 (£20,305, £44,275)	1.66 (0.20, 2.99)	£18,231

Figure 49: Cost-effectiveness acceptability curves for sample pt. #2



Male, 65 years old, NYHA II, Ischemic etiology, QRS ≥150ms, LVEF between 20 and 25%, with LBBB

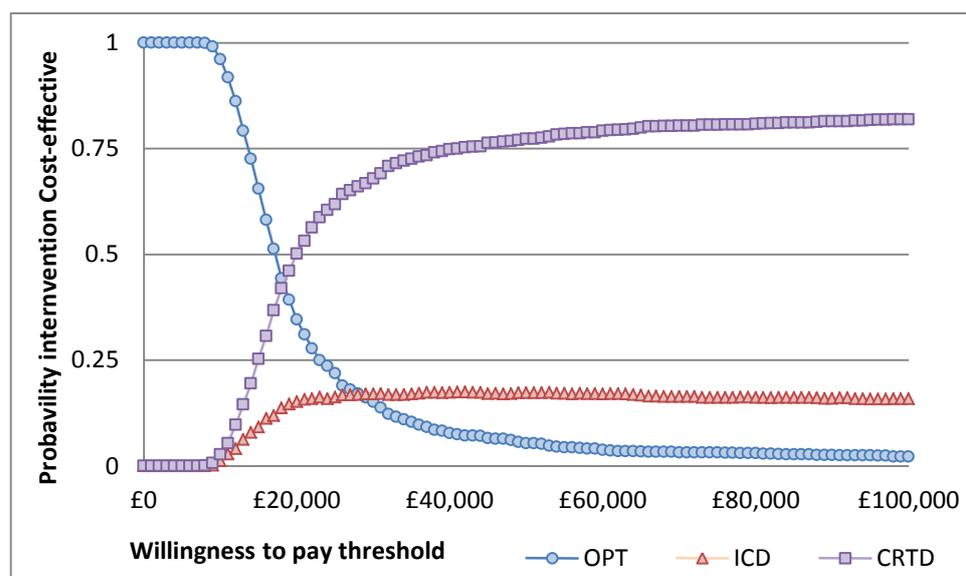
Table 42: Deterministic cost-effectiveness results for sample pt. #3

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	£20,242	0.74	Extended Dominated
CRT-D	£28,116	1.59	£17,645

Table 43: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #3

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£21,171 (£14,200, £31,123)	0.70 (-0.61, 1.98)	Extended Dominated
CRT-D	+£29,161 (£19,331, £43,339)	1.52 (0.08, 2.78)	£19,132

Figure 50: Cost-effectiveness acceptability curves for sample pt. #3



Female, 65 years old, NYHA II, Ischemic etiology, QRS \geq 150ms, LVEF between 20 and 25%, with LBBB

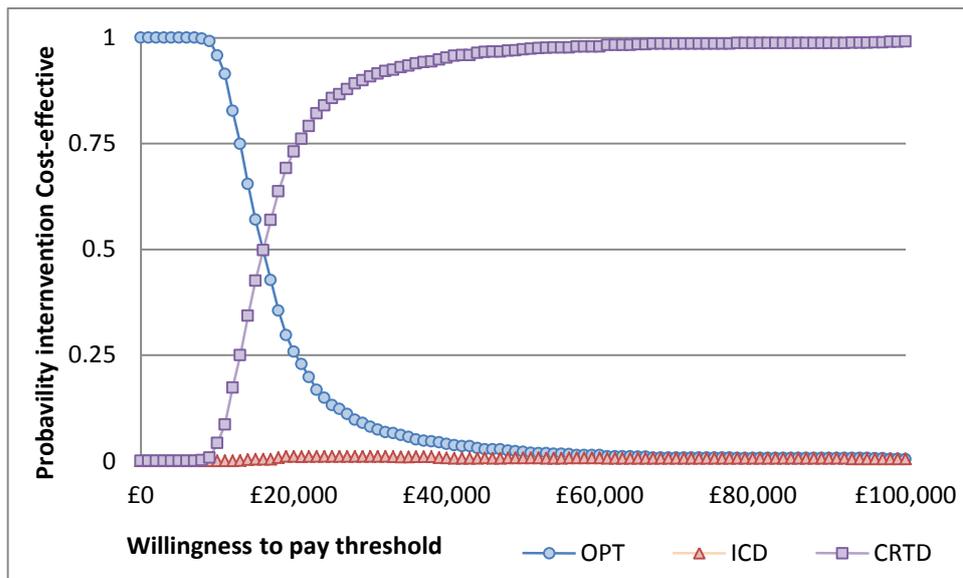
Table 44: Deterministic cost-effectiveness results for sample pt. #4

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	£19,342	0.06	Extended Dominated
CRT-D	£29,849	2.03	£14,718

Table 45: Probabilistic cost-effectiveness results (mean, 95% CI) for sample pt. #4

Intervention	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
OPT	+0.00	+0.00	
ICD	+£20,248 (£12,734, £30,594)	0.04 (-1.10, 1.22)	Extended Dominated
CRT-D	+£31,171 (£20,783, £45,263)	1.93 (0.56, 3.00)	£16,153

Figure 51: Cost-effectiveness acceptability curves for sample pt. #4



Dear Jeremy,

On behalf of Arrhythmia Alliance we would like to make the following statement in response to the above guidance review.

Arrhythmia Alliance is pleased that this seems to cover all of the patient groups that would benefit from the therapies and we feel that it will only benefit patients further by combining the guidance for ICD and CRT devices which they have done. The value placed on quality of life for those affected has been considered and there are no additional groups that we feel would be suitable for these treatment options. Perhaps our only point would be to emphasise the importance of primary prevention, ensuring screening for those who are at risk of arrhythmias that lead to SCA and may require an ICD/CRT device.

Please can you confirm receipt of this and if there is anything else that you require.

Many thanks

Yours sincerely,

■

Kind Regards,

■■■■■■■■■■ Head of Strategic Operations
Arrhythmia Alliance | Tel: +44 (0) 1789 451823 | Fax: +44 (0) 1789 450682 | PO Box 3697 | Stratford upon Avon | Warwickshire | CV37 8YL | England | www.heartrhythmcharity.org.uk

NATIONAL INSTITUTE FOR HEALTH
AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

**Implantable cardioverter defibrillators for
the treatment of arrhythmias and cardiac
resynchronisation therapy for the treatment
of heart failure (review of TA95 and TA120)**

Submission for:

Heart Rhythm UK

Prepared by:

██████████
████████████████████
██

Contents

Abbreviations	6
Clinical trial acronyms and principal publications	7
1) Executive summary	8
1.1) Implantable cardioverter defibrillators (ICDs)	8
Key points:.....	8
1.2) Cardiac resynchronisation therapy (CRT)	9
Key points:.....	9
1.3) Treatment delivery	9
1.4) Guidance Recommendations	10
2) Background information	11
2.1) Arrhythmias	11
2.2) Implantable cardioverter defibrillators (ICDs).....	11
2.3) Heart failure	11
2.4) Left ventricular ejection fraction	12
2.5) New York Heart Association functional class	13
2.6) Cardiac resynchronisation therapy (CRT)	13
2.7) Optimal pharmacological therapy (OPT)	14
2.8) Cardiac rhythm management device therapy	14
2.9) Cardiac conditions associated with heart failure and/or arrhythmias.....	15
Structural heart disease	15
2.9.1) Ischaemic heart disease.....	15
2.9.2) Non-ischaemic cardiomyopathy	15
2.9.3) Hypertrophic cardiomyopathy.....	16
2.9.4) Arrhythmogenic right ventricular cardiomyopathy.....	16
2.9.5) Left ventricular non-compaction	16
2.9.6) Congenital Heart Disease.....	16
No structural heart disease.....	17
2.9.7) Brugada syndrome.....	17
2.9.8) Long-QT syndromes	17
2.9.9) Short-QT syndrome.....	17
2.9.10) Catecholaminergic polymorphic ventricular tachycardia.....	17
2.9.11) Cardiac arrest without an identifiable aetiology	17
3) Healthcare professional perspective	18
3.1) What is the place of the technology in current practice?	18
3.2) The advantages and disadvantages of the technology	18

3.3) Additional sources of evidence.....	19
3.4) Implementation issues.....	19
4) Implantable cardioverter defibrillator therapy	20
4.1) Secondary prevention.....	20
4.1.1) Current national international guidance	20
4.1.1.1) UK.....	20
4.1.1.2) North America.....	21
4.1.1.3) European Society of Cardiology.....	21
4.1.2) Resuscitated cardiac arrest.....	22
4.1.2.1) Ischaemic heart disease.....	22
4.1.2.2) Non-ischaemic cardiomyopathy	23
4.1.2.3) Hypertrophic cardiomyopathy.....	23
4.1.2.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)	24
4.1.2.5) Left ventricular non-compaction	24
4.1.2.6) Congenital heart disease	24
4.1.2.7) Brugada syndrome.....	25
4.1.2.8) Long QT syndromes	26
4.1.2.9) Short QT syndrome	26
4.1.2.10) Catecholaminergic polymorphic ventricular tachycardia (CPVT).....	26
4.1.2.11) Ventricular arrhythmias of unknown aetiology.....	26
4.1.3) Syncope.....	26
4.1.3.1) Ischaemic heart disease.....	27
4.1.3.2) Non-ischaemic cardiomyopathy	27
4.1.3.3) Hypertrophic cardiomyopathy.....	28
4.1.3.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)	29
4.1.3.5) Left ventricular non-compaction	30
4.1.3.6) Congenital heart disease	30
4.1.3.7) Brugada syndrome.....	30
4.1.3.8) Long QT syndromes	31
4.1.3.9) Short QT syndromes	31
4.1.3.10) Catecholaminergic polymorphic ventricular tachycardia.....	31
4.1.3.11) Ventricular tachycardia without haemodynamic compromise.....	31
4.2) Primary prevention	33
4.2.1) Current national and international guidance	33
4.2.1.1) UK.....	33
4.2.1.2) North America.....	33

4.2.1.3) European Society of Cardiology	34
4.2.2) Published evidence	35
4.2.2.1) Ischaemic heart disease	35
4.2.2.2) Non-ischaemic cardiomyopathy	40
4.2.2.2.1) CAT	40
4.2.2.2.2) AMIOVERT	40
4.2.2.2.3) DEFINITE	40
4.2.2.2.4) SCD-HeFT	41
4.2.2.3) Hypertrophic cardiomyopathy (HCM)	42
4.2.2.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)	42
4.2.2.5) Left ventricular non-compaction	43
4.2.2.6) Congenital heart disease	43
4.2.2.7) Long QT syndromes	44
4.2.2.8) Short QT syndromes	45
4.2.2.9) Brugada syndrome	45
4.2.2.10) Catecholaminergic polymorphic ventricular tachycardia (CPVT)	45
4.2.2.11) Patients awaiting cardiac transplantation	46
4.2.2.12) Children, adolescents and adults with congenital heart disease	46
5) Cardiac resynchronisation therapy	47
5.1) Current national and international guidance	47
5.1.1) UK	47
5.1.2) North America	47
5.1.3) European Society of Cardiology	48
5.2) Published data	50
5.2.1) Left ventricular function	50
5.2.2) Dys-synchrony	50
5.2.2.1) QRS <120ms	51
5.2.2.2) QRS ≥120ms	51
Mechanical dyssynchrony	52
QRS duration and morphology	54
5.2.3) Symptoms	55
5.2.3.1) NYHA class I	55
5.2.3.2) NYHA class II	56
5.2.3.3) NYHA class III	56
5.2.3.4) NYHA class IV	57
5.2.4) QRS prolongation due to right ventricular pacing	58

Heart Rhythm UK

5.2.5) Patients with heart failure and an indication for bradycardia pacing.....	58
5.2.6) Atrial fibrillation	59
5.2.7) Conclusions	59
6) Contraindications to device therapy.....	61
6.1) sepsis.....	61
6.2) coagulopathy	61
6.3) life-expectancy.....	61
6.4) NYHA IV for ICD.....	62
6.5) Incessant or frequent ventricular tachycardia or ventricular fibrillation	62
6.6) Ventricular tachycardia in the presence of normal cardiac function	63
7) Other sections.....	64
7.1) Patient choice	64
7.2) End of life care	64
7.3) National data collection.....	64
7.4) Reassessment.....	64
7.6) Implantation and follow-up	65
8) Conclusions	66
8.1) Evolution of guidance on the use of ICD and CRT	66
8.2) Key points in the current analysis.....	66
8.2) Summary recommendations	68
References.....	69

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AF	atrial fibrillation
ARVC	arrhythmogenic right ventricular cardiomyopathy
AVJ	atrio-ventricular junction (node)
BHF	British Heart Foundation
CASQ2	cardiac caldesmon gene 2
cMR	cardiac magnetic resonance imaging
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRT	cardiac resynchronisation therapy
CRT-D	implantable cardioverter defibrillator delivering cardiac resynchronisation therapy
CRT-P	pacemaker delivering cardiac resynchronisation therapy
DCM	dilated cardiomyopathy
ECG	electrocardiogram
EF	ejection fraction
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
HF	heart failure
HRS	Heart Rhythm Society
ICD	implantable cardioverter defibrillator
IHD	ischaemic heart disease
LBBB	left bundle branch block
LQTS	long QT syndrome
LV	left ventricle
LVEF	left ventricular ejection fraction
LVNC	non-compaction of the left ventricle
MI	myocardial infarction
MuGA	multi-gated acquisition (scan)
NICM	non-ischaemic cardiomyopathy
NYHA	New York Heart Association (functional class)
ms	millisecond
OPT	optimal pharmacological (medical) therapy
QT	ECG interval between first deflection of the QRS complex and end of the T wave
QTc	QT interval corrected for heart rate
RBBB	right bundle branch block
RYR2	cardiac ryanodine receptor gene 2
SCD	sudden cardiac death
SICD	subcutaneous implantable cardioverter defibrillator
SPECT	single photon emission computed tomography (scan)
TdP	torsades de pointes
TGA	transposition of the great arteries
ToF	tetralogy of Fallot
VF	ventricular fibrillation
VT	ventricular tachycardia

Clinical trial acronyms and principal publications

Acronym	Trial name	Abbreviated reference
AMIOVERT	Amiodarone Versus Implantable Cardioverter-Defibrillator	<i>J Am Coll Cardiol</i> 2003; 41 :1707–12
AVID	Antiarrhythmics Versus Implantable Defibrillators	<i>N Engl J Med</i> 1997; 337 :1576-83
CABG-Patch	Coronary Artery Bypass Graft Patch	<i>N Engl J Med</i> 1997; 337 :1569-75
CARE-HF	Cardiac Resynchronization Heart Failure	<i>N Engl J Med</i> 2005; 352 :1539-49.
CASH	Cardiac Arrest Study Hamburg	<i>Circulation</i> 2000; 102 :748-754
CAT	Cardiomyopathy Trial	<i>Circulation</i> 2002, 105 :1453-1458
CIDS	Canadian Implantable Defibrillator Study	<i>Circulation</i> 2000; 101 :1660-1664
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure	<i>N Engl J Med</i> 2004; 350 :2140-50
CONTAK-CD	Boston Scientific device name	<i>J Am Coll Cardiol</i> 2003; 42 :1454–9
DEFINITE	Defibrillators in Non-Ischaemic cardiomyopathy Treatment Evaluation	<i>Circulation</i> 2006; 113 :776-782
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial	<i>N Engl J Med</i> 2004; 351 :2481-8
HOBIPACE	Homburg Biventricular Pacing Evaluation	<i>J Am Coll Cardiol</i> 2006; 47 :1927–37
MADIT	Multicenter Automatic Defibrillator Implantation Trial	<i>N Engl J Med</i> 1996; 335 :1933-40
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II	<i>N Engl J Med</i> 2002; 346 :877-83
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial Cardiac Resynchronization Trial	<i>N Engl J Med</i> 2009; 361 :1329-38
MIRACLE ICD	Multicenter InSync ICD Randomized Clinical Evaluation	<i>JAMA</i> 2003; 289 :2685-2694
MOST	Mode Selection Trial	<i>Circulation</i> 2003; 107 :2932–7
MUSTIC	Multicenter InSync Randomized Clinical Evaluation	<i>N Engl J Med</i> 2002; 346 :1845-53
MUSTT	Multicenter UnSustained Tachycardia Trial	<i>J Am Coll Cardiol</i> 2001; 38 :344 –51
PROSPECT	Predictors of Response to CRT	<i>Circulation</i> 2008; 117 :2608-2616
RAFT	Resynchronization–Defibrillation for Ambulatory Heart Failure Trial	<i>N Engl J Med</i> 2010; 363 :2385-95
RethinQ	Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS trial	<i>N Engl J Med</i> 2007; 357 :2461-71
REVERSE	REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction	<i>J Am Coll Cardiol</i> 2008; 52 :1834–43
SCD-HeFT	Sudden Cardiac Death Heart Failure Trial	<i>N Engl J Med</i> 2005; 352 :225-37

1) Executive summary

This appraisal concerns implanted devices which deliver electrical therapy to the heart to treat life-threatening heart rhythm disorders (implantable cardioverter defibrillators, ICDs) and/or dyssynchrony of cardiac contraction (cardiac resynchronisation therapy, CRT). A single device can deliver either or both of these therapies. The therapies have different indications, but the indications are often present in the same individuals so it is appropriate to consider the technologies together in a single appraisal process. This mirrors clinical decision making where a choice is first made between continuing medical therapy and device implantation and then between treatment modalities. Since the publication of NICE guidance covering ICDs in 2006 and CRT in 2007, further trial data, meta-analyses and international guidance have been published making it appropriate to revise and combine this guidance. All patients should receive optimal pharmacological therapy – any device should be considered as an addition to this. Contraindications to device therapy should also be assessed. Patients should have their condition and treatment options clearly explained in order to make a fully informed decision.

1.1) Implantable cardioverter defibrillators (ICDs)

ICDs monitor and treat ventricular arrhythmias automatically within seconds. They are used in patients who have survived a cardiac arrest because of the high risk of recurrence (secondary prevention), and in patients at high risk of sudden cardiac death but who may have no history of ventricular arrhythmia (primary prevention). The majority of ICD patients have structural heart disease due to myocardial infarction or cardiomyopathy, a much smaller number have primary inherited electrical abnormalities. The pivotal clinical trials of ICD therapy in secondary prevention were conducted in the 1990s with more recent clinical trials in primary prevention. Increasing data from rarer conditions have subsequently become available.

Key points:

- ICD therapy is superior to medical therapy for patients surviving a cardiac arrest or spontaneous sustained ventricular arrhythmia with haemodynamic compromise – it is considered unethical to perform further clinical trials in this population.
- Syncope has been shown to be prognostically equivalent to spontaneous recovery from a cardiac arrest or spontaneous ventricular arrhythmia with haemodynamic compromise in high-risk individuals.
- The cause of cardiomyopathy – ischaemic or non-ischaemic – does not significantly influence the effectiveness of ICD therapy and these should be regarded as equivalent indications.
- Left ventricular function is a significant predictor of risk. Other stratifiers including non-sustained ventricular tachycardia, ventricular tachycardia induced by programmed electrical stimulation and QRS duration have limited sensitivity or specificity to predict those who will and will not benefit from ICD implantation.
- Measurement of left ventricular ejection fraction is imprecise. Currently available measurement techniques require estimation of left ventricular volumes and have inherent uncertainty. Although clinical trials used a variety of LVEF levels as inclusion criteria, the patients randomised in the major clinical trials had relatively uniform LVEF estimates. For these reasons, we advocate the adoption of a single threshold of severe left ventricular systolic impairment equivalent to an LVEF of $\leq 35\%$.

- There are rare conditions associated with sudden cardiac death for which there is no prospect of a randomised controlled trial of ICD therapy. In these situations the best available data and clinical judgement should be used to inform treatment decisions.

1.2) Cardiac resynchronisation therapy (CRT)

The implantation of a CRT device, which stimulates contraction of the left and right ventricles, can significantly improve electrical synchronisation, reducing heart failure symptoms and all-cause mortality. Recent trials have shown benefit in patients with mild heart failure symptoms.

Key points:

- Patients with severe left ventricular impairment (LVEF $\leq 35\%$), evidence of dyssynchrony on ECG (QRS ≥ 120 ms) and heart failure symptoms despite optimal pharmacological therapy benefit from CRT with improved symptoms, reduced hospitalisation and reduced all-cause mortality.
- Other measures of mechanical dyssynchrony have not shown sufficient sensitivity and specificity to be clinically useful in the identification of patients who will benefit from CRT.
- The full benefit of CRT is achieved in those receiving a high proportion of biventricular pacing – for patients in atrial fibrillation this may require pharmacological or ablation therapy to induce atrioventricular block.

1.3) Treatment delivery

To achieve the clinical and cost-effectiveness outcomes demonstrated in clinical trials requires a high quality, efficient assessment, implantation and follow-up service. The patients who benefit from ICD and/or CRT treatment often have complex medical conditions with multiple co-morbidities and are implanted with complex devices which require highly specialised programming. Much device follow-up can now be achieved through remote internet-based data transfer, reducing the burden of travel on patients and their carers. Heart Rhythm UK recommends that device implantation and follow-up should be performed by high-volume operators in appropriately resourced high-volume centres.

Access to ICD and CRT therapy is low and uneven across the UK compared to other developed countries. This is caused by differences in ascertainment, differences in assessment and the complexity of current UK and international guidance. The exclusion of non-ischaemic cardiomyopathy from previous NICE guidance has contributed to differences in practice across the UK. It is important to develop guidance which is clear, memorable and efficient to deliver. Clinical trial protocols are developed to test specific hypotheses. The direct adoption of their inclusion and exclusion criteria into guidance would lead to complex and potentially contradictory treatment indications. We recommend a pragmatic approach, taking the best available evidence as a whole to produce clear, workable guidance to improve access to evidence-based treatments equitably across the UK.

1.4) Guidance Recommendations

Based on the currently available data, we recommend that patients on optimal pharmacological therapy, in the absence of a fully reversible cause (including an arrhythmia which can be prevented by ablation therapy), with expectation of life expectancy of ≥ 1 year and with a quality of life acceptable to the patient:

Patients with LVEF $\leq 35\%$ (regardless of aetiology) should routinely be considered for a device based on their symptoms (NYHA functional class) and QRS duration:

	NYHA I	NYHA II	NYHA III	ambulant NYHA IV
QRS $< 120\text{ms}$	ICD	ICD	ICD	OPT
120-149 no LBBB	ICD	ICD	CRT-D	CRT-D
120-149 + LBBB	CRT-D	CRT-D	CRT-D	CRT-D
$\geq 150\text{ms}$	CRT-D	CRT-D	CRT-D	CRT-D

CRT-P (pacemaker) implantation should be offered in place of CRT-D (defibrillator) when ICD therapy is contraindicated or declined by the patient.

1) **Patients with LVEF $> 35\%$** (without NYHA IV symptoms):

- with spontaneous sustained ventricular arrhythmias
- or**
- with inherited conditions with high risk features for sudden cardiac death according to the best available evidence

should routinely be considered for: ICD

2) ICD implantation should not be performed within 4 weeks of a myocardial infarction or revascularisation unless the patient has a secondary prevention indication.

2) Background information

2.1) Arrhythmias

The heart is a muscular pump controlled by specialised electrical tissues. Normal heart function requires optimal electrical coordination of contraction. Any abnormal cardiac rhythm, or arrhythmia, which disturbs normal physiological sinus rhythm, reduces cardiac efficiency. Arrhythmias arising in the ventricles, ventricular tachycardia (VT) and ventricular fibrillation (VF), can result in insufficient blood being pumped by the heart to sustain life. This is the mechanism of over 80% of sudden cardiac deaths, killing 90,000 people in the UK each year. The most common risk factor for sudden cardiac death is ischaemic heart disease but other causes of reduced cardiac function such as cardiomyopathy also increase this risk. There are also many rare inherited conditions which increase the risk of ventricular arrhythmias and sudden death, particularly in younger people.

The most effective way to prevent cardiac arrhythmias is to treat the underlying heart condition with medications and other interventions. Prevention is an essential part of every patient's management, but the only effective treatment once a life-threatening ventricular arrhythmia has occurred is electrical defibrillation. This can be performed with an external defibrillator but unfortunately, because of the short time before irreversible brain damage occurs, only 5% of people survive a cardiac arrest outside a hospital. The alternative is implantation of an automatic device, an implantable cardioverter defibrillator (ICD).

2.2) Implantable cardioverter defibrillators (ICDs)

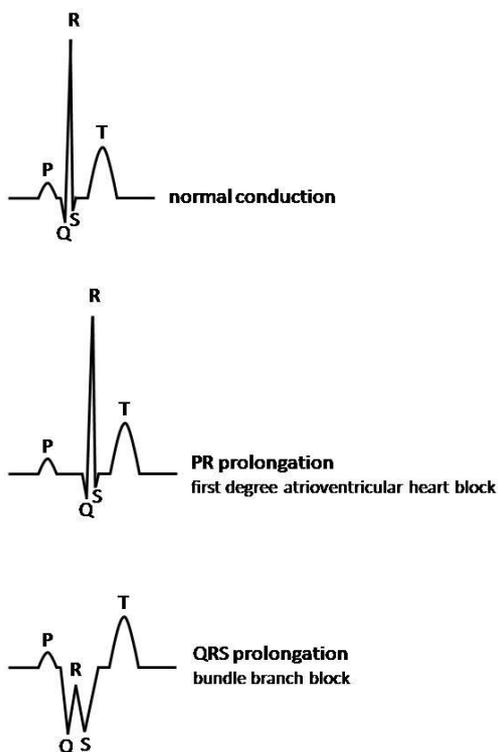
An ICD is an electronic device implanted in a patient at increased risk of life-threatening arrhythmias. It monitors cardiac rhythm continuously and automatically delivers therapy in the form of rapid low-voltage pacing and/or high voltage defibrillation shocks within a few seconds of a dangerous ventricular arrhythmia being detected. Most devices implanted in the UK comprise one or more leads placed transvenously in the heart and connected to a device implanted beneath the skin of the chest. These devices are all capable of pacing functions to treat slow heart rhythms (bradycardia). This technology is recommended in NICE technology appraisal 95 which states that ICD implantation is indicated for primary (no previous cardiac arrest or ventricular arrhythmia with haemodynamic compromise) and secondary (resuscitated cardiac arrest or ventricular arrhythmia with haemodynamic compromise) prevention. A recently developed subcutaneous ICD (SICD) is able to detect arrhythmias and deliver defibrillation using a lead which is placed under the skin of the chest but does not enter the heart. SICDs represent an alternative method of delivering ICD therapy. This assessment examines indications for therapy rather than methods of delivering therapy. The SICD is being considered by the Interventional Procedures Advisory Committee (IPAC - <http://guidance.nice.org.uk/IP/1012>).

2.3) Heart failure

Heart failure is a complex syndrome of signs and symptoms which results from the heart's inability to supply the circulatory requirements of the body. Heart failure is common, affecting around 900,000 people in the UK with almost as many again having asymptomatic left ventricular dysfunction. The incidence and prevalence of heart failure increase steeply with age, so our ageing population, improvements in the survival of people with ischaemic heart disease and more effective medical and interventional treatments, mean that the number of people affected will

continue to increase. Heart failure has a worse prognosis than many cancers, with up to 40% of patients dying within a year of diagnosis, and a greater effect on quality of life than many other chronic diseases such as chronic lung disease and arthritis. Most heart failure is caused by structural heart disease resulting from ischaemic or non-ischaemic cardiomyopathy. Heart failure also occurs in patients with preserved ejection fraction. These patients have not been shown to benefit from device therapy and are not included in the remit of this document. The medical management of heart failure in adults in primary and secondary care is described in the NICE National Clinical Guideline Centre (2010) Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. London: National Clinical Guideline Centre (<http://guidance.nice.org.uk/CG108/Guidance/pdf/English>).

People with normal cardiac function have considerable cardiovascular reserve and can tolerate significant physiological and pathological cardiovascular stresses. People with reduced cardiac function have greatly reduced reserve. Anything which reduces cardiac efficiency further can have a dramatic effect on their symptoms and quality of life. Approximately 30% of patients with heart failure due to left ventricular systolic dysfunction have sub-optimal coordination of heart contraction. This is described as atrio-ventricular and/or intra-ventricular dyssynchrony which is seen on the 12-lead ECG as a prolonged PR interval and/or increased QRS complex duration:



2.4) Left ventricular ejection fraction

The left ventricular ejection fraction (LVEF) represents the proportion of blood expelled by the left ventricle during systolic contraction. It was originally developed as an estimate of cardiac function and was derived from contrast ventriculography. It is now most commonly estimated from echocardiography although nuclear scans (multi-gated acquisition, MuGA, and SPECT) and cardiac magnetic resonance imaging (cMR) are alternatives. Each of these modalities has its limitations and sources of error. Because of these differences, a patient undergoing LVEF estimation by different modalities will have different estimates. Equally, it must be recognised that LVEF is not

fixed but varies with loading conditions, biochemical and neuro-hormonal status. Nevertheless, multiple invasive and non-invasive risk stratifiers have been developed and used in clinical trials but none has surpassed LVEF as a predictor of sudden cardiac death.

Clinical trials have adopted a variety of LVEF inclusion criteria: MUSTT used LVEF $\leq 40\%$ although the median ejection fraction of randomised patients was 30% with a range of 20 to 35%. Most other trials adopted $\leq 35\%$ although MADIT II used $\leq 30\%$ resulting in a mean of $25 \pm 5\%$ in the ICD treated group. As current North American device guidance states, “the determination of LVEF lacks a “gold standard” and ... there may be variation among the commonly used clinical techniques. All clinical methods of LVEF determination lack precision, and the accuracy of techniques varies amongst laboratories and institutions”. Heart Rhythm UK recommends the adoption of “severely impaired” as the most clinically appropriate criterion for increased risk of sudden cardiac death and likely benefit from CRT. This is internationally defined by echocardiography as an LVEF of $\leq 35\%$ (Lang *et al. J Am Soc Echocardiogr* 2005;**18**:1440–1463) and is consistent with the majority of published cardiac rhythm management device trial data.

2.5) New York Heart Association functional class

The current classification of heart failure symptoms was first proposed by the New York Association of Cardiac Clinics and published by White and Myers in 1921 (*JAMA* 1921;**77**:1414-1415). It evolved with increasing cardiovascular knowledge into the New York Heart Association functional classification. The currently accepted definitions were published by the Criteria Committee of the New York Heart Association in Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Edition Boston, Mass: Little, Brown & Co; 1994:253-256.

Functional Capacity Objective Assessment	
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Despite the day-to-day variability in patients’ symptoms and the subjective nature of some of the assessments, NYHA functional class has proven to be robust in its clinical utility and prognostic accuracy. It remains the best assessment of functional capacity available in heart failure patients.

2.6) Cardiac resynchronisation therapy (CRT)

Conventional bradycardia pacemakers comprise leads connecting the right atrium and/or ventricle to a computerised device implanted beneath the skin of the chest. They monitor heart rhythm continuously and deliver electrical stimulation to induce myocardial contraction when the heart falls below a pre-specified rate or ventricular contraction does not follow atrial contraction after a

pre-specified interval. In this way, they can prevent bradycardia and restore synchronisation between atrial and ventricular contraction.

In heart failure patients with abnormal electrical conduction, synchronisation can be improved by the implantation of a device which can sense and stimulate the right atrium and/or ventricle as in a conventional pacemaker but with the addition of a lead directly pacing the left ventricle. This is usually placed in a branch of the coronary sinus, the vein draining blood from the muscle of the left ventricle into the right atrium. This CRT functionality can be added to a pacemaker (CRT-P) or an ICD (CRT-D) and can improve cardiac function and reduce heart failure symptoms.

2.7) Optimal pharmacological therapy (OPT)

There is excellent evidence for the efficacy of medical treatments in reducing mortality and improving quality of life for patients with cardiovascular disease:

- Chronic heart failure (CG108)
- Hypertension (CG127)
- Hypertension in pregnancy (CG107)
- Atrial fibrillation (CG36)
- Stable angina (CG126)
- Chest pain of recent onset (CG95)
- Unstable angina and NSTEMI (CG94)
- MI: secondary prevention (CG48)
- Lipid modification (CG67)
- Familial hypercholesterolaemia (CG71)
- Stroke (CG68)

Optimal pharmacological therapy (OPT) is the corner stone of the treatment of these conditions and should be received by all patients.

2.8) Cardiac rhythm management device therapy

When assessing whether a patient would benefit from the implantation of an ICD or CRT device, clinicians assess the risk of a life-threatening ventricular arrhythmia and also the likelihood of symptomatic and prognostic benefit from CRT. This is a complex process as these indications overlap very considerably, either or both functions can be combined in a single device and patient wishes regarding the practical aspects of the procedure and long-term effects are paramount.

For people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment, the treatment decision is between cardiac resynchronisation therapy (CRT) with OPT against OPT alone. CRT may be delivered as a CRT-P (pacemaker) or CRT-D (defibrillator) depending on whether or not the patient has an additional requirement for ICD therapy.

For people at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment, the treatment decision is between a defibrillator with OPT against OPT alone. Defibrillator therapy may be delivered as ICD or CRT-D depending on whether or not the patient has a requirement for CRT.

We recommend that the clearest way to define the populations and their comparators is in a 2x2 matrix:

	People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment (OPT)	People without an increased risk of sudden cardiac death
People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment (OPT)	Intervention: CRT-D + OPT [Comparator: OPT alone]	Intervention: CRT-P + OPT [Comparator: OPT alone]
People without heart failure	Intervention: ICD + OPT [Comparator: OPT alone]	Intervention: OPT alone

2.9) Cardiac conditions associated with heart failure and/or arrhythmias

The conditions in which cardiac rhythm management device implantation may be appropriate can be divided into those associated with structural abnormalities and those where the heart appears structurally and functionally normal.

Structural heart disease

2.9.1) Ischaemic heart disease

Ischaemic heart disease (IHD) is the commonest cause of cardiovascular morbidity and mortality in the UK. Coronary artery atheroma results in acute and chronic shortage of blood to the myocytes which constitute the muscle of the heart. This ischaemia can result in loss of myocytes, reduced muscular contractility and heart failure. Ischaemia and myocardial scar also increase the electrical instability of the myocardium and can trigger arrhythmias.

2.9.2) Non-ischaemic cardiomyopathy

A small proportion of patients with reduced myocardial function have a primary abnormality of myocytes, a cardiomyopathy. Non-ischaemic cardiomyopathy (NICM) encompasses a

heterogeneous group of conditions unified only by the absence of myocardial ischaemia as its aetiology. NICM has many causes including haemodynamic stress, infection, immunologically mediated inflammation and the direct effects of toxins. Genetic factors are increasingly recognised to underlie the predisposition to the development of the cardiomyopathy phenotype but our knowledge of the genes involved and their specific actions remains at an early stage.

2.9.3) Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the commonest inherited structural heart disease affecting approximately 1 in 500 people. It is usually inherited as an autosomal dominant trait with variable clinical penetrance and expression, as a mutation in genes encoding cardiac sarcomeric proteins. HCM is characterised by hypertrophy, thickening of the myocardium of the left ventricle, typically affecting the interventricular septum, in the absence of pressure overload, infiltration or storage disease. Myocyte and myofibril disarray with myocardial fibrosis are thought to form the substrate for ventricular arrhythmias. The diagnosis is usually made on echocardiography, although cardiac magnetic resonance imaging with late gadolinium enhancement is increasingly being used because of its sensitivity and specificity. The clinical course in HCM is highly variable between individuals. Most patients have a normal life expectancy with few symptoms but all patients should be followed up and assessed for their risk of sudden cardiac death as HCM is the commonest cause of cardiac arrest in people under the age of 40-years.

2.9.4) Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart muscle disorder characterised by fibro-fatty replacement of the ventricular myocardium. Diagnosis is often difficult, especially in the early stages of the disease (Marcus *et al. European Heart J* 2010;**31**:806-814). Inheritance is autosomal dominant although recessive forms are recognised. To date, seven genes have been characterised with genetic mutations in the desmosomes responsible for cell-to-cell binding. It is associated with an increased risk of sudden cardiac death due to ventricular arrhythmias.

2.9.5) Left ventricular non-compaction

Non-compaction of the left ventricular myocardium (LVNC) is a rare inherited cardiomyopathy characterised by prominent trabeculation of the left ventricle without impairment of systolic function due to arrest in the compaction process during the first trimester of inter-uterine life. It is a genetically inherited condition with autosomal dominant or X-linked transmission. It is associated with heart failure, arrhythmias, sudden cardiac death and systemic embolic events. Sudden cardiac death is the most common cause of mortality and is attributed to complex ventricular arrhythmias.

2.9.6) Congenital Heart Disease

Congenital heart disease represents a broad range of inherited structural cardiac abnormalities which together represent the commonest form of birth defect, affecting 1 in 125 babies. There have been remarkable advances in the diagnosis and treatment of these conditions over the past 50 years and most children now live into adulthood with excellent quality of life. However, sudden cardiac deaths due to brady- and/or tachy-arrhythmias account for 15-26% of deaths after the initial surgical post-operative period and patients should be assessed for these risks.

No structural heart disease

2.9.7) Brugada syndrome

Since its first description in 1992 as a pattern of abnormal repolarisation on the ECG, usually in leads V1-V3, without structural heart disease, Brugada syndrome has been associated with sudden cardiac death, typically at rest or during sleep. More than 100 mutations in seven different genes have now been found to be associated with Brugada syndrome which is usually inherited in an autosomal dominant pattern and affects approximately 5 per 10,000 of the population.

2.9.8) Long-QT syndromes

The inherited long QT syndromes are characterised by prolonged QT intervals on the ECG, syncope and sudden cardiac death due to ventricular arrhythmias – characteristically the polymorphic ventricular tachycardia, torsades de pointes. Many mutations in cardiac ion channels and membrane proteins have been reported in LQTS which is now classified into at least ten subtypes.

2.9.9) Short-QT syndrome

Short QT syndrome is a very rare abnormality of cardiac ion channels. It is inherited in an autosomal dominant fashion and is associated with sudden cardiac death. The ECG is characterized by a short QT interval (usually <320 ms) and tall, peaked, narrow-based T waves. Gain-of-function mutations have been found in 3 genes encoding potassium channels.

2.9.10) Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited arrhythmia syndrome, characterised by polymorphic ventricular tachycardia induced by adrenergic stress. CPVT is associated mutations the cardiac ryanodine receptor gene (RYR2) or mutations in the cardiac calsequestrin gene CASQ2. Patients with CPVT often present with syncope induced by exercise or emotion although its first presentation can also be with sudden cardiac death.

2.9.11) Cardiac arrest without an identifiable aetiology

Despite the advances in our understanding of cardiac arrhythmias in recent decades, there remain patients with clinically significant ventricular arrhythmias which cannot be classified into any known disease entity. In the absence of a structural or biochemical target for preventative therapy, the only form of treatment available to prevent sudden cardiac death is the implantation of an ICD.

3) Healthcare professional perspective

There are many healthcare professionals involved in the identification, treatment and follow-up of patients with indications for ICD and CRT therapy. Primary and secondary care physicians identify and treat patients with heart failure and increased risk of sudden cardiac death. Identification of these patients is essential to the delivery of evidence-based care and lack of awareness and complex selection criteria contribute to inequity of access. Cardiologists specialising in electrophysiology, device therapy or heart failure are those primarily responsible for determining whether device therapy is indicated, implanting the devices and providing specialist clinical follow-up. Heart failure nurses play a major part in the follow-up of heart failure patients, particularly in the community. Device programming and follow-up is largely provided by highly specialised physiologists in the UK. Long-term coordination of these healthcare professionals throughout the patient journey is essential for optimal care.

3.1) What is the place of the technology in current practice?

Cardiology practice has developed very rapidly in the past 20 years. In the field of heart rhythm management, drug therapy remains important in the treatment of underlying heart disease, but multiple trials have shown that so-called anti-arrhythmic drugs may alleviate symptoms but do not improve prognosis. The only effective treatment for life-threatening arrhythmias is the implantation of an ICD. These devices have become safer to implant, more reliable, more sophisticated in avoiding unnecessary therapy and now have significantly improved battery life. Indications for their implantation have evolved from purely secondary prevention after a resuscitated cardiac arrest, to include primary prevention in those at high risk of sudden cardiac death. Simple assessment based on LVEF and underlying cardiac disease can predict those who benefit from ICD implantation. CRT has revolutionised the treatment of severe heart failure in those with dyssynchrony. Again, simple assessment based on LVEF and the duration of the QRS complex on the standard 12-lead ECG can predict those who are likely to benefit.

In the UK, implantation rates are increasing, but remain well-below rates in Western Europe or North America. Analysis of the National Devices Database (www.devicesurvey.com) and other audits show that access to device therapy is not uniform across the UK and suggest that failure to identify patients suitable for device therapy is responsible for this disparity. A simplification of indications and investigations in line with trial evidence and international guidelines would reduce this inequity of access.

3.2) The advantages and disadvantages of the technology

In selected patients, ICD implantation reduces the risk of death while CRT implantation reduces the burden of heart failure symptoms and mortality. The disadvantages of the technology are the discomfort and risk of the implantation procedure, its complications, the burden of regular device follow-up and social effects including restriction of driving. These have been assessed in the clinical trial dataset and the benefits of device therapy remain significant and sustained. Adverse events can be minimised by appropriate patient selection, highly competent implantation and follow-up services using remote technologies. The identification of an increased risk of sudden cardiac death, ICD implantation and subsequent therapy can adversely affect quality of life and psychological well-being. All centres implanting and following-up ICD and CRT patients should provide psychological assessment and support whenever necessary. Current UK practice has become significantly more efficient since the publication of the pivotal clinical trials – patients wait

less long for treatment and have shorter admissions to hospital for device implantation. Devices have also become more reliable with longer battery life, improving cost-effectiveness.

3.3) Additional sources of evidence

By the nature of clinical trial publications, they refer to selected populations and previous generations of devices. It is important to include contemporaneous UK data. We are fortunate to have analyses from UK national data collection. The Pacemaker and ICD database has collected data from all implanting centres and increasingly detailed annual reports have been published (www.devicesurvey.com). This has revealed incremental increases in implantation rates but these remain far below those in other developed countries. We have also found great differences in rates between adjacent areas of the UK emphasising the importance of referral from non-specialists and the role of clear national guidance.

Because the lifetime cost of ICD therapy is highly sensitive to device longevity, we would suggest that the characteristics of currently implanted devices should be used in cost effectiveness modelling, rather than historical data from devices with previous generations of battery technology.

Further data relating to device therapy in the UK may become available during the appraisal process.

3.4) Implementation issues

To achieve equity of access to ICD and CRT therapy will require changes in practice and an increase in device implantation, particularly in low implanting areas. Any increase in ICD and/or CRT implantation and follow-up will clearly have cost and logistical implications. The NHS has proved highly capable of increasing capacity in response to demand for device therapy and delivering this within shortened waiting-time targets. Implantation and follow-up resources have not limited access to treatment and this is not anticipated in the future. For clinical governance and efficiency reasons, Heart Rhythm UK recommends ICD and CRT device implantation by high-volume operators working in high-volume centres. As was seen with previous NICE guidance, increases in implantation rates will occur progressively rather than suddenly. This will minimise the impact on commissioning and service delivery.

4) Implantable cardioverter defibrillator therapy

Since the introduction into routine clinical practice of the ICD in the 1980s and CRT in the 1990s, these technologies have been tested in multiple clinical trials and used clinically in millions of patients. The technologies, and the evidence to support their use, continue to improve. Here we present a summary of the available evidence.

ICD therapy is the delivery of rapid ventricular pacing or a defibrillation shock to treat potentially lethal ventricular arrhythmias. The implantation of a device after a patient has survived a malignant ventricular arrhythmia is classified as secondary prevention. This is often after a resuscitated cardiac arrest or recorded sustained ventricular arrhythmia but this recording may be absent if the arrhythmia terminated spontaneously. Primary prevention in this context requires the implantation of an ICD into people at high risk of sudden cardiac death but who are not known to have suffered a malignant ventricular arrhythmia.

4.1) Secondary prevention

Cardiac arrest outside a hospital environment carries a high mortality - only 1 in 20 patients survive to leave hospital in the UK. The commonest cause is acute myocardial infarction and the availability of immediate external defibrillation is one of the major benefits of early medical intervention. Cardiac arrest which occurs without a clear reversible cause, such as acute myocardial infarction or extreme biochemical derangement, has a high risk of recurrence resulting in sudden death. These patients have been shown to benefit from the implantation of an ICD for secondary prevention.

4.1.1) Current national international guidance

4.1.1.1) UK

Current NICE guidance (Technology Appraisal 95: Implantable cardioverter defibrillators for arrhythmias, January 2006 www.nice.org.uk/TA095) states:

1.1 ICDs are recommended for patients in the following categories.

1.11 'Secondary prevention', that is, for patients who present, in the absence of a treatable cause, with one of the following:

- having survived a cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF)
- spontaneous sustained VT causing syncope or significant haemodynamic compromise
- sustained VT without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF of less than 35%) (no worse than class III of the New York Heart Association functional classification of heart failure).

A Heart Rhythm UK position statement on clinical indications for ICD implantation in adults with familial sudden cardiac death syndromes was published in 2010 (Garratt *et al.* *Europace*

2010;**12**:1156-1175). This details the available evidence in these rare syndromes and is used in this section of the document.

4.1.1.2) North America

Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *J Am Coll Cardiol* 2008;**51**;e1-e62 <http://content.onlinejacc.org/cgi/content/full/51/21/e1>).

Class I (procedure should be performed) and **IIa** (it is reasonable to perform the procedure):

CLASS I

1. ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. (*Level of Evidence: A*) (16,319–324)
2. ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. (*Level of Evidence: B*) (16,319–324)
3. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study. (*Level of Evidence: B*) (16,322)

CLASS IIa

1. ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM. (*Level of Evidence: C*)
5. ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers. (*Level of Evidence: B*) (349–354)
7. ICD implantation is reasonable for patients with Brugada syndrome who have had syncope. (*Level of Evidence: C*)
9. ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blockers. (*Level of Evidence: C*)

4.1.1.3) European Society of Cardiology

ESC guidance on acute and chronic heart failure (McMurray *et al. European Heart Journal* 2012;**33**:1787–1847) states:

Recommendations for the use of implanted cardioverter defibrillators in patients with heart failure

Recommendations	Class ^a	Level ^b	Ref ^c
Secondary prevention An ICD is recommended in a patient with a ventricular arrhythmia causing haemodynamic instability, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death.	I	A	144-147

4.1.2) Resuscitated cardiac arrest

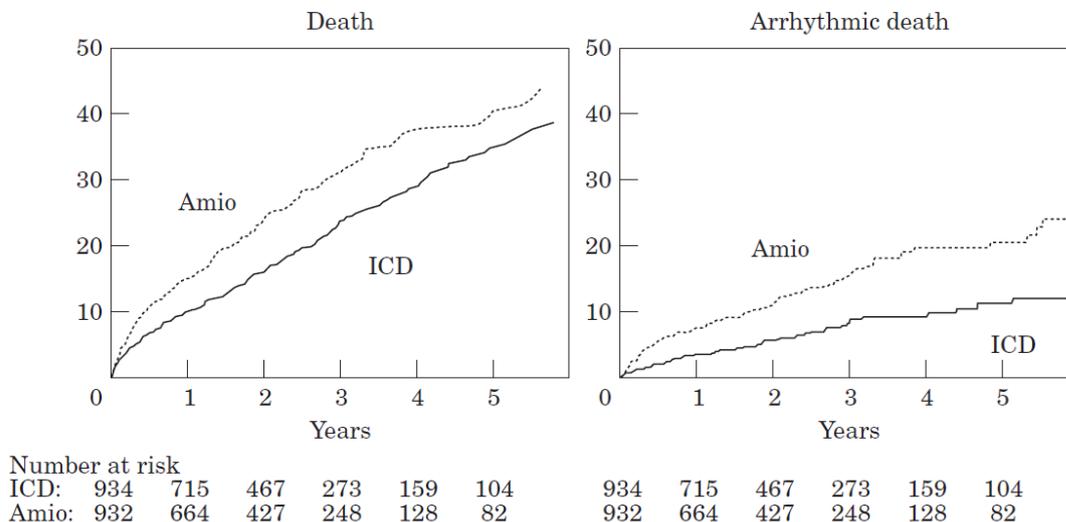
Before ICDs were part of routine clinical practice, patients surviving malignant ventricular arrhythmias were treated with a variety of rhythm modifying drugs including amiodarone, sotalol and class I agents (e.g. flecainide, encainide, propafenone). However, the only intervention to demonstrate improved patient survival is the implantation of an ICD.

No new secondary prevention trial data have been produced since the publication of NICE TA 95 in 2006, nor is any further evidence likely to be published in the future as it is considered unethical not to offer ICD therapy to cardiac arrest survivors.

4.1.2.1) Ischaemic heart disease

Four randomised controlled trials have assessed the efficacy of ICD implantation in the secondary prevention of sudden cardiac death from cardiac arrest and these have been subjected to meta-analysis. (Wever *et al. Circulation* 1995;**91**:2195-2203, AVID: *N Engl J Med* 1997;**337**:1576-1583, CASH: Kuck *et al. Circulation* 2000;**102**:748-754, CIDS: Connolly SJ *et al. Circulation* 2000;**101**:1297-1302, Meta-analysis: Connolly SJ *et al. Eur Heart J* 2000;**21**:2071-2078).

Despite their different protocols and inclusion criteria, patients enrolled in these trials had remarkably homogenous characteristics and the results of the trials comparing ICD therapy with drug treatment were remarkably consistent: A meta-analysis (Connolly *et al. Eur Heart J* 2000;**21**:2071-2078) demonstrates a relative risk reduction in all-cause mortality of 28% (a 3.5% annual absolute risk reduction) favouring ICD implantation which resulted almost entirely from a 50% reduction in arrhythmic death:



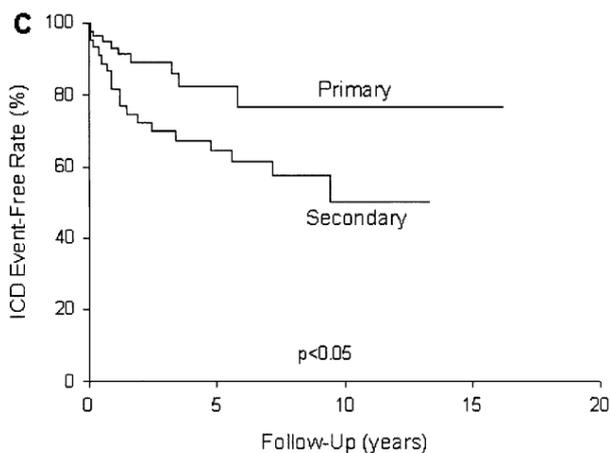
The majority of patients included in these trials had a history of prior myocardial infarction, but those with other heart disease showed similar benefit from ICD implantation.

4.1.2.2) Non-ischaemic cardiomyopathy

Although patients with non-ischaemic cardiomyopathy (sometimes referred to as dilated cardiomyopathy, DCM) represented only 14% of patients in the secondary prevention trials (15% in AVID, 11% in CASH and 10% in CIDS), the point estimates of benefit are essentially the same as those for patients with ischaemic cardiomyopathy: The hazard ratio for ICD therapy in patients with non-ischaemic cardiomyopathy was 0.77 compared with 0.78 for patients with ischaemic cardiomyopathy. These patients should therefore be regarded as at similar risk of recurrent life-threatening arrhythmia and receive ICD therapy according to the same selection criteria (Connolly *et al. Eur Heart J* 2000;**21**:2071-2078).

4.1.2.3) Hypertrophic cardiomyopathy

There are no randomised controlled trials of ICD therapy for secondary prevention in HCM. In a consecutive series of 132 patients with HCM receiving ICD implantation, the rate of death or appropriate ICD therapy following resuscitated cardiac arrest was 39% rate over 5-years' follow-up (Begley *et al. PACE* 2003;**26**:1887-1896).



Other observational data show a survival free from death or appropriate ICD discharge of 59% at 5 years (Maron *et al. N Engl J Med* 2000;**342**:365-373, Elliott *et al. J Am Coll Cardiol* 2006;**27**:1933-1941):

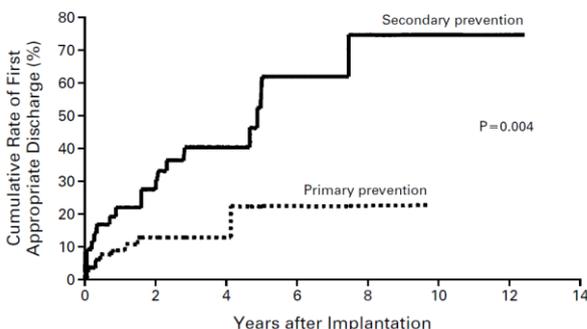


Figure 4. Estimated Cumulative Rates of First Appropriate Discharges, Calculated Separately for the 85 Patients with Defibrillators for Primary Prevention and the 43 Patients with Defibrillators for Secondary Prevention.

This is consistent with multi-centre registry data which report annual rates of appropriate ICD therapy of approximately 11% per year following resuscitation from VT or VF (Maron *et al. N Engl J*

Med 2000;**342**:365-373, Begley *et al. Pacing Clin Electrophysiol* 2003;**26**:1887-1896, Maron *et al. JAMA* 2007;**298**:405-412).

Patients with hypertrophic cardiomyopathy presenting with ventricular fibrillation, cardiac arrest or sustained ventricular tachycardia without reversible cause should undergo ICD implantation.

4.1.2.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)

There are no randomised controlled trials of ICD therapy for secondary prevention in ARVC but observational studies show a consistent benefit of ICD therapy with high proportions of patients receiving appropriate ICD therapy during follow-up.

In a multicentre study of 132 patients with ARVC (Corrado *et al. Circulation*. 2003;**108**:3084-3091) 9 of the 13 (69%) patients implanted with an ICD following cardiac arrest had life-saving ICD therapy at a rate of 21% per year. This is consistent with other reported series:

ARVC patients with ICD for secondary prevention receiving appropriate therapy	mean follow-up (months)	publication
7 of 9 (78%)	32	Tavernier <i>et al. Heart</i> 2001; 85 :53-56
9 of 13 (69%)	39	Corrado <i>et al. Circulation</i> . 2003; 108 :3084-3091
39 of 56 (70%)	80	Wichter <i>et al. Circulation</i> . 2004; 109 :1503-1508
11 of 16 (69%)	8.2	Pezawas <i>et al. Int J Cardiol</i> 2006; 107 :360-368

ARVC patients presenting with ventricular fibrillation, cardiac arrest or haemodynamically significant ventricular tachycardia should be offered ICD implantation.

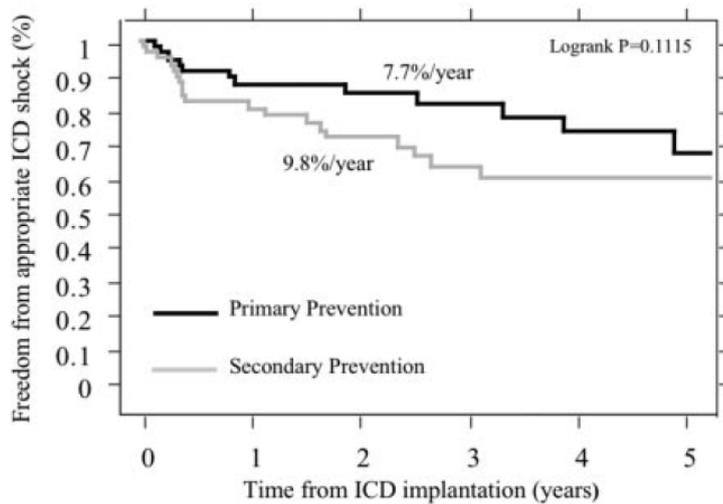
4.1.2.5) Left ventricular non-compaction

There are no prospective trials of ICD implantation for secondary prevention in patients with LVNC. In a series of 12 patients with LVNC undergoing ICD implantation (Kobza *et al. Pacing Clin Electrophysiol* 2008;**31**:461-467), 8 had prior cardiac arrest. Of those, 4 (50%) received appropriate ICD therapy over a mean follow-up of 36 months (17% per year). This supports a strategy of ICD implantation following a resuscitated cardiac arrest in this condition (Yasukawa *et al. Pediatr Cardiol* 2001;**22**:512-514, Celiker *et al. Pacing Clin Electrophysiol* 2004;**27**:104-108).

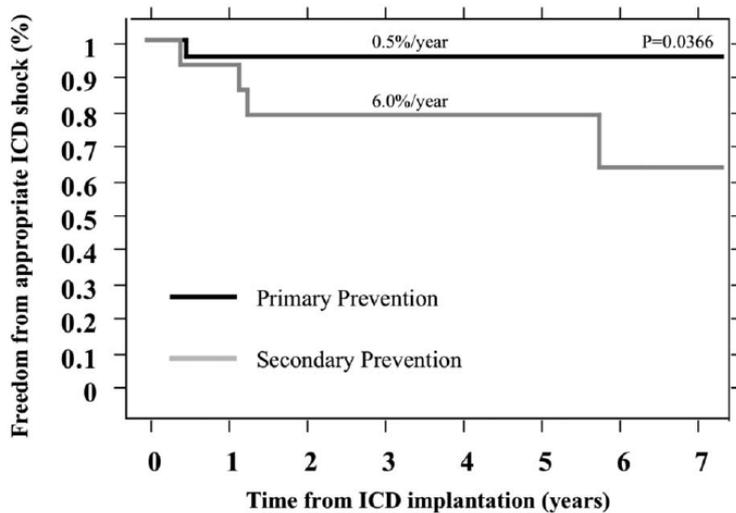
4.1.2.6) Congenital heart disease

A multicentre series of 53 patients with tetralogy of Fallot implanted with an ICD after sustained ventricular tachyarrhythmia (37 patients, 69.8%) or resuscitated sudden death (16 patients, 30.2%) showed an annual rate of appropriate shocks of 9.8% (Khairy *et al. Circulation* 2008;**117**:363-370).

Heart Rhythm UK



A multicentre series of 14 patients with transposition of the great arteries (TGA) treated with a Mustard or a Senning procedure with an intra-atrial baffle implanted with ICDs following a resuscitated cardiac arrest (10 patients, 71.4%) or sustained VT (4 patients, 28.6%), showed a 6.6% annual rate of appropriate ICD shocks (Khairy *et al. Circulation Electrophysiol* 2008;**1**:250-257).



ICD implantation is appropriate following resuscitated cardiac arrest or sustained VT in patients with high-risk congenital heart disease.

4.1.2.7) Brugada syndrome

There is no randomised controlled trial of ICD therapy for secondary prevention in Brugada syndrome. Five international registries of patients with Brugada syndrome have been analysed for risk factors for sudden cardiac death (Brugada & Brugada *J Am Coll Cardiol* 1992;**20**:1391-1396, Brugada, Brugada & Brugada *Circulation* 1998;**97**:457-460, Brugada *et al. Circulation* 2002;**105**:73-78, Brugada *et al. Circulation* 2003;**108**:3092-3096, Brugada *et al. J Cardiovasc Electrophysiol* 2003;**14**:455-457, Priori *et al. Circulation* 2000;**102**:2509-2515, Priori *et al. Circulation* 2002;**105**:1342-1347, Eckardt *et al. Eur Heart J* 2002;**23**:1394, Eckardt *et al. Circulation* 2005;**111**:257-263, Probst *et al. Circulation* 2010;**121**:635-643, Takagi *et al. J Cardiovasc Electrophysiol* 2007;**18**:1244-1251, Sacher *et al. Circulation* 2006;**114**:2317-2324, Sarkozy *et al. Eur Heart J* 2007;**28**:334-344).

Observational series estimate the annual risk of death or appropriate ICD discharge at between 7.7% and 13.8% and ICD implantation is therefore recommended (Brugada *et al. Circulation* 2002;**105**:73-78, Sacher *et al. Circulation* 2006;**114**:2317-2324, Takagi *et al. J Cardiovasc Electrophysiol* 2007;**18**:1244-1251, Sarkozy *et al. Eur Heart J* 2007;**28**:334-344, Probst *et al. Circulation* 2010;**121**:635-643):

Table 1 Cardiac event rates per annum from different study populations for different clinical presentations of Brugada syndrome calculated from available data

	Brugada <i>et al.</i> ⁴¹	Sacher <i>et al.</i> ⁵⁰	Takagi <i>et al.</i> ⁴⁹	Sarkozy <i>et al.</i> ⁵¹	Probst <i>et al.</i> ⁴⁸
Total patient numbers	334	220	188	47	1029
Prior cardiac arrest	13.8%	10.7%	9.8%	Not studied	7.7%
Previous syncope	8.8%	3.15%	1.9%	2.9%	1.9%
Asymptomatic	(72% FH) 3.74%	(54% FH) 1.7%	(10% FH) 0%	(57% FH) 4.8%	(37% FH) 0.5%
Asymptomatic spontaneous type 1 ECG	6.4%	2.54%	0%	Unavailable	0.81%
Asymptomatic drug-induced type 1 ECG	0%	0.73%	0%	Unavailable	0.35%

Event rates are rates per annum of sudden cardiac death, ventricular fibrillation, or (in patients with ICDs) appropriate shocks per annum.

Brugada syndrome patients presenting with VF or cardiac arrest without reversible precipitant should be offered ICD implantation.

4.1.2.8) Long QT syndromes

There are no prospective trials of the risk of recurrent cardiac arrest in long QT syndrome (LQTS) patients. In a report of historical control patients (Zareba *et al. J Cardiovasc Electrophysiol* 2003;**14**:337-341), 27 out of 89 patients (30.3%) died or suffered recurrent cardiac arrest over 9 years' follow-up – a risk of 3.4% per year. LQTS patients presenting with ventricular fibrillation or cardiac arrest without reversible precipitant should be offered ICD implantation in addition to oral beta-blocker therapy.

4.1.2.9) Short QT syndrome

There are no randomised controlled trial data in this very rare condition. Because of the high risk of arrhythmias and sudden cardiac death, ICD implantation is recommended for secondary prevention in patients with short QT syndrome (Priori *et al. Circ Res* 2005;**96**:800-807, Veltmann *et al. Herz* 2009;**34**:518–527, Cross *et al. J Interv Card Electrophysiol* 2011;**31**:25–31). Care must be taken in device programming to prevent inappropriate therapy due to T-wave over-sensing in this condition (Schimpf *et al. J Cardiovasc Electrophysiol* 2003;**14**:1273-1277).

4.1.2.10) Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Patients with CPVT presenting with aborted cardiac arrest have been shown to be at increased risk of life-threatening arrhythmias with a mortality of 1.2% per year despite beta-blockade (Hayashi *et al. Circulation* 2009;**119**:2426-2434). ICD implantation is recommended in addition to beta blockade for CPVT patients presenting with VF or cardiac arrest without reversible cause.

4.1.2.11) Ventricular arrhythmias of unknown aetiology

A small number of patients resuscitated from cardiac arrest are found to have no structural abnormality, reversible cause or known ion-channel abnormality. ICD implantation is appropriate for secondary prevention in these patients.

4.1.3) Syncope

Syncope, a sudden loss of consciousness due to global cerebral hypoperfusion, is most commonly due to an uncomplicated faint, which is benign. A careful history, examination and focused

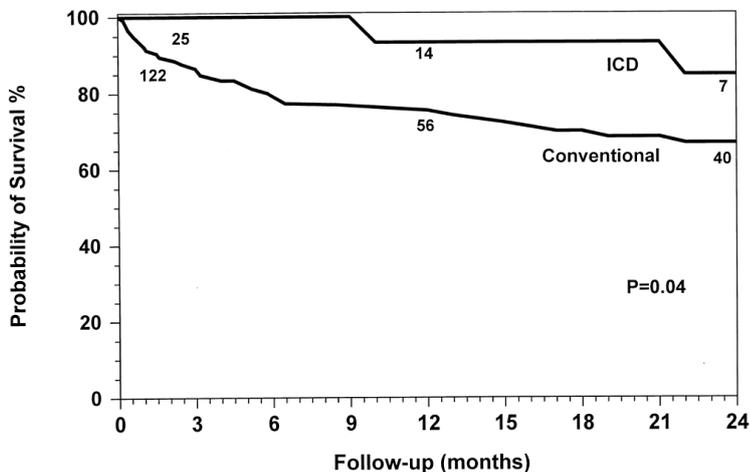
investigations are required to make this diagnosis (NICE CG109, Transient loss of consciousness in adults and young people, August 2010). However, when syncope is associated with cardiac dysfunction or arrhythmia, it is associated with a high mortality. In high-risk cardiac conditions, syncope carries a similar prognosis to resuscitated cardiac arrest, the most likely mechanism being spontaneous termination of the life-threatening arrhythmia.

4.1.3.1) Ischaemic heart disease

CIDS (Connolly SJ *et al. Circulation* 2000;**101**:1297-1302) included 92 patients (14%) presenting with syncope in the absence of documented ventricular arrhythmia. All had subsequent documentation of either spontaneous VT ≥ 10 seconds or inducible sustained monomorphic VT. The all-cause mortality of patients included because of syncope was higher (13.4%) than those with documented arrhythmias (8.7%, $p=0.034$). The AVID registry (Anderson *et al. Circulation* 1999;**99**:1692-1699) included 158 patients presenting with unexplained syncope. These patients had a 15.9% 2-year mortality, similar to those with demonstrated arrhythmias. ICD implantation is recommended in patients with ischaemic heart disease and LVEF $\leq 35\%$ presenting with syncope.

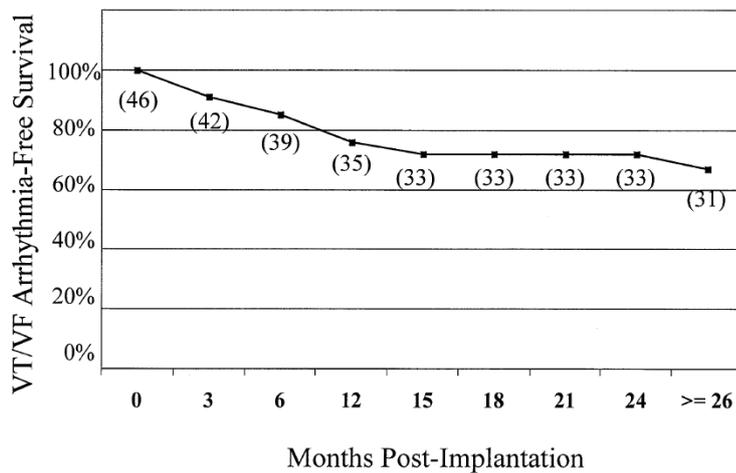
4.1.3.2) Non-ischaemic cardiomyopathy

In a series of 147 patients with heart failure due to non-ischaemic cardiomyopathy with LVEF $\leq 35\%$ and a history of syncope but no prior history of sustained ventricular tachycardia (Fonarow *et al. Am J Cardiol* 2000;**85**:981-985), 25 patients were managed with an ICD and 122 patients managed with conventional medical therapy. During a mean follow-up of 22 months, there were 31 deaths, 18 sudden, in patients treated with conventional therapy, whereas there were 2 deaths, none sudden, in patients treated with an ICD. An appropriate shock occurred in 40% of the ICD patients. Actuarial survival at 2 years was 84.9% with ICD therapy and 66.9% with conventional therapy ($p = 0.04$).



70% of these patients received appropriate ICD therapy for sustained ventricular arrhythmias with a mean follow-up of 17 months:

Heart Rhythm UK

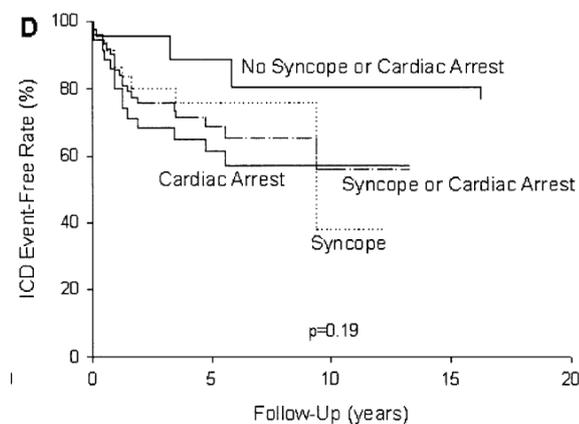


SCD-HeFT (Bardy *et al. N Engl J Med* 2005;**352**:225-37) randomised only 162 patients (6%) with a history of syncope but analysis (Olshansky *et al. J Am Coll Cardiol* 2008;**51**:1277-82) has shown that pre-randomisation syncope was associated with an increased risk of appropriate ICD therapy 38% versus 19% (HR 1.75, 95% CI 1.10 to 2.80, p=0.019).

Thus, in patients with non-ischemic cardiomyopathy, LVEF \leq 35% and syncope, therapy with an ICD is associated with a reduction in sudden death and an improvement in overall survival (Fonaro GC *et al. Am J Cardiol* 2000;**85**:981-985, Russo *et al. Am J Cardiol* 2001;**88**:1444-1446) similar to that seen in patients surviving a cardiac arrest.

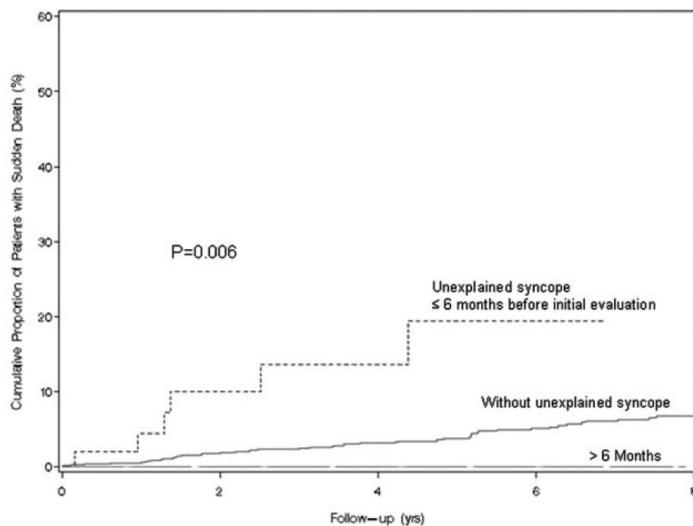
4.1.3.3) Hypertrophic cardiomyopathy

In a consecutive series of 132 HCM patients receiving ICD implantation, 24% of those with unexplained syncope had appropriate ICD therapy during 5-years' follow-up (Begley *et al. PACE* 2003;**26**:1887-1896). This is similar to the risk in those resuscitated from cardiac arrest.



A large study of 1511 patients with HCM showed a 20% risk of sudden death within 5 years of unexplained syncope (Spirito *et al. Circulation* 2009;**119**:1703-1710):

Heart Rhythm UK

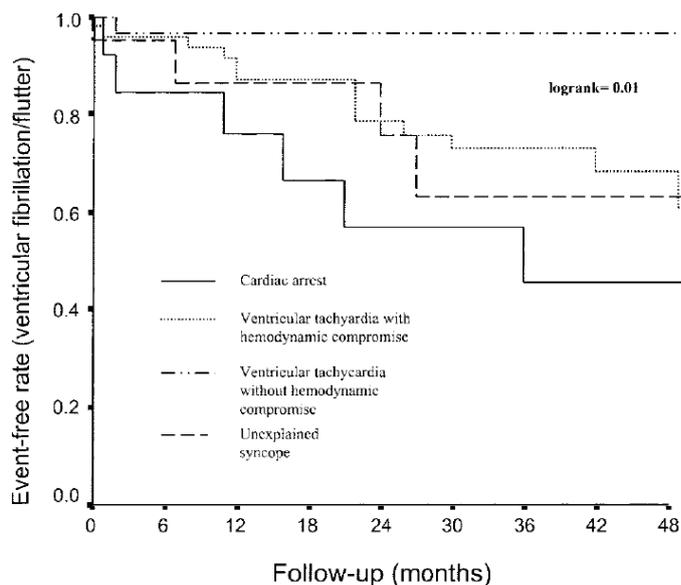


This is consistent with another report showing that patients receiving ICDs with unexplained syncope as their sole risk marker had a 5% annual rate of appropriate interventions compared with an annual rate of 3.5% in the overall study group with primary prevention ICDs (Maron *et al.* *JAMA* 2007;**298**:405-412). Multivariate analysis of a single centre series of 917 patients (Elliott *et al.* *Eur Heart J* 2006;**27**:1933-1941) confirmed that syncope was a significant predictor of sudden death with a hazard ratio of 2.27 (1.2-4.2, $p=0.01$).

These data strongly support the use of ICD therapy following cardiac syncope in patients with hypertrophic cardiomyopathy.

4.1.3.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Observational studies support the use of ICD implantation in high risk patients identified by unexplained syncope. In the Corrado *et al.* series (*Circulation*. 2003;**108**:3084-3091), the clinical presentation was unexplained syncope in 21 patients (16%). Over a mean follow-up of 39 months, 8 of these patients (38%) received appropriate ICD therapy for ventricular arrhythmia:



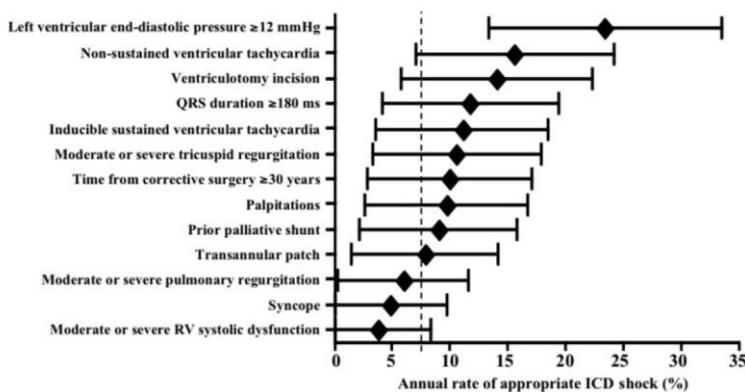
ARVC patients presenting with syncope, when VT and VF have not been excluded as the cause, should be offered ICD implantation.

4.1.3.5) Left ventricular non-compaction

In a series of 12 patients with LVNC (Kobaza *et al. PACE* 2008;31:461-467), only one underwent ICD implantation because of syncope. He received 2 appropriate ICD therapies over a 39-month follow-up period. There is too little information on which to formulate evidence-based recommendations for ICD implantation in this situation. Expert opinion recommends ICD implantation in patients with LVNC presenting with syncope, symptomatic ventricular arrhythmias or with severely impaired LV systolic function (LVEF $\leq 35\%$) (Oechslin E, Jenni R. *European Heart Journal* 2011;32:1446-1456).

4.1.3.6) Congenital heart disease

In a multicentre series (Khairy *et al. Circulation* 2008;117:363-370), 30 patients with tetralogy of Fallot underwent ICD implantation because of syncope. Their annual rate of appropriate ICD therapy was 5%.



In a similar multicentre series (Khairy *et al. Circulation Electrophysiol* 2008;1:250-257), 8 patients with transposition of the great arteries underwent ICD implantation because of syncope. Their rate of appropriate ICD therapy was not reported separately from the primary prevention group, but overall this was only 0.5%.

On the available evidence, ICD implantation appears to be indicated following syncope in patients with Tetralogy of Fallot. There are insufficient data to make a recommendation in patients with transposition of the great arteries.

4.1.3.7) Brugada syndrome

Published series show that in patients with Brugada syndrome the risk of sudden cardiac death or appropriate ICD therapy following previous syncope is between 1.9% and 8.8% per year (Garratt *et al. Europace* 2010;12:1156-1175).

Table 1 Cardiac event rates per annum from different study populations for different clinical presentations of Brugada syndrome calculated from available data

	Brugada et al. ⁴¹	Sacher et al. ⁵⁰	Takagi et al. ⁴⁹	Sarkozy et al. ⁵¹	Probst et al. ⁴⁸
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Asymptomatic	(72% FH) 3.74%	(54% FH) 1.7%	(10% FH) 0%	(57% FH) 4.8%	(37% FH) 0.5%
Asymptomatic spontaneous type 1 ECG	6.4%	2.54%	0%	Unavailable	0.81%
Asymptomatic drug-induced type 1 ECG	0%	0.73%	0%	Unavailable	0.35%

Event rates are rates per annum of sudden cardiac death, ventricular fibrillation, or (in patients with ICDs) appropriate shocks per annum.

ICD implantation is recommended for Brugada syndrome patients with syncope when VT/VF has not been excluded as the cause of syncope.

4.1.3.8) Long QT syndromes

Patients with LQTS presenting with syncope should receive evidence-based beta blocker treatment. A published series (Zareba *et al. J Cardiovasc Electrophysiol* 2003;**14**:337-341) showed that 11 of 72 patients (2.2% per year) with recurrent syncope died or had a cardiac arrest during 7 years' follow-up. Although there are differences between the LQTS sub-types, there is insufficient evidence to base recommendations on these.

LQTS patients experiencing continuing syncope despite beta-blockade (or left cervical sympathetic denervation) when VT/VF has not been excluded as the cause of syncope should be offered ICD implantation.

4.1.3.9) Short QT syndromes

There are no randomised controlled trial data in this syndrome. A high incidence of sudden cardiac death has been reported in affected families and unstable ventricular arrhythmias are often inducible on electrophysiology study. Published expert opinion is to offer ICDs to these patients for primary prevention (Cross B *et al. J Interv Card Electrophysiol* 2011;**31**:25-31)

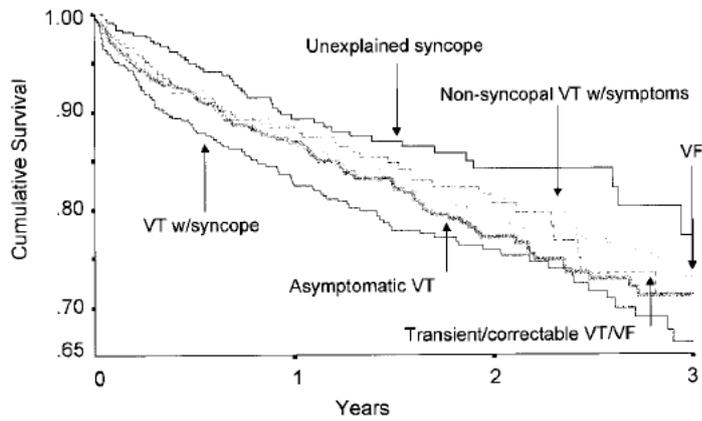
4.1.3.10) Catecholaminergic polymorphic ventricular tachycardia

There are no trials of continuing medical therapy with beta blockade in CPVT patients presenting with recurrent syncope. ICD implantation is recommended because of the high risk of sudden cardiac death in this small patient group (Hayashi *et al. Circulation* 2009;**119**:2426-2434).

4.1.3.11) Ventricular tachycardia without haemodynamic compromise

Not all ventricular arrhythmias cause circulatory collapse and result in syncope or sudden cardiac death. The index event in 34% (345) of patients in the AVID registry and 25% (165) in CIDS was asymptomatic ventricular tachycardia. Survival was lower in patients in the AVID registry (Anderson *et al. Circulation*. 1999;**99**:1692-1699) with asymptomatic VT than with VF as their presenting arrhythmia:

Heart Rhythm UK



arrhythmia	number of patients	2-year mortality
VF	1399	20.3%
VT with syncope	598	24.3%
Non-syncopal VT with symptoms	1065	18.7%
Asymptomatic VT	497	22.6%
Transient/correctable VT/VF	270	19.4%
Unexplained syncope	390	15.9%

ICD implantation is recommended for patients with severe left ventricular impairment (LVEF $\leq 35\%$) and documented sustained ventricular arrhythmia regardless of its acute haemodynamic effects.

4.2) Primary prevention

In medicine, the risk of an event occurring for a second time is generally significantly higher than for any identifiable at-risk group in which this event has not yet occurred. Thus, the number needed to treat is generally lower for secondary than primary prevention. ICD therapy represents a unique situation where we are able to identify groups of patients on simple clinical criteria who have not suffered a cardiac arrest but are at higher absolute risk than those who have, and gain more from ICD therapy with a lower number needed to treat to save a life.

4.2.1) Current national and international guidance

4.2.1.1) UK

Current NICE guidance (Technology Appraisal 95 Implantable cardioverter defibrillators for arrhythmias, January 2006) states:

1.1.2 'primary prevention', that is for patients who have:

- A history of previous (more than four weeks) myocardial infarction (MI) and:
either
 - Left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure), and
 - Non-sustained VT on Holter (24 hour electrocardiogram [ECG]) monitoring, and
 - Inducible VT on electrophysiological (EP) testing**or**
 - Left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure),**and**
 - QRS duration of equal to or more than 120ms
- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, or arrhythmogenic right ventricular dysplasia (ARVD), or have undergone surgical repair of congenital heart disease

A Heart Rhythm UK position statement on clinical indications for ICD implantation in adults with familial sudden cardiac death syndromes was published in 2010 (Garratt *et al.* *Europace* 2010;**12**:1156-1175). This details the available evidence in these rare syndromes and is used in this section of the document.

4.2.1.2) North America

Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (Epstein *et al.* Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American ACC/AHA/HRS 2008. *J Am Coll Cardiol* 2008;**51**:e1-e62 <http://content.onlinejacc.org/cgi/content/full/51/21/e1>):

Class I (procedure should be performed) and **IIa** (it is reasonable to perform the procedure):

CLASS I

4. ICD therapy is indicated in patients with LVEF less than or equal to 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III. (*Level of Evidence: A*) (16,333)
5. ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III. (*Level of Evidence: B*) (16,333,369,379)
6. ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30%, and are in NYHA functional Class I. (*Level of Evidence: A*) (16,332)
7. ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than or equal to 40%, and inducible VF or sustained VT at electrophysiological study. (*Level of Evidence: B*) (16,327,329)

CLASS IIa

2. ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function. (*Level of Evidence: C*)
3. ICD implantation is reasonable for patients with HCM who have 1 or more major risk factors for SCD. (*Level of Evidence: C*)
4. ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD. (*Level of Evidence: C*)
6. ICD implantation is reasonable for non hospitalized patients awaiting transplantation. (*Level of Evidence: C*)
8. ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest. (*Level of Evidence: C*)
10. ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. (*Level of Evidence: C*)

4.2.1.3) European Society of Cardiology

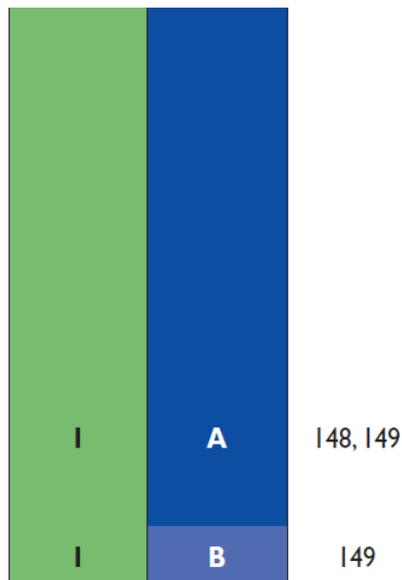
Current ESC guidance (Guidance on the diagnosis and treatment of acute and chronic heart failure 2012, McMurray *et al.* *European Heart Journal* 2012;**33**:1787-1847) states:

Primary prevention

An ICD is recommended in a patient with symptomatic HF (NYHA class II-III) and an EF \leq 35% despite \geq 3 months of treatment with optimal pharmacological therapy, who is expected to survive for $>$ 1 year with good functional status, to reduce the risk of sudden death

(i) Ischaemic aetiology and $>$ 40 days after acute myocardial infarction

(ii) Non-ischaemic aetiology



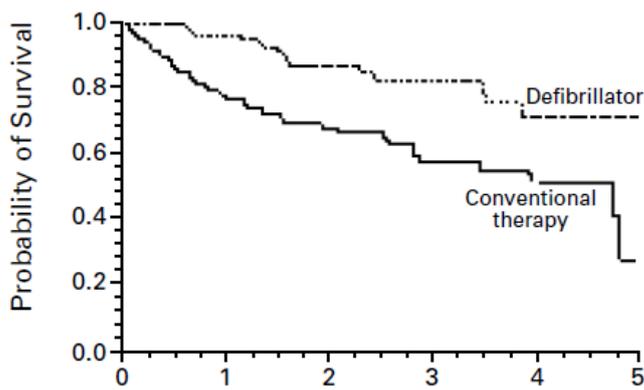
4.2.2) Published evidence

4.2.2.1) Ischaemic heart disease

The Multicenter Automatic Defibrillator Implantation Trial (MADIT, Moss *et al. N Engl J Med* 1996;**335**:1933-40) randomised 95 patients to ICD implantation and 101 to medical therapy while in the Multicenter UnSustained Tachycardia Trial (MUSTT, Buxton *et al. N Engl J Med* 2000; **342**:1937-1945, Wyse *et al. J Am Coll Cardiol* 2001;**38**:344 –51) 351 patients were randomised to electrophysiology guided strategy and 161 patients received ICD implantation while 190 received medical therapy. All patients had a history of prior myocardial infarction, spontaneous non-sustained ventricular tachycardia and left ventricular impairment. The selection criteria for LVEF were slightly different in the two trials (\leq 35% in MADIT and \leq 40% in MUSTT) but the randomised patients had very similar LVEFs:

	MADIT		MUSTT	
	ICD	Conventional therapy	EP guided strategy	No antiarrhythmic therapy
LVEF	0.25 \pm 0.07	0.27 \pm 0.07	30 (20-35)	29 (22-35)

MADIT demonstrated a 22.8% absolute reduction in all-cause mortality (39/101, 38.6% compared to 15/95, 15.8%) and a 54% relative reduction in all-cause mortality with ICD therapy:



	Year					
NO. OF PATIENTS	0	1	2	3	4	5
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

Figure 2. Kaplan–Meier Analysis of the Probability of Survival, According to Assigned Treatment.

The difference in survival between the two treatment groups was significant ($P = 0.009$).

MUSTT demonstrated a 29.4% absolute reduction in all-cause mortality and a 60% relative reduction in all-cause mortality with ICD therapy:

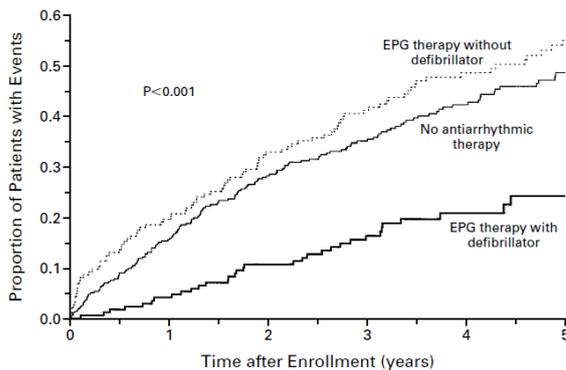


Figure 4. Kaplan–Meier Estimates of the Rates of Overall Mortality According to Whether the Patients Received Treatment with a Defibrillator.

The P value refers to two comparisons: between the patients in the group assigned to electrophysiologically guided (EPG) therapy who received treatment with a defibrillator and those who did not receive such treatment, and between the patients assigned to electrophysiologically guided therapy who received treatment with a defibrillator and those assigned to no antiarrhythmic therapy.

MADIT II (Moss *et al.* *N Engl J Med* 2002;**346**:877-883) enrolled 1232 patients with ischaemic cardiomyopathy and LVEF $\leq 30\%$ without any further risk stratification. In fact, the patients' LVEF were very similar to those in MADIT and MUSTT with a mean of $23 \pm 5\%$:

Heart Rhythm UK

MADIT II demonstrated a 5.6% absolute reduction in all-cause mortality and a 31% relative reduction in all-cause mortality with ICD therapy:

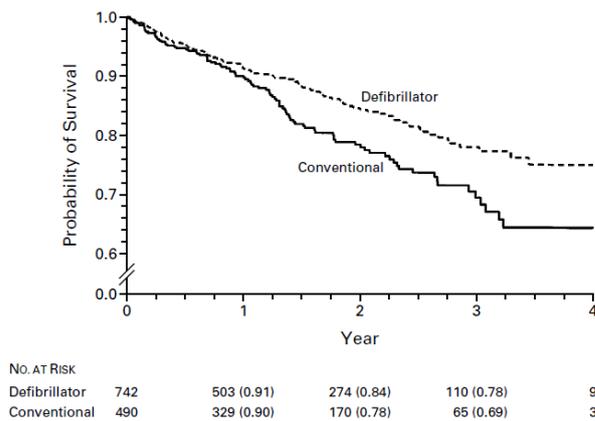


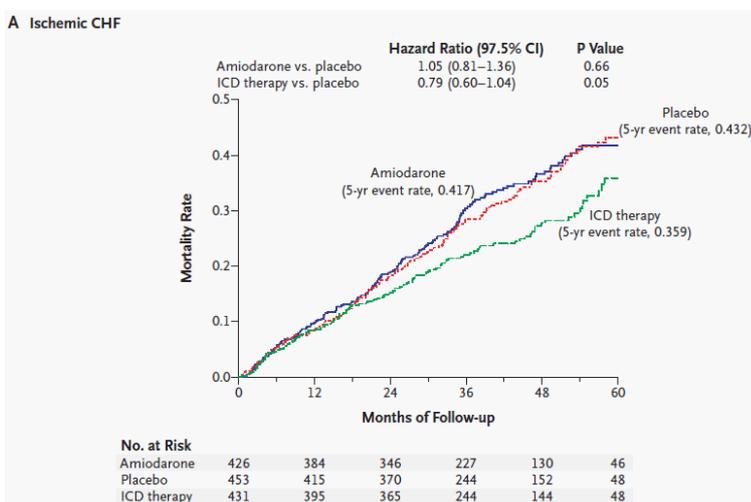
Figure 2. Kaplan–Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy. The difference in survival between the two groups was significant (nominal $P=0.007$, by the log-rank test).

Mortality in the ICD treated groups is strikingly similar in the two MADIT trials at approximately 25% at 4 years. The mortality in the non-ICD, conventional treatment groups, was however much lower in MADIT 2 resulting in a lower relative risk reduction. This is likely to be due to the improved optimal medical management in the later trial:

non-ICD patients	MADIT (1996)	MADIT 2 (2002)
β -blocker use	15%	70%
ACE-inhibitor use	55%	72%

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT, Bardy *et al.* *N Engl J Med* 2005;**352**:225–37) randomised 1311 patients with ischaemic heart disease, LVEF $\leq 35\%$ and NYHA II/III heart failure symptoms to ICD or amiodarone therapy over a median follow-up of 45.5 months.

The median LVEF was 25% (20–30%). There was a 7.3% absolute and a 21% relative risk reduction in all-cause mortality in the ICD group with ischaemic aetiology:



The selection criteria in MADIT and MUSTT required inducibility of ventricular arrhythmia by programmed electrical stimulation whereas MADIT 2 and SCD-HeFT did not. The all-cause mortality after 4-years' follow-up in patients receiving ICD implantation was similar in all 4 trials suggesting that inducibility does not select a higher risk group or a group with more to gain from ICD therapy:

	EPS selection criterion	4-year all-cause mortality	
		ICD group	conventional group
MADIT (1996)	yes	25%	44%
MUSTT (2001)	yes	22%	41%
MADIT 2 (2004)	no	25%	36%
SCD-HeFT (2005)	no	26%	36%

Sub-set analysis of the MADIT-II data was used in previous NICE guidance to restrict ICD therapy to those with QRS duration >120ms and LVEF ≤30%. However, analysis of the trial data has shown that there were no significant differences in the effect of ICD therapy on survival when patients were stratified by age, sex, ejection fraction, NYHA class, or the QRS duration. This sub-set stratification is therefore not statistically valid and has never been tested in a clinical trial.

Two trials did not demonstrate benefit from ICD implantation. The coronary artery bypass graft-patch trial (CABG-Patch, Bigger *et al. N Engl J Med* 1997;**337**:1569-75) randomised 900 patients with LVEF ≤35% and abnormal signal-averaged ECG (duration of the filtered QRS complex, ≥114 ms; root-mean-square voltage in the terminal 40ms of the QRS complex, <20µV; or duration of the terminal filtered QRS complex at <40µV, >38 ms) to epicardial ICD implantation at the time of planned coronary artery bypass grafting. Over a mean of 36 months' follow-up, there was no difference in overall mortality between the randomised groups with a hazard ratio for death from any cause was 1.07 (0.81-1.42; p=0.64).

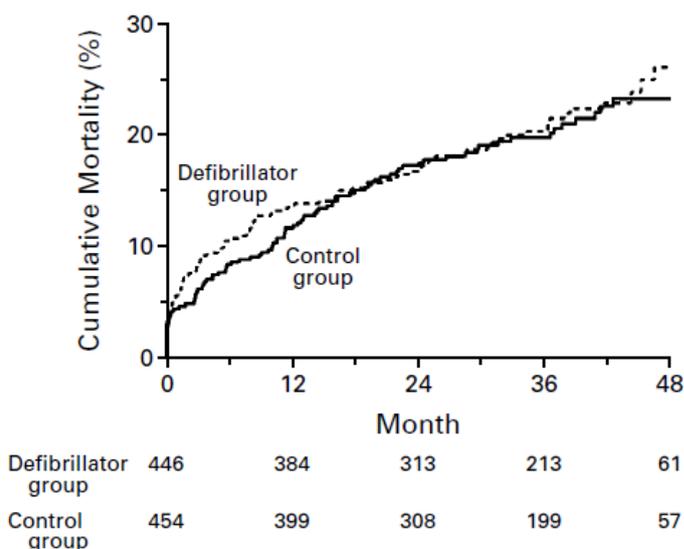
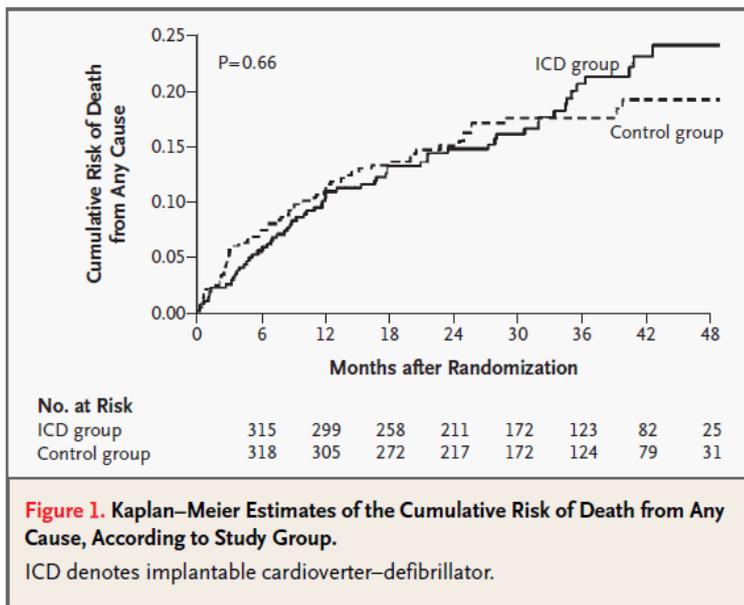


Figure 1. Kaplan–Meier Analysis of the Probability of Death According to Study Group.

The defibrillator in acute myocardial infarction trial (DINAMIT, Hohnloser *et al. N Engl J Med* 2004;**351**:2481-2488), the only study of ICD implantation early after myocardial infarction, randomised 674 patients with LVEF ≤35% and impaired cardiovascular autonomic function 6 to 40 days after myocardial infarction to endocardial ICD implantation or conventional medical therapy.

Over a mean follow-up of 30 months, there was no reduction in all-cause mortality (7.5%/y ICD, 6.9%/y control, hazard ratio 1.08 (0.76-1.55; p=0.66):



There was, however, a significant reduction in arrhythmic death in the ICD group (1.5%/y ICD, 3.5%/y control, hazard ratio 0.42; p=0.009), but this was cancelled out by a significant increase in non-arrhythmic death (6.1%/y ICD, 3.5%/y control, hazard ratio 1.75; p=0.02).

The most likely explanation of this finding is that, early after myocardial infarction, patients defibrillated from ventricular fibrillation are at increased risk of non-arrhythmic death and that in this group of patients the ICD is changing the mode of death rather than overall-mortality. The hypothesis that the proximity of recent myocardial infarction identifies a group of patients who benefit less from ICD implantation is supported by an analysis of the MADIT II trial (Wilber *et al. Circulation. 2004;109:1082-1084*) in which there was a smaller all-cause mortality benefit in patients receiving ICD implantation in the lowest quartile (18 months) after myocardial infarction compared to later time points.

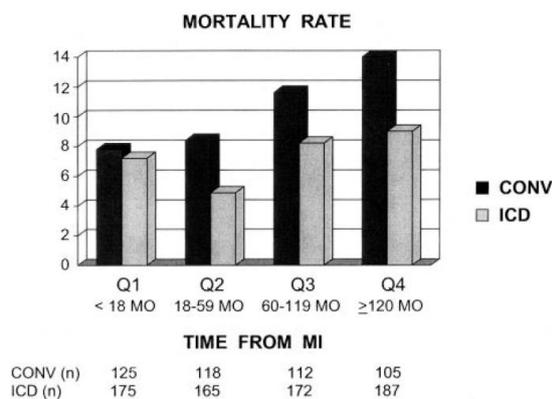


TABLE 1. Effect of the ICD by Elapsed Time From MI

MI Time, mo	HR	95% CI	P
<18	0.98	0.52–1.84	0.95
18–59	0.52	0.26–1.05	0.07
60–119	0.50	0.28–0.91	0.02
≥120	0.62	0.36–1.08	0.09

HR indicates hazard ratio for ICD vs conventional therapy.

This and other studies demonstrate that patients at increased arrhythmic risk after myocardial infarction remain at increased risk over long-term follow-up. The absence of arrhythmia many years after the infarction does not imply a low risk.

4.2.2.2) Non-ischaemic cardiomyopathy

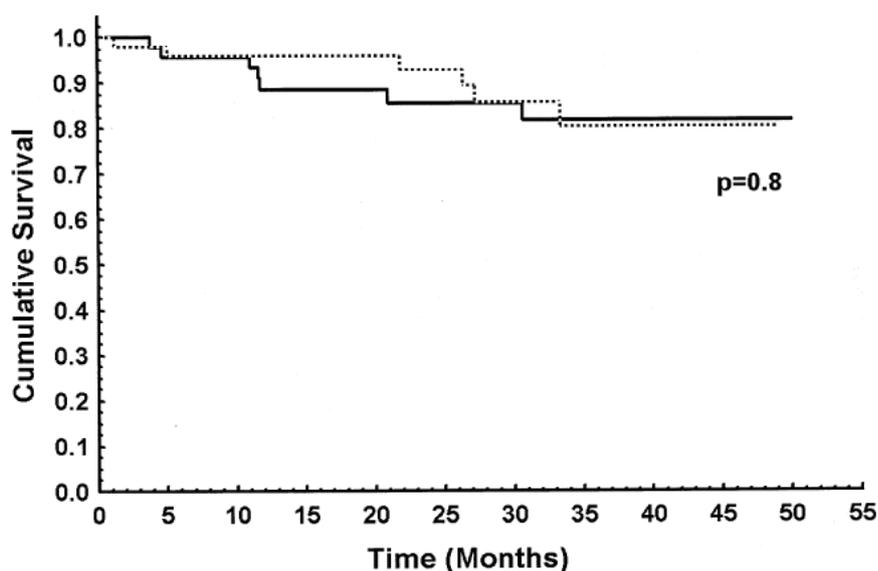
There have been multiple randomised prospective trials investigating the role of ICD implantation in the primary prevention of sudden cardiac death in patients with non-ischaemic cardiomyopathy.

4.2.2.2.1) CAT

The cardiomyopathy trial (CAT, Bänsch *et al. Circulation*. 2002;**105**:1453-1458) randomised 104 patients within 9 months of a diagnosis of non-ischaemic cardiomyopathy with LVEF $\leq 30\%$ to ICD or medical care. All-cause mortality was much lower than expected at 26% in the ICD group and 31% in the medical group resulting in a lack of power to demonstrate a statistical difference.

4.2.2.2.2) AMIOVERT

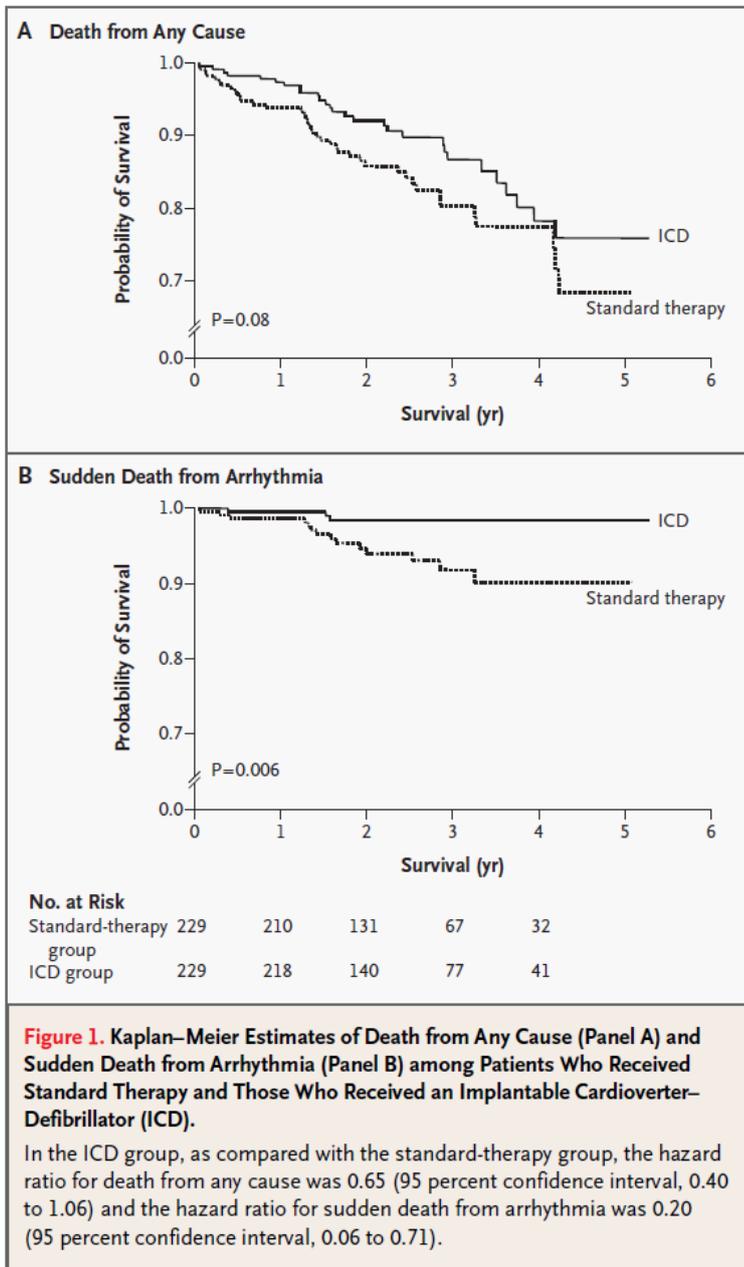
The amiodarone versus implantable defibrillator in patients with non-ischaemic cardiomyopathy and asymptomatic non-sustained ventricular tachycardia (AMIOVERT, Strickberger *et al. J Am Coll Cardiol* 2003;**41**:1707–12) trial randomised 103 patients with chronic dilated cardiomyopathy, non-sustained VT (3 beats to 30s at >100 bpm) and LVEF $\leq 35\%$ to ICD or amiodarone. All-cause mortality did not differ significantly between the groups (11.8% ICD, 13.5% amiodarone; $p=0.8$):



4.2.2.2.3) DEFINITE

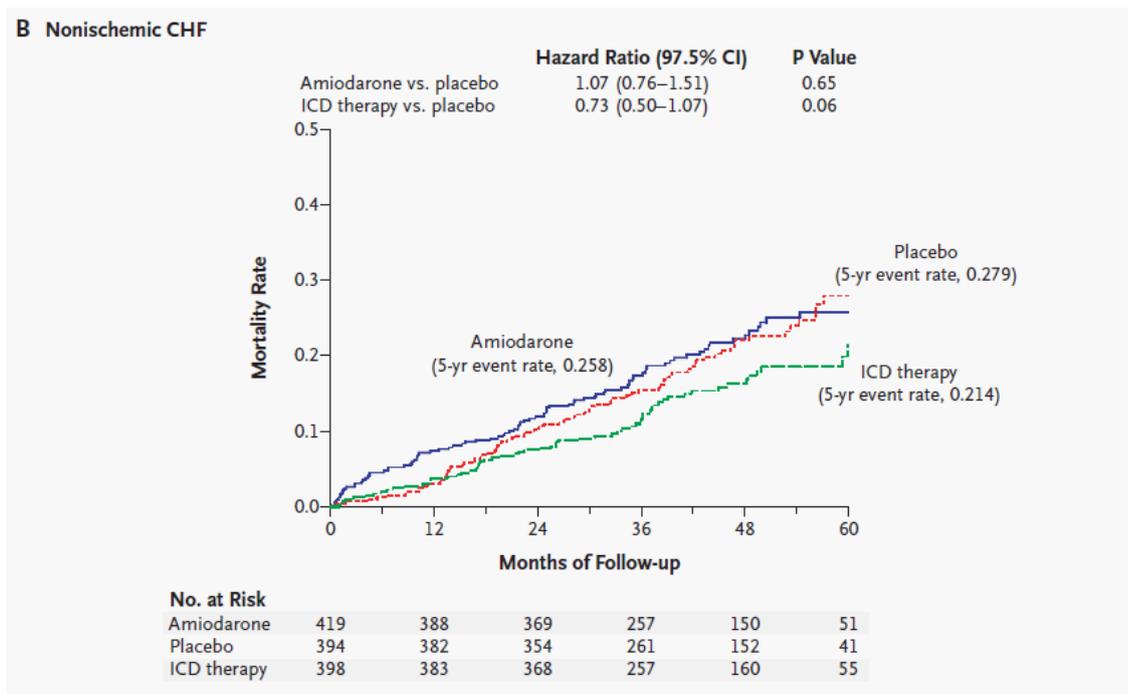
The defibrillators in non-ischaemic cardiomyopathy treatment evaluation (DEFINITE, Kadish *et al. N Engl J Med* 2004;**350**:2151-8) trial randomised 458 patients with non-ischaemic cardiomyopathy, NYHA I to III heart failure symptoms (99, 21.6%, patients were NYHA I), LVEF $\leq 35\%$, >10 ventricular premature beats per hour or non-sustained ventricular tachycardia to ICD or continued medical therapy. There were numerically fewer deaths in the ICD group at 1 and two year follow up but this did not reach statistical significance. Sudden death was reduced with an absolute reduction of 4.8% over a mean follow-up of 29 months (hazard ratio 0.21; $p=0.006$):

	ICD + OPT	OPT	
1y all-cause mortality	2.6%	6.2%	ns
2y all-cause mortality	7.9%	14.1%	ns
sudden cardiac death	1.3%	6.1%	HR 0.20, $p=0.006$



4.2.2.2.4) SCD-HeFT

The sudden cardiac death heart failure trial (SCD-HeFT, Bardy *et al.* *N Engl J Med* 2005;**352**:225-37) randomised 1210 patients with non-ischaemic cardiomyopathy (and 1311 with ischaemic cardiomyopathy as described above), NYHA II or III and LVEF \leq 35% to ICD, amiodarone or placebo. Over a median follow-up of 45.5 months, there was a 6.5% absolute and a 27% relative risk reduction in all-cause mortality in the ICD group with non-ischaemic aetiology (p=0.06):



	ischaemic	non-ischaemic
5y all-cause mortality – placebo	43.2%	27.9%
5y all-cause mortality - ICD	35.9%	21.4%
absolute mortality reduction with ICD	7.3%	6.5%
relative risk reduction	21%	27%
p value	0.05	0.06

The relative risk reduction was actually greater in the non-ischaemic (27%) than the ischaemic (21%) group. The lower event rate in the non-ischaemic group resulted in similar absolute risk reductions in both groups.

4.2.2.3) Hypertrophic cardiomyopathy (HCM)

There have been no randomised controlled trials of ICD implantation for primary prevention in HCM, but there are multiple non-randomised, observational and registry publications. The risk factors identified represent surrogate markers for the arrhythmia risk inherent in the underlying myocardial disease.

Prior cardiac arrest and syncope have been discussed above. Other major risk factors identified from observational studies include sustained or non-sustained ventricular tachycardia (HR >2.5), family history of sudden cardiac death (HR 1.27), left ventricular septal thickness of ≥30mm (HR 4.0) and abnormal blood pressure response on exercise (HR 2.4 to 9.6). Other risk factors include atrial fibrillation, myocardial ischaemia, left ventricular out-flow tract obstruction, high-risk mutations and intensive physical exertion (Garratt *et al. Eur Heart J* 2010;**12**:1156-1175).

Based on the best evidence currently available, ICD implantation is recommended in patients with one or more of these risk factors for sudden cardiac death.

4.2.2.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Observational data and registries have identified the risk factors of inducible VT, non-sustained VT, male gender, severe dilation or extensive right ventricular involvement, left ventricular involvement, age less than 5-years at presentation, prior cardiac arrest, unexplained syncope and

high-risk genotypes. Hodgkinson *et al.* (*J Am Coll Cardiol* 2005;**45**:400-8) described a genetically homogeneous ARVC population considered at high risk. There were no deaths in the ICD treated group, compared with a five year mortality of 28% in matched high risk males without ICDs and 9% in matched high risk females. The majority of patients reported in these series have received ICD implantation following a clinical arrhythmia. There is less information on the risk of appropriate ICD therapy in patients with other presentations. There are insufficient data to make recommendations on the implantation of an ICD in asymptomatic patients with mild structural disease and these decisions must be individualised and based on the best available data.

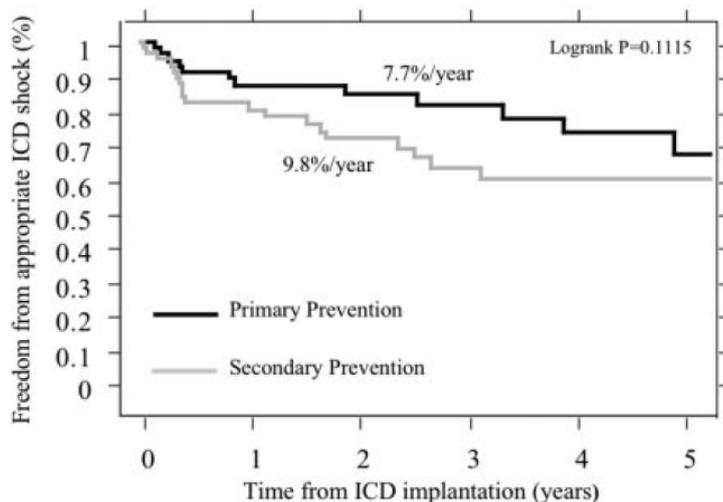
ICD therapy is indicated as primary prevention in ARVC patients with high risk features.

4.2.2.5) Left ventricular non-compaction

LVNC is usually diagnosed following a symptomatic arrhythmia or because of heart failure. There are no published data on the efficacy of ICD therapy in truly asymptomatic individuals. Expert opinion recommends that in addition to optimal pharmacological therapy, ICD implantation for primary prevention is appropriate in patients with LVNC presenting severely impaired LV systolic function (LVEF $\leq 35\%$) (Oechslin E, Jenni R. *European Heart Journal* 2011;**32**:1446–1456, Chin *et al.* *Circulation* 1990;**82**:507-513, Celiker *et al.* *Pacing Clin Electrophysiol* 2004;**27**:104-108).

4.2.2.6) Congenital heart disease

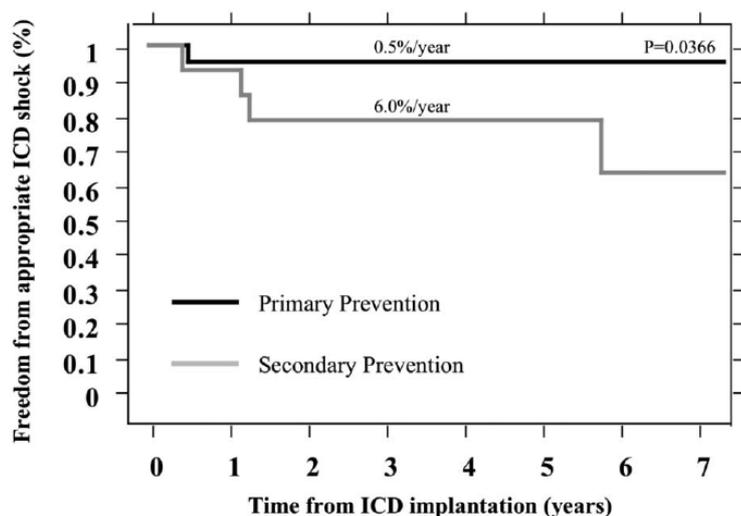
A multicentre series of 68 patients with tetralogy of Fallot were implanted with an ICD for primary prevention because of presyncope (13 patients, 19.1%), syncope (30 patients, 44.1%), palpitations (33, 48.5%), QRS duration >180 ms (19 patients, 27.9%), non-sustained ventricular tachycardia (25 patients, 36.8%), left ventricular ejection fraction $\leq 35\%$ (2, 2.9%) or inducible sustained ventricular tachycardia (28, 41.2%). These patients showed an annual rate of appropriate shocks of 7.7% (Khairy *et al.* *Circulation* 2008;**117**:363-370).



Multivariate analysis showed that factors associated with appropriate shocks were higher LV end diastolic pressure (HR 1.3 per mmHg), and non-sustained ventricular tachycardia (HR 3.7). The authors devised a risk score, based on clinical characteristics, allowing patients to be categorised as low, intermediate or high risk for appropriate shocks. The high risk group had an annualised rate of appropriate shocks of 17.5%, the intermediate group 3.8% and the low risk group did not receive appropriate shocks.

A multicentre series of 23 patients with transposition of the great arteries (TGA) (Khairy *et al.* *Circulation Electrophysiol* 2008;**1**:250-257) treated with a Mustard or a Senning procedure

including an intra-atrial baffle underwent ICD implantation for primary prevention indications (presyncope in 3 patients (13.0%), syncope in 8 patients (34.8%), palpitations in 12 patients (52.2%), non-sustained ventricular tachycardia in 11 patients (47.8%), systemic right ventricular ejection fraction $\leq 35\%$ in 8 patients (34.8%), QRS duration $\geq 180\text{ms}$ in 7 patients (30.4%), and inducible sustained ventricular tachycardia in 7 patients (30.4%)). These patients showed a 0.5% annual rate of appropriate ICD shocks.



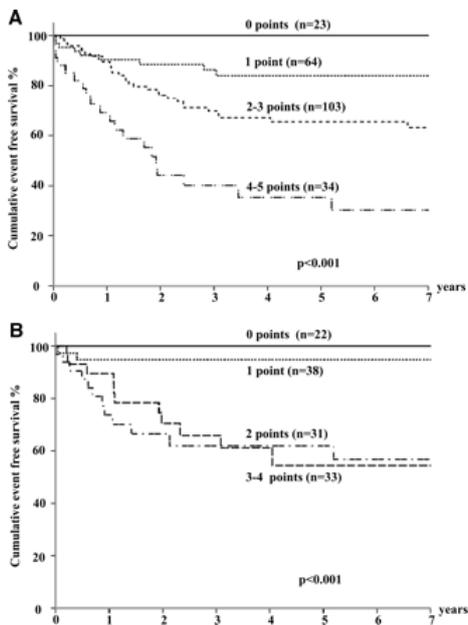
On the available evidence, ICD implantation appears to be indicated for primary prevention indications in patients with Tetralogy of Fallot. There are insufficient data to make a recommendation in patients with transposition of the great arteries.

4.2.2.7) Long QT syndromes

Asymptomatic patients with LQTS represent a lower risk group than those with a history of syncope or cardiac arrest, with a risk of death of $<1\%$ per year (Patrio *et al. N Engl J Med* 2003;**348**:1866-1874). All should receive optimal pharmacological therapy including beta-blockade. Of the commonest genotypes, LQT1 is associated with the lowest risk of 0.3% per year while LQT2 and LQT3 have similar risks of 0.6% per year. Patients with corrected QT intervals over 500ms represent a high-risk sub-group with a hazard ratio of 3.34 for QT intervals 500-549ms and 6.35 for those with $QTc \geq 500\text{ms}$ (Schwartz *et al. Heart Rhythm* 2009;**6**:113-120, Sauer *et al. J Am Coll Cardiol* 2007;**49**:329-337).

Schwartz *et al. (Circulation* 2010;**122**:1272-82) described an international registry of 233 patients with LQTS and ICD implantation. Only 9 were asymptomatic; two of these received appropriate ICD therapy during follow up. A risk score, based on symptoms, length of QT and age was developed, and distinguished those in the whole group who received appropriate therapy from those who did not, and can be used to guide selection for ICD implantation.

Heart Rhythm UK



A study from the same registry examined the risk to an individual with LQTS when a sibling with LQTS has died. Sibling death was not significantly associated with cardiac arrest (Kaufman *et al. Heart Rhythm* 2008;**5**:831-836).

ICD implantation is appropriate in asymptomatic LQTS patients with high-risk features based on the best available data.

4.2.2.8) Short QT syndromes

There are no randomised controlled trial data in this very rare syndrome. A high incidence of sudden cardiac death has been reported in affected families and unstable ventricular arrhythmias are often inducible on electrophysiology study. Published expert opinion is to offer ICD implantation to these patients for primary prevention (Cross B *et al. J Interv Card Electrophysiol* 2011;**31**:25-31).

4.2.2.9) Brugada syndrome

Brugada syndrome patients without symptoms or a spontaneous type 1 ECG abnormality represent a low-risk sub-group where ICD implantation has not been shown to improve survival.

The available data are consistent that asymptomatic patients with Brugada syndrome and a spontaneous type 1 ECG abnormality are at increased risk of sudden death, but series vary in the magnitude of that risk from <math>< 1\%</math> to 6.4% per year (Garratt *et al. Europace* 2010;**12**:1156-1175). Both a conservative strategy and ICD implantation guided by electrophysiology study are supported by published series although the value of electrophysiology study in this context remains to be fully established.

4.2.2.10) Catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT patients not receiving beta-blockers are at high risk of fatal or near fatal arrhythmias with an incidence of 3.1% per year. All patients with the CPVT gene mutations should be treated with beta-blockers regardless of symptoms. Data on further risk stratification is scarce because of the rarity of the condition and electrophysiology testing does not appear to have sufficient sensitivity or specificity to be clinically useful in this condition (Zipes *et al. J Am Coll Cardiol* 2006;**48**:e247-

346, Priori *et al. Eur Heart J* 2001;**22**:1374-1450, Marks *et al. J Cell Physiol* 2002;**190**:1-6). A decision on ICD implantation must be individualised and made on the best available data.

4.2.2.11) Patients awaiting cardiac transplantation

By definition, patients awaiting cardiac transplantation for heart failure have severe cardiac disease and a high short-term mortality. This is demonstrated by a high rate of sudden cardiac death in patients on the transplant waiting list. Whilst, if transplantation were not to take place, many patients would not survive 12 months, with transplantation 10-year survival exceeds 50%. It is therefore reasonable to implant an ICD in patients with a high likelihood of surviving to transplantation in the absence of a ventricular arrhythmia.

4.2.2.12) Children, adolescents and adults with congenital heart disease

It must be recognised that the dataset for ICD therapy is almost entirely derived from studies in adults. In addition, there are factors unique to the young people that increase both the risks and benefits of ICD therapy (Chatrath *et al. Mayo Clin Proc* 2002;**77**:226-231). Nevertheless, data from non-randomised studies support the use of ICD implantation in young people resuscitated from cardiac arrest following the exclusion of a reversible or curable cause with the same indications as adults.

There are few data specifically related to primary prevention in children and adolescents. Some have been derived from the international long QT registry, and were discussed above. There are some data available in adolescents and adults following surgery for congenital heart disease. This was also discussed above.

5) Cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT) is a technology which increases the efficiency of left ventricular contraction by direct electrical stimulation of the left ventricle. Its original indication was to improve symptoms of heart failure but more recent data also show evidence of improved survival, the prevention of heart failure symptoms and reduced admission to hospital with decompensation.

Heart failure due to left ventricular systolic dysfunction is often accompanied by reduced electrical synchronisation. The most common abnormalities being delayed conduction through the atrioventricular node – PR prolongation, first degree heart block – and slowed ventricular depolarisation – QRS prolongation, bundle-branch block. This results in delayed contraction of parts of the left ventricle which can reduce ejection fraction, increase metabolic demands and cause functional mitral regurgitation with dilation of the heart. These electrical abnormalities are seen in approximately 1/3 of patients with advanced heart failure and are associated with heart failure progression, sudden cardiac death and all-cause mortality.

5.1) Current national and international guidance

5.1.1) UK

Current NICE guidance (NICE technology appraisal guidance 120: Cardiac resynchronisation therapy for the treatment of heart failure TA120, May 2007, www.nice.org.uk/TA120) states:

1.1 Cardiac resynchronisation therapy with a pacing device (CRT-P) is recommended as a treatment option for people with heart failure who fulfil all the following criteria.

- They are currently experiencing or have recently experienced New York Heart Association (NYHA) class III-IV symptoms.
- They are in sinus rhythm:
 - **either** with a QRS duration of 150ms or longer estimated by standard electrocardiogram (ECG)
 - **or** with a QRS duration of 120-149ms estimated by ECG **and** mechanical dyssynchrony that is confirmed by echocardiography.
- They have a left ventricular ejection fraction of 35% or less.
- They are receiving optimal pharmacological therapy.

1.2 Cardiac resynchronisation therapy with a defibrillator device (CRT-D) may be considered for people who fulfil the criteria for implantation of a CRT-P device in section 1.1 and who also separately fulfil the criteria for the use of an ICD device as recommended in NICE technology appraisal guidance 95.

5.1.2) North America

Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm

Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *J. Am. Coll. Cardiol.* 2008;**51**:e1-e62

<http://content.onlinejacc.org/cgi/content/full/51/21/e1>

Class I (procedure should be performed) and **Ila** (it is reasonable to perform the procedure):

CLASS I

1. For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy. (Level of Evidence: A) (222,224,225,231)

CLASS Ila

1. For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy. (Level of Evidence: B) (220,231)
2. For patients with LVEF less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable. (Level of Evidence: C) (231)

CLASS Iib

1. For patients with LVEF less than or equal to 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered. (Level of Evidence: C) (231)

5.1.3) European Society of Cardiology

Current ESC guidance (Focused Update of ESC Guidelines on device therapy in heart failure 2010. Dickstein *et al. European Heart Journal* 2010;**31**:2677–2687) states:

Recommendation in patients with heart failure in New York Heart Association function class III/IV

Recommendation	Patient population	Class ^a	Level ^b	Ref. ^c
CRT-P/CRT-D is recommended to reduce morbidity and mortality ^d	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms, SR Optimal medical therapy Class IV patients should be ambulatory ^e	I	A	5–19

Recommendation in patients with heart failure in New York Heart Association function class II

Recommendation	Patient population	Class ^a	Level ^b	Ref. ^c
CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression ^d	NYHA function class II LVEF \leq 35%, QRS \geq 150 ms, SR Optimal medical therapy	I	A	9, 20–22

Recommendations in patients with heart failure and permanent atrial fibrillation

Recommendations	Patient population	Class ^a	Level ^b	Ref. ^c
CRT-P/CRT-D ^d should be considered to reduce morbidity	NYHA function class III/IV LVEF \leq 35%, QRS \geq 130 ms Pacemaker dependency induced by AV nodal ablation	IIa	B	27–40
CRT-P/CRT-D ^d should be considered to reduce morbidity	NYHA function class III/IV LVEF \leq 35%, QRS \geq 130 ms Slow ventricular rate and frequent pacing ^e	IIa	C	—

Recommendations in patients with heart failure and a concomitant class I pacemaker indication

Recommendations	Patient population	Class ^a	Level ^b	Ref. ^c
CRT-P/CRT-D ^d is recommended to reduce morbidity	NYHA function class III/IV LVEF \leq 35%, QRS \geq 120 ms	I	B	41–48
CRT-P/CRT-D ^d should be considered to reduce morbidity	NYHA function class III/IV LVEF \leq 35%, QRS <120 ms	IIa	C	—
CRT-P/CRT-D ^d may be considered to reduce morbidity	NYHA function class II LVEF \leq 35%, QRS <120 ms	IIb	C	—

Current ESC guidance on acute and chronic heart failure states (McMurray *et al. Eur Heart J* 2012;**33**:1787-1847):

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class III and ambulatory class IV heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy

Recommendations	Class ^a	Level ^b	Ref. ^c
LBBB QRS morphology CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of \geq 120 ms, LBBB QRS morphology, and an EF \leq 35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	156, 157
Non-LBBB QRS morphology CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of \geq 150 ms, irrespective of QRS morphology, and an EF \leq 35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.	IIa	A	156, 157

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class II heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy

Recommendations	Class ^a	Level ^b	Ref ^c
LBBB QRS morphology CRT, preferably CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥ 130 ms, LBBB QRS morphology, and an EF $\leq 30\%$, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	154, 155
Non-LBBB QRS morphology CRT, preferably CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥ 150 ms, irrespective of QRS morphology, and an EF $\leq 30\%$, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.	IIa	A	154, 155

Recommendations for the use of CRT where the evidence is uncertain—patients with symptomatic HF (NYHA functional class II–IV) and a persistently reduced EF despite optimal pharmacological therapy and in AF or with a conventional pacing indication

Recommendations	Class ^a	Level ^b	Ref ^c
Patients in permanent AF			
CRT-P/CRT-D may be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥ 120 ms and an EF $\leq 35\%$, who are expected to survive with good functional status for >1 year, to reduce the risk of HF worsening if: <ul style="list-style-type: none"> The patient requires pacing because of an intrinsically slow ventricular rate The patient is pacemaker dependent as a result of AV nodal ablation The patient's ventricular rate is ≤ 60 b.p.m. at rest and ≤ 90 b.p.m. on exercise. 	IIb	C	–
	IIb	C	–
	IIb	C	–
Patients with an indication for conventional pacing and no other indication for CRT			
In patients who are expected to survive with good functional status for >1 year: <ul style="list-style-type: none"> CRT should be considered in those in NYHA functional class III or IV with an EF $\leq 35\%$, irrespective of QRS duration, to reduce the risk of worsening of HF CRT may be considered in those in NYHA functional class II with an EF $\leq 35\%$, irrespective of QRS duration, to reduce the risk of worsening of HF. 	IIa	C	–
	IIb	C	–

5.2) Published data

CRT was developed as an electrical treatment for heart failure symptoms in patients with severe left ventricular impairment and impaired synchronisation of left ventricular contraction. Early studies confirmed symptomatic benefit in these patients with more recent data demonstrating a mortality benefit and defining groups of patients who are most likely to benefit from this treatment. The data are presented according to the selection criteria of left ventricular function, dyssynchrony and symptoms:

5.2.1) Left ventricular function

CRT trials have been conducted almost exclusively in patients with severely impaired left ventricular systolic function (LVEF $\leq 35\%$). Small studies (Chung *et al. Eur J Heart Fail* 2010;**12**:581–87, Fung *et al. J Cardiovasc Electrophysiol* 2006;**17**:1288–92) have shown benefit in selected patients with less severe systolic impairment but at present there are currently insufficient data to recommend CRT in patients with LVEF $>35\%$. There are no data to support the implantation of a CRT device in patients with normal left ventricular systolic function.

5.2.2) Dys-synchrony

CRT is an electrical treatment allowing the stimulation of the right and left ventricles. Its benefit is thought to derive from resynchronisation of cardiac contraction. Initial studies inferred dyssynchrony from prolonged QRS duration (≥ 120 ms) on the standard ECG. Later studies investigated the concept of mechanical dyssynchrony in those with and without QRS prolongation.

5.2.2.1) QRS <120ms

Small single centre studies have suggested benefit from CRT in patients with normal QRS duration selected in a variety of ways. A small randomised clinical trial of CRT in 126 patients with LVEF $\leq 35\%$, NYHA III symptoms, QRS <120ms and mechanical dyssynchrony (Beshai *et al. N Engl J Med* 2007;**357**:2461-2471) showed an increase in the proportion of patients improving by one NYHA class (29% versus 48% $p=0.04$) but there was no significant improvement in other end points, including the quality-of-life, 6-minute walking distance, left ventricular function or peak oxygen consumption. A large on-going trial (EchoCRT, NCT00683696) in patients with QRS <130ms should provide additional information in this important group of patients but at present there are insufficient data to recommend CRT in patients with normal QRS duration.

5.2.2.2) QRS ≥ 120 ms

There are multiple clinical trials demonstrating significant sustained symptomatic benefit in patients with heart failure, LVEF $\leq 35\%$ and QRS ≥ 120 ms:

Table 1 Inclusion criteria in randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial	Patients	NYHA class	LVEF (%)	LVEDD (mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR ¹⁶	58	III	≤ 35	≥ 60	SR	≥ 150	No
MIRACLE ⁵	453	III, IV	≤ 35	≥ 55	SR	≥ 130	No
MUSTIC AF ³⁵	43	III	≤ 35	≥ 60	AF	≥ 200	No
PATH CHF ⁶	41	III, IV	≤ 35	NA	SR	≥ 120	No
MIRACLE ICD ⁸	369	III, IV	≤ 35	≥ 55	SR	≥ 130	Yes
CONTAK CD ⁵⁴	227	II, IV	≤ 35	NA	SR	≥ 120	Yes
MIRACLE ICD II ⁹	186	II	≤ 35	≥ 55	SR	≥ 130	Yes
PATH CHF II ⁵⁵	89	III, IV	≤ 35	NA	SR	≥ 120	Yes/no
COMPANION ¹⁰	1520	III, IV	≤ 35	NA	SR	≥ 120	Yes/no
CARE HF ¹¹	814	III, IV	≤ 35	≥ 30	SR	≥ 120	No
CARE HF ¹⁷	813	III, IV	≤ 35	≥ 30	SR	≥ 120	No
REVERSE ^{21,22}	610	I, II	≤ 40	≥ 55	SR	≥ 120	Yes/no
MADIT CRT ²⁰	1800	I, II	≤ 30	NA	SR	≥ 130	Yes
RAFT ⁵⁶	1800 Canada	II, III	≤ 30	> 60	SR/AF	≥ 130 $\geq 200^a$	Yes

The mean improvement in NYHA function class was 0.5 to 0.8, with a 20% increase in 6 minute walk distance and an increase in peak oxygen consumption of 10 to 15%. The trials have also shown improvements in ejection fraction, mitral regurgitation and a reduction in left ventricular dilation:

Table 2 Endpoints, design, and main findings of the randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial	Endpoints	Design	Main findings
MUSTIC-SR ¹⁶	6MWT, QoL, pVO ₂ , Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved: 6MWT, QOL, pVO ₂ ; reduced Hosp
MIRACLE ⁸	NYHA class, QoL, pVO ₂	Double-blinded, controlled, 6 months	CRT-P improved: NYHA, pVO ₂ , 6MWT
MUSTIC AF ³⁵	6MWT, QoL, pVO ₂ , Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved all; reduction of Hosp
PATH CHF ⁶	6MWT, pVO ₂	Single-blinded, controlled, crossover, 12 months	CRT-P improved: 6MWT; pVO ₂
MIRACLE ICD ⁸	6MWT, QoL, Hosp	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved all from baseline (not ICD)
CONTAK CD ⁵⁴	All-cause death + HF Hosp, pVO ₂ , 6MWT, NYHA class, QoL, LVEDD, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: pVO ₂ , 6MWT; reduced LVEDD and increased LVEF
MIRACLE ICD II ⁹	VE/CO ₂ , pVO ₂ , NYHA, QoL, 6MWT, LV volumes, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: NYHA, VE/CO ₂ volumes, LVEF
COMPANION ¹⁰	(i) All-cause death or Hosp	Double-blinded, controlled, OMT, CRT-D, CRT-P, ~15 months	CRT-P/CRT-D: reduced (i)
CARE-HF ¹¹	(i) All-cause death or CV event (ii) All-cause death	Double-blinded, controlled, OMT, CRT-P, 29 months	CRT-P reduced (i) and (ii)
REVERSE ²¹	(i) % worsened by clinical composite endpoint, (ii) LVESVi (iii) HF Hosp, (iv) all-cause death	Double-blinded, controlled, OMT, CRT-P \pm ICD, 12 months	Primary endpoint NS; CRT-P/CRT-D reduced (ii) and (iii) Hosp but not (iv)
MADIT-CRT ²⁰	(i) HF event or death, (ii) All-cause death, (iii) LVESV	Controlled, CRT-P, CRT-D, 2.4 years	CRT-D reduced (i) and (iii) but not (ii)

Heart Rhythm UK

A meta-analysis of 4 early trials of CRT in 1634 patients reporting death and hospitalisation for heart failure or arrhythmia (Bradley *et al.* *JAMA* 2003;**289**:730-740) showed an absolute 1.8% (relative risk reduction 51%, hazard ratio 0.49; 0.25-0.93) reduction in heart failure mortality, a significant absolute 4.4% (relative risk reduction 29%, hazard ratio 0.71; 0.53-0.96) reduction in heart failure hospitalisation, but no significant change in non-heart failure mortality although there was a trend to a reduction in all-cause mortality (absolute 1.4%, relative risk reduction 23%, hazard ratio 0.77; 0.51-1.18):

Figure 2. Death Among Patients Randomized to Cardiac Resynchronization vs No Resynchronization

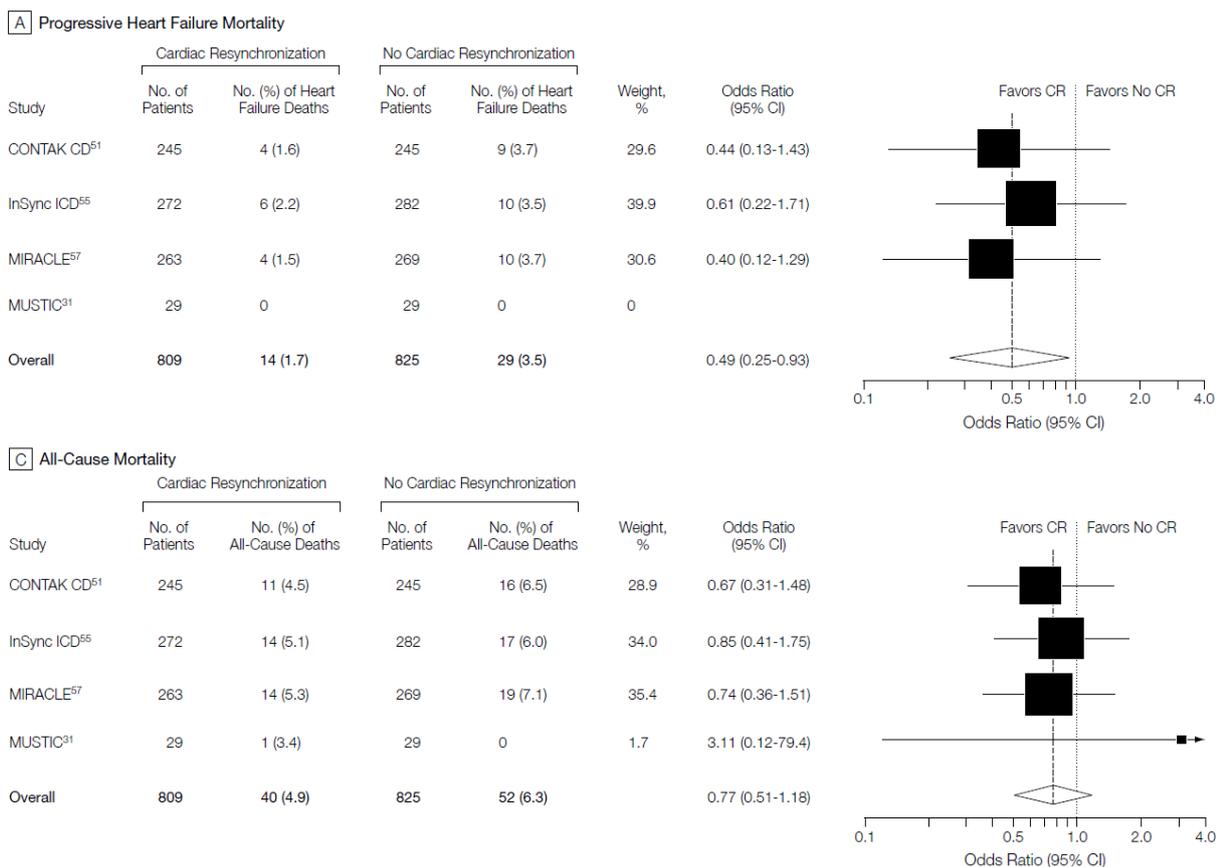
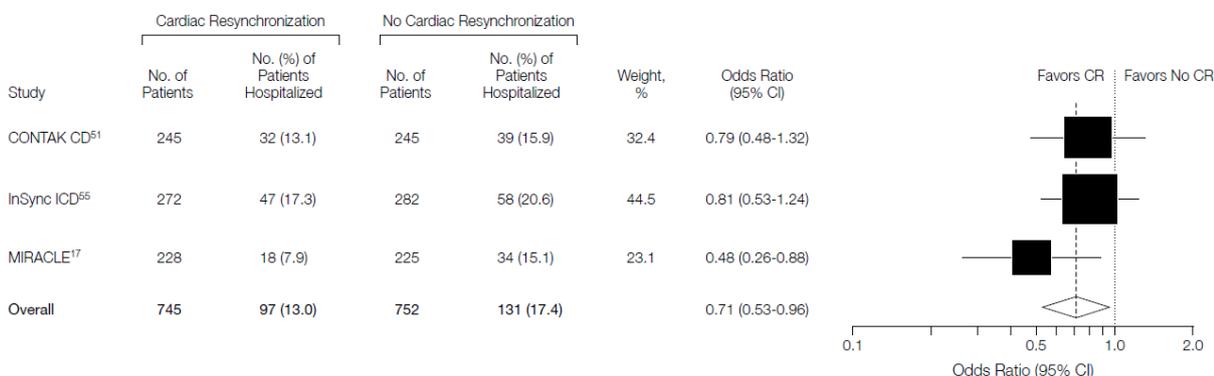


Figure 3. Heart Failure Hospitalization Among Patients Randomized to Cardiac Resynchronization vs No Cardiac Resynchronization

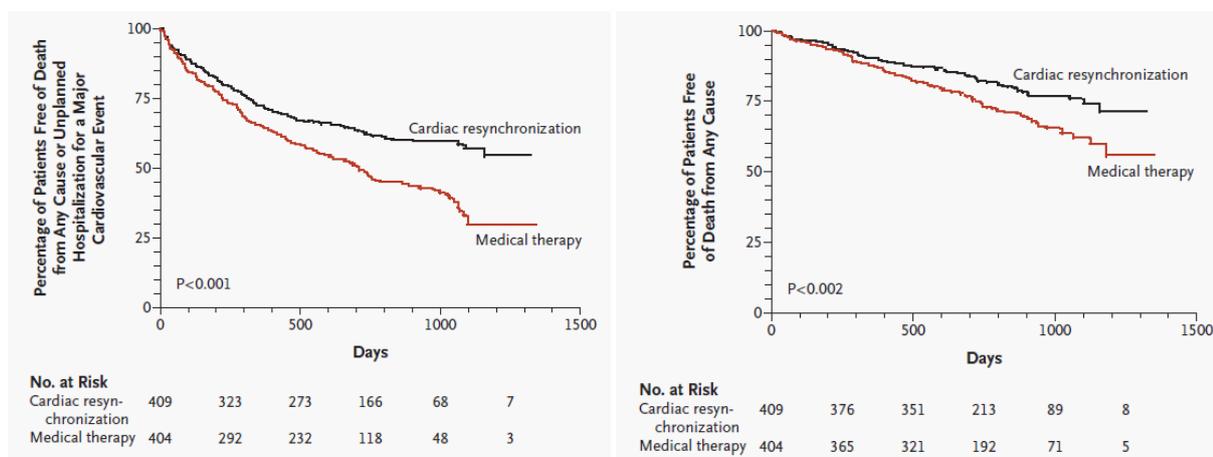


Mechanical dyssynchrony

In an attempt to increase the proportion of patients with QRS ≥ 120 ms who show objective clinical benefit from CRT, trials have assessed a variety of indices of mechanical dyssynchrony and QRS durations:

Heart Rhythm UK

Multiple small single centre reports described echocardiographic indices correlating with response to CRT and these indices of mechanical dyssynchrony were used as an empirical selection criterion for patients with QRS 120-149ms in the CArdiac REsynchronisation in Heart Failure trial (CARE-HF; Cleland *et al.* *N Engl J Med* 2005;**352**:1539-49). This randomised 813 patients with NYHA III/IV heart failure symptoms, LVEF $\leq 35\%$ and QRS ≥ 150 ms or ≥ 120 ms with echocardiographic dyssynchrony (an aortic pre-ejection delay of more than 140ms, an interventricular mechanical delay of more than 40ms, or delayed activation of the posterolateral left ventricular wall) to optimal pharmacological therapy with or without the implantation of a pacemaker capable of CRT (CRT-P). Over a mean follow-up of 29.4 months there was a 16% absolute reduction in the primary end-point of death or heart failure hospitalisation (37% relative risk reduction, hazard ratio, 0.63; 95 percent confidence interval, 0.51 to 0.77; $P < 0.001$), with a highly significant 10% absolute all-cause mortality reduction (36% relative risk reduction, hazard ratio 0.64; 95 percent confidence interval, 0.48 to 0.85; $P < 0.002$):



However, only 92 randomised patients (11.3%) were selected on the basis of a QRS duration 120-149ms and mechanical dyssynchrony. These patients appeared to derive less benefit from CRT (HR 0.74; 0.54-1.02) than those with QRS durations ≥ 150 ms (HR 0.60; 0.46-0.79) (Stavrakis *et al.* *J Cardiovasc Electrophysiol* 2012;**23**:163-168).

Because of a lack of agreement on the echocardiographic measurements for CRT selection, the PROSPECT trial (Chung *et al.* *Circulation.* 2008;**117**:2608-2616) assessed 498 patients with standard CRT indications. Twelve echocardiographic parameters of dyssynchrony, using conventional and tissue Doppler-based techniques, were evaluated. The ability of the echocardiographic parameters to predict a clinical composite score response varied widely, with sensitivity ranging from 6% to 74% and specificity ranging from 35% to 91%; for predicting left ventricular end-systolic volume response, sensitivity ranged from 9% to 77% and specificity from 31% to 93%. For all the parameters, the area under the receiver-operating characteristics curve for positive clinical or volume response to CRT was ≤ 0.62 . There was large variability in the analysis of the dyssynchrony parameters.

Currently available measurements of dyssynchrony do not have sufficient sensitivity and specificity to extend or restrict CRT indications based on symptoms, QRS duration and LVEF. It is possible that future research will demonstrate mechanical dyssynchrony criteria which refine CRT selection criteria but at present there is insufficient evidence for their routine clinical use in patient selection for CRT therapy.

QRS duration and morphology

A recent meta-analysis (Stavrakis *et al. J Cardiovasc Electrophysiol* 2012;**23**:163-168) suggests that the majority of benefit from CRT was seen in those with a QRS ≥ 150 ms (HR = 0.58, 95% CI: 0.50–0.68; P < 0.000010):

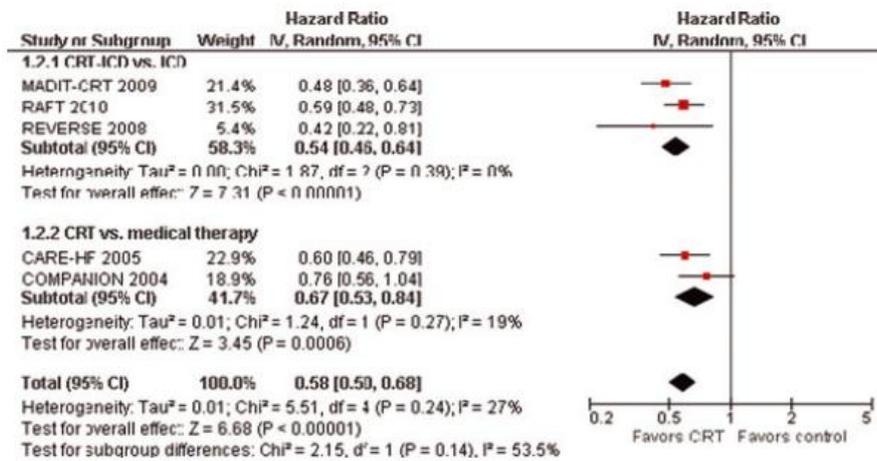


Figure 2. Forest plot of study-specific and pooled hazard ratio and 95% confidence interval for the primary endpoint among patients with QRS ≥ 150 ms assigned to cardiac resynchronization therapy (CRT) versus control. ICD = implantable cardioverter defibrillator.

with a non-significant benefit in those with QRS <150ms:

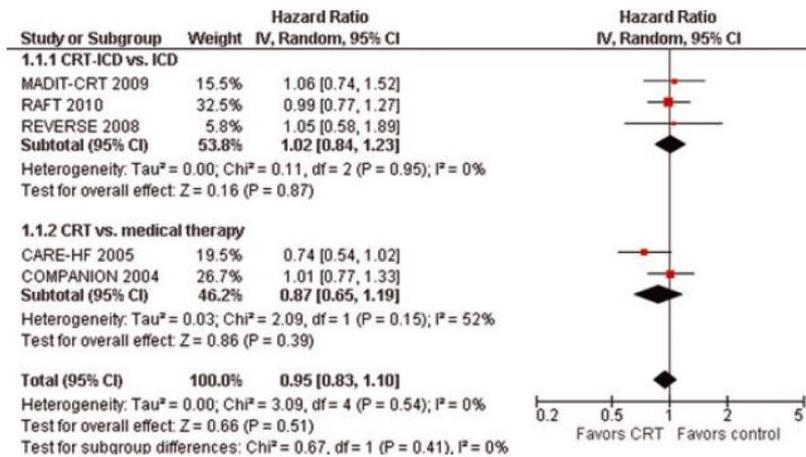
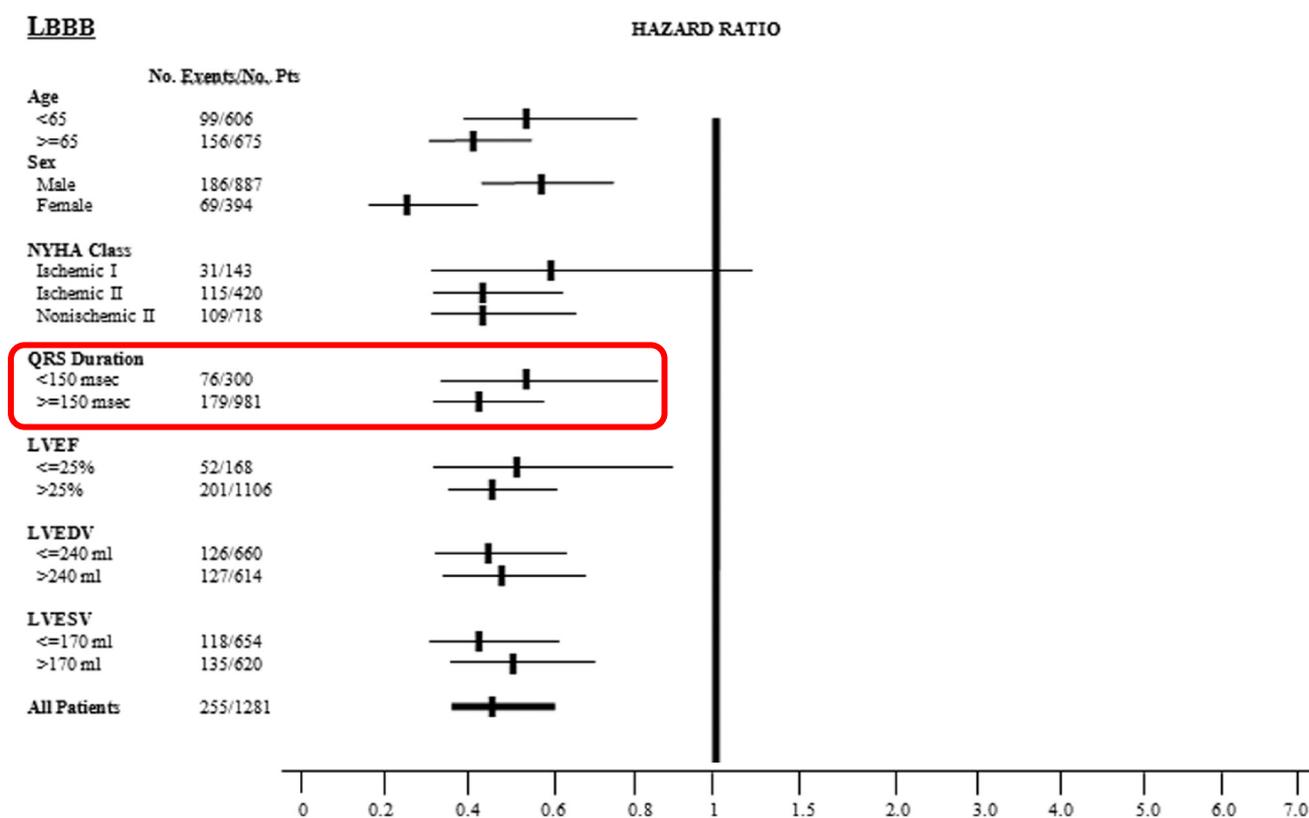


Figure 3. Forest plot of study-specific and pooled hazard ratio and 95% confidence interval for the primary endpoint among patients with QRS < 150 ms assigned to cardiac resynchronization therapy (CRT) versus control. ICD = implantable cardioverter defibrillator.

QRS duration can be prolonged by a number of different conduction delays. The commonest in heart failure patients is left bundle branch block (LBBB) but others show right bundle branch block (RBBB) or non-specific conduction delays. There are theoretical reasons why patients with LBBB might benefit more from CRT than patients with other patterns of QRS prolongation as LBBB results in delayed contraction of the left ventricular free wall, the area specifically stimulated in CRT.

Analysis of MADIT-CRT (Zareba *et al. Circulation*. 2011;**123**:1061-1072) in less symptomatic patients, suggests similar benefit in those with QRS prolongation due to left bundle branch block (LBBB) for QRS durations of 120-149ms and >150ms:



It is recognised that QRS ≥150ms is strongly correlated with the presence of left bundle branch block (LBBB). Combining data from MADIT-CRT analysed by Zareba *et al. Circulation* 2011;**123**:1061-1072 and Stavrakis *et al. J Cardiovasc Electrophysiol* 2012;**23**:163-168 shows benefit of CRT in less symptomatic patients with QRS ≥150ms or QRS 120-149ms with LBBB:

	QRS 120-149ms	QRS ≥150ms	ALL patients
LBBB	n=300 HR = 0.54	n=981 HR = 0.43	n= 1281 HR = 0.47
RBBB/IVCD	n=343 HR = 1.5	n=193 HR = 0.98	n=536 HR = 1.24
TOTAL	n=643 HR = 1.06	n=1174 HR = 0.48	

n= number of patients
HR = hazard ratio

5.2.3) Symptoms

Early CRT trials randomised patients with severe heart failure symptoms (NYHA III/IV). More recent trials have tested the technology in less symptomatic patients.

5.2.3.1) NYHA class I

Two trials of CRT randomised patients without heart failure symptoms (NYHA I) REVERSE (Linde *et al. J Am Coll Cardiol* 2008;**52**:1834–43) and MADIT-CRT(Moss *et al. N Engl J Med* 2009;**361**:1329–38). REVERSE included 75 patients in NYHA I with EF <40% and LVEDD >55mm. There was a trend to a reduction in heart failure events (hazard ratio 0.87; 0.37-2.03), but no significant effect on all-cause mortality which was only 2% in both groups.

Clinical Composite Response Detail	CRT-OFF (n = 191)	CRT-ON (n = 419)
Worsened, n (%)	41 (21)	67 (16)
Death	3 (2)	9 (2)
Hospitalization due to or associated with worsening HF	14 (7)	12 (3)
Crossover due to worsening HF	5 (3)	1 (<1)
Worsened patient global assessment and NYHA functional class	0 (0)	2 (<1)
Worsened NYHA functional class only	18 (9)	40 (10)
Worsened patient global assessment only	1 (1)	3 (1)
Improved, n (%)	76 (40)	228 (54)
Improved on patient global assessment and NYHA functional class	11 (6)	69 (16)
Improved NYHA functional class only	28 (15)	59 (14)
Improved patient global assessment only	37 (19)	100 (24)
Unchanged	74 (39)	124 (30)

MADIT-CRT randomised 152 patients in NYHA I with a history of ischaemic heart disease and LVEF $\leq 30\%$. There was a trend to reduced heart failure end-points with a non-significant hazard ratio of approximately 0.77.

A recent meta-analysis of these trials (Adabag *et al. J Am Coll Cardiol* 2011;**58**:935–41) has shown statistically significant benefit in heart failure hospitalisation (11.9% versus 20.5%, HR 0.57, NNT 12, $p=0.04$) and a trend to reduced mortality (6.0% versus 7.1%, HR 0.85, NNT 88, $p=0.71$).

Table 3

Pooled Mortality and HF Events/Hospitalizations With CRT Among Asymptomatic or Mildly Symptomatic Patients With HF

	CRT	ICD	RR	95% CI	p Value	NNT
NYHA functional class I/II						
Mortality	8.0%	11.5%	0.81	0.65–0.99	0.04	29
HF hospitalization	11.6%	18.2%	0.68	0.59–0.79	<0.001	15
Combined	17.5%	26.4%	0.72	0.65–0.81	<0.001	
NYHA functional class II						
Mortality	9.6%	13.1%	0.78	0.65–0.95	0.011	28
HF hospitalization	14.6%	21.5%	0.67	0.57–0.79	<0.001	14
Combined	20.7%	29.3%	0.73	0.64–0.83	<0.001	
NYHA functional class I						
Mortality	6.0%	7.1%	0.85	0.36–2.01	0.71	88
HF hospitalization	11.9%	20.5%	0.57	0.34–0.97	0.04	12
Combined	15.5%	22.1%	0.70	0.44–1.13	0.14	

5.2.3.2) NYHA class II

Five randomised trials included patients with NYHA class II symptoms: CONTAK-CD (Higgins *et al. J Am Coll Cardiol* 2003;**42**:1454–9), MIRACLE ICD (Young *et al. JAMA* 2003;**289**:2685–2694), REVERSE (Linde *et al. J Am Coll Cardiol* 2008;**52**:1834–43), MADIT-CRT (Moss *et al. N Engl J Med* 2009;**361**:1329–38) and RAFT (Tang *et al. N Engl J Med* 2010;**363**:2385–95). A meta-analysis (Adabag *et al. J Am Coll Cardiol* 2011;**58**:935–41) demonstrates significant reductions in all-cause mortality (absolute 3.5%, hazard ratio 0.78 (0.65–0.95) $p=0.011$) and heart failure hospitalisation (absolute 6.9%, hazard ratio 0.67 (0.57–0.79) $p<0.001$) as shown above.

5.2.3.3) NYHA class III

Trials of CRT have consistently shown benefit in morbidity and mortality in patients with severe left ventricular impairment (LVEF $\leq 35\%$) prolonged QRS duration (≥ 120 ms) and moderate or severe heart failure symptoms (NYHA III/IV). The data are reviewed above.

5.2.3.4) NYHA class IV

Although clinical benefit has been seen from CRT in patients with NYHA class IV symptoms, only 10% of those randomised in the clinical trials were in NYHA IV and those were ambulatory out-patients on oral medication without recent hospital admission. These patients have high heart failure mortality and have been regarded as having a contraindication to ICD therapy.

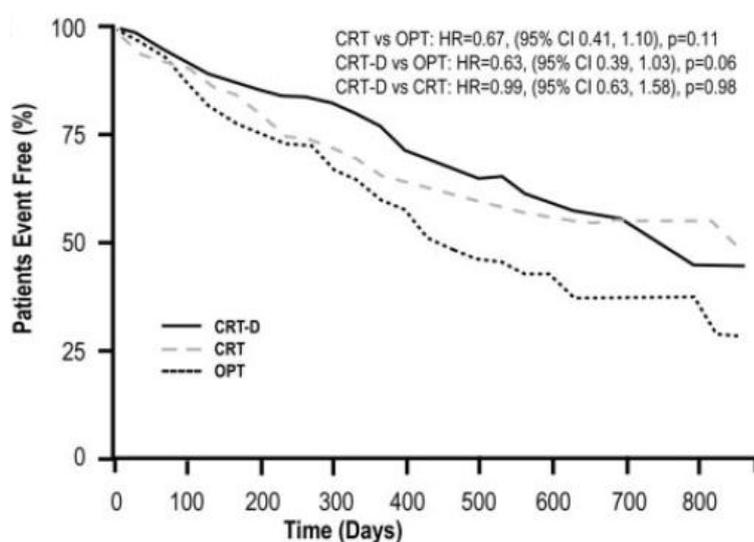
In NYHA IV patients randomised in the COMPANION trial (Lindenfeld *et al. Circulation* 2007;**115**:204-212), the primary end point of time to death or hospitalisation for any cause was significantly prolonged by both CRT-P (HR, 0.64; P=0.02) and by CRT-D (HR, 0.62; P=0.01) compared with optimal medical therapy (OPT). There were significant improvements in quality of life and NYHA function class with 67% of the 217 NYHA IV patients improving their symptoms to NYHA III. This is the same proportion of patients improving as in other NYHA functional classes:

TABLE 4. Functional Capacity in NYHA Class IV Patients: Change From Baseline to 6 Months

Indicator	Number	Median (Q1, Q3)	% Improved	P
6-Minute walk				
CRT/CRT-D	69	45.6 (-15.2, 106.4)	...	0.55
OPT	12	45.6 (-22.3, 60.9)
Quality of life				
CRT/CRT-D	109	-25.0 (-44.0, -8.0)	...	<0.01
OPT	29	-4.0 (-20, 9.0)
NYHA				
CRT/CRT-D	119	...	78	<0.01
OPT	27	...	52	...

Q indicates quartile.

44% of NYHA IV patients receiving OPT patients died in the first year, compared with 36% of CRT-P and 30% of CRT-D patients. Their 2-year mortality was non-significantly reduced with a hazard ratio of 0.67 for CRT-P and 0.63 for CRT-D compared to OPT:



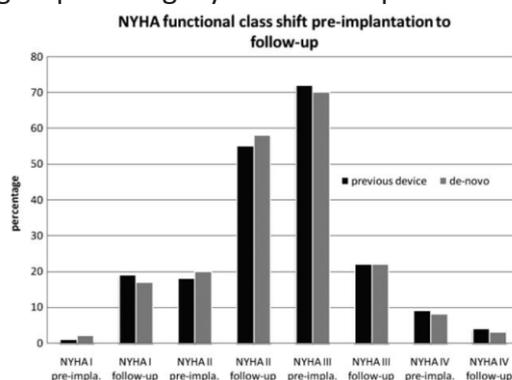
NYHA IV symptoms are not a contraindication to CRT therapy but the incremental benefit of CRT-D over CRT-P may be smaller than in less symptomatic patients because of the high risk of heart failure death.

5.2.4) QRS prolongation due to right ventricular pacing

The adverse acute and chronic haemodynamic effects of right ventricular pacing have been described in many publications over the past century. In patients with preserved LV function, RV pacing increased the risk for heart failure hospitalization (MOST, Sweeney *et al. Circulation* 2003;**107**:2932-7) while in patients with LV dysfunction, the detrimental effect of RV stimulation was even more marked with a 60% increase in the combined endpoint of heart failure hospitalization or death (DAVID, Wilkoff *et al. JAMA* 2002;**288**:3115-23). An analysis of heart failure patients in the MADIT II trial (Barsheshet *et al. Heart Rhythm* 2011;**8**:212-8) showed reduced survival benefit in those with >50% RV pacing (HR = 0.89, P = 0.45) compared to those with ≤50% RV pacing (HR = 0.60, P < 0.001).

Some patients with a requirement for ventricular bradycardia pacing experience severe heart failure symptoms and are found to have severe left ventricular impairment. Their QRS duration is prolonged by right ventricular pacing for bradycardia. There are no randomised controlled trials of upgrade to a CRT device but observational studies have shown similar benefits to those seen in *de novo* CRT implantation (Witte *et al. J Card Fail* 2006;**12**:199-204, Nägele *et al. Pacing Clin Electrophysiol* 2008;**31**:1265-1271, Wokhlu *et al. Heart Rhythm* 2009;**6**:1439-1447, Fröhlich *et al. Eur Heart J* 2010;**31**:1477-1485).

The European CRT Survey (Bogale *et al. European Journal of Heart Failure* 2011;**13**:974-983) included 2367 CRT implant procedures of which 692 (29.2%) were upgrades to CRT from standard right ventricular pacemakers or ICDs. Procedural complications were not increased in upgrade procedures and patients' NYHA class improvements and other outcomes were similar between the groups during 1 year follow-up:



Upgraded patients have comparable symptom and mortality outcomes at 1 year to those receiving *de novo* CRT implants, and implant procedural complications are not significantly higher in upgraded patients.

5.2.5) Patients with heart failure and an indication for bradycardia pacing

Given the detrimental haemodynamic effects of RV pacing and the demonstrated benefits of upgrade to CRT, the Homburg Biventricular Pacing Evaluation (HOBIPACE, Kindermann *et al. J Am Coll Cardiol* 2006;**47**:1927-37) randomised 30 patients with a standard indication for permanent ventricular pacing, an LV end-diastolic diameter ≥60 mm and an ejection fraction ≤40%. Statistically significant benefit from CRT compared to RV pacing was demonstrated for symptoms (The Minnesota Heart Failure score was six points lower with CRT versus RV pacing (p < 0.010), NYHA functional class was an average of 0.6 lower with CRT versus RV pacing (p < 0.015)) and left ventricular function (LVEF was 6.3% higher with CRT and RV pacing (p < 0.001)).

5.2.6) Atrial fibrillation

Atrial fibrillation is common in patients with heart failure, affecting 25-50% of patients with NYHA class III/IV symptoms. Thus, approximately 20% of patients undergoing CRT implantation in Europe are in permanent atrial fibrillation.

A meta-analysis (Upadhyay *et al. J Am Coll Cardiol* 2008;**52**:1239-1246) of 1164 patients in the 5 prospective cohort studies which included both patients in sinus rhythm and those in atrial fibrillation showed that patients in atrial fibrillation had clinically and statistically significant improvements with CRT: a mean 8.6%, increase in LVEF (7.1% - 10.1%, $p < 0.0001$) a mean improvement of 0.8 NYHA functional class (0.7 - 1.0, $p < 0.0001$), a mean 11.6m increase in 6-minute walk distance (13.51 to 19.59m, $p < 0.005$) and a 9.4 points improvement in self-perceived quality of life score (MLWHF, 13.38 -5.37 points, $p < 0.0001$).

NYHA class improved similarly for patients in atrial fibrillation and sinus rhythm (0.90 for SR patients, 0.84 for AF patients) and all-cause mortality was not significantly different at 1 year (relative risk ratio: 1.57, 95% confidence interval 0.87-2.81). Those in sinus rhythm showed a mean 11.6m greater improvement in the 6-min walk distance than those in AF (11.6 (CI: 10.4 to 12.8 m) and Minnesota score (3.9 points less, 95% CI: 3.4 to 4.5 points) than AF patients. AF patients showed a statistically significant greater increase in ejection fraction (0.39% greater increase in ejection fraction, 95% CI: 0.22% to 0.55%).

The available data show that patients in AF benefit similarly to those in sinus rhythm when a high proportion of ventricular beats are biventricularly paced. Koplan *et al. (JACC* 2009;**53**:355-360) found patients with 93-100% pacing dependence had a 44% reduction in mortality and hospitalisation for heart failure compared to subjects paced 0% to 92% (HR 0.56, $p < 0.00001$). This may be achieved with conventional heart failure treatment with β -blockade but may require AV node ablation. This was performed in 56% of patients in these trials:

Table 2 Use of AVJ Ablation in AF Patients

Study	AF Patients		
	Total AF Patients	No. of Received AVJ Ablation	% Received AVJ Ablation
Delnoy <i>et al.</i> (22), 2007	96	21	22%
Gasparini <i>et al.</i> (21), 2006	162	114	70%
Molhoek <i>et al.</i> (20), 2004	30	17	57%
Linde <i>et al.</i> (18), 2002	64	40	63%
Leclercq <i>et al.</i> (19), 2000	15	15	100%

5.2.7) Conclusions

- 1) CRT is indicated in patients with severely impaired LV systolic function (LVEF $\leq 35\%$) and ECG evidence of dyssynchrony (QRS duration ≥ 120 ms)
- 2) The greatest benefits are seen in the most symptomatic patients (NYHA III/IV)
- 3) Less information is available on the benefits of CRT in patients with mild heart failure symptoms. Meta-analysis of NYHA I patients has shown statistically significant benefit in heart failure hospitalisation and a trend to reduced mortality. In NYHA II patients in the same meta-analysis demonstrated highly significant reductions in heart failure hospitalisation and mortality.

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- 4) In those with mild to moderate symptoms (NYHA I/II), a greater likelihood of clinical response is seen in those with left bundle branch block and/or QRS duration ≥ 150 ms
- 5) Current indices of mechanical dyssynchrony derived by echocardiographic imaging have insufficient sensitivity and specificity to be clinically useful in patient selection
- 6) Patients with QRS prolongation caused by right ventricular pacing benefit from upgrade to a CRT device
- 7) Patients with a requirement for ventricular bradycardia pacing and severe left ventricular impairment (LVEF $\leq 35\%$) should be considered for implantation of a CRT device regardless of native QRS duration
- 8) Patients in atrial fibrillation show similar benefit from CRT providing a high proportion of biventricular stimulation is achieved by pharmacological or ablation therapy

6) Contraindications to device therapy

Unlike pacing for bradycardia where emergency treatment may be life-saving, CRT and ICD implantation is usually an elective or semi-elective procedure before which modifiable risks can be minimised. An exception occurs when a patient with a CRT and/or ICD indication has an urgent requirement for bradycardia pacing. In this situation the competing risks of temporary pacing and complications from the implantation of a permanent device have to be weighed.

6.1) sepsis

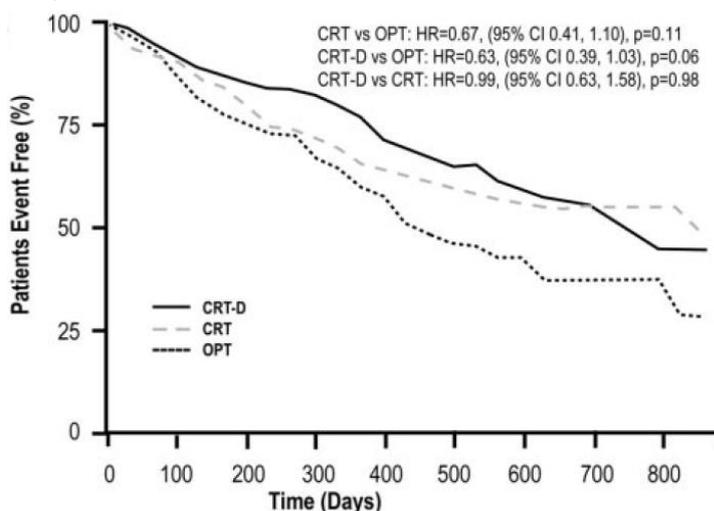
- active bacterial infection or colonisation such that the risks of device implantation outweigh the expected benefits
- temporary pacing may be indicated while the infection is treated

6.2) coagulopathy

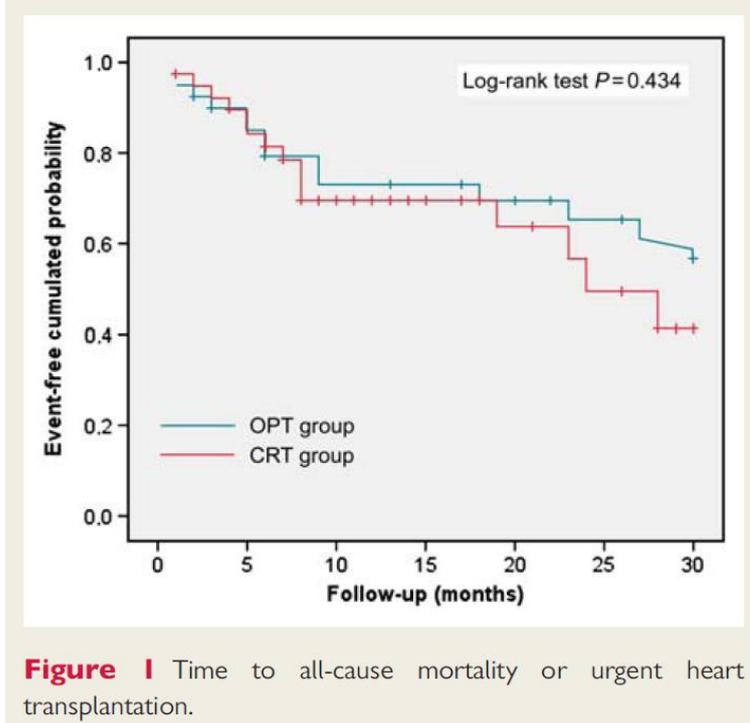
- iatrogenic anti-coagulation and/or anti-platelet therapy increase the risks of haematoma and device-related infection
- the risks of reversing anticoagulation must be weighed against the risks of thrombosis

6.3) life-expectancy

- mortality is unpredictable for the majority of the population
- age alone is a poor predictor as life expectancy. US government actuarial statistics (<http://www.ssa.gov/oact/STATS/table4c6.html>) show that life expectancy is more than one year for males up to the age of 112, and in females 113 years. At the age of 80, life expectancy is 7.9 years in men and 9.4 years in women.
- cancer is the only disease type where robust data exist on life expectancy and this must be carefully individualised
- significant co-morbidities may limit both life expectancy and potential benefit received from an ICD. These co morbidities include but are not confined to severe renal impairment and severe chronic obstructive lung disease.
- patients with NYHA IV symptoms have a life expectancy of significantly more than 1 year as demonstrated in an analysis of the COMPANION study (Lindenfeld *et al. Circulation* 2007;**115**:204-212) where at 1-year 44% of OPT, 36% of CRT-P and 30% of CRT-D treated patients had died:



This is consistent with a published series (Castel *et al. Europace* 2010;**12**:1136–1140) of 40 patients in NYHA IV receiving CRT matched to 40 managed with OPT alone where 1-year mortality was 30.5% in the CRT group and 27% in the OPT group:



6.4) NYHA IV for ICD

It is generally accepted that ICD therapy should not be offered to patients with persistent NYHA IV symptoms because of their poor quality of life and limited life expectancy. Current North American device guidance (Epstein *et al. JACC* 2008;**51**:e1-62) states that “Once patients have persistent or frequently recurrent Class IV symptoms despite optimal management, life expectancy is less than 12 months, and ICD implantation is not indicated, regardless of patient and family preferences.” although there are no recent published data to support this assessment. There is, however, clear benefit from CRT in patients with NYHA IV symptoms and most of these patients will improve to NYHA III functional class.

Whilst ICD implantation is therefore relatively contraindicated in patients with NYHA IV symptoms, it is reasonable to offer those with a life expectancy of at least 1 year, implantation of a CRT-D device if they have a CRT indication while those with a worse prognosis can be offered CRT-P. Those without a CRT indication should be managed with optimal pharmacological therapy and reassessed as an out-patient after 1 month.

6.5) Incessant or frequent ventricular tachycardia or ventricular fibrillation

ICDs do not prevent ventricular arrhythmias, they simply treat those that occur with anti-tachycardia pacing and/or defibrillation shocks. Incessant or frequently occurring VT or VF requires urgent pharmacological and/or ablation therapy. Only if the arrhythmia can be satisfactorily controlled can an ICD provide acceptable treatment as frequent shocks are extremely unpleasant and poorly tolerated, causing significant and sometimes severe psychological morbidity.

6.6) Ventricular tachycardia in the presence of normal cardiac function

Patients with episodes of VT (not VF) in the presence of normal or near normal ventricular function require careful electrophysiology assessment as these tachycardias can often be cured by radiofrequency ablation, avoiding the need for ICD therapy.

7) Other sections

7.1) Patient choice

While a patient may have a recognised cost-effective indication for an ICD and/or a CRT device, they may have carefully considered reasons why they do not want to undergo such a procedure. The advantages and disadvantages of the treatment options must be clearly and honestly discussed and, as far as possible, individualised for that patient in order for them to come to a fully informed decision. Patient literature and decision aids should be developed to help in this discussion and decision making. The patient's wishes must be respected.

7.2) End of life care

Defibrillators can be deactivated by simple non-invasive re-programming, and this is appropriate in a patient receiving terminal care for heart failure cancer or any other reason. Deactivation of defibrillator therapy will prevent the patient receiving painful and futile shocks at the end of their life. It is both legal and ethical to deactivate implanted devices after full discussion and agreement with a competent patient. Advice is provided in a British Heart Foundation booklet written by Dr James Beattie in 2009, Implantable cardioverter defibrillators in patients who are reaching the end of life" which is available from the BHF website (<http://publications.bhf.org.uk/publications.aspx> M105 ICDs end of life booklet).

Deactivation of CRT and/or bradycardia pacing is not required in this situation as pacing stimulation is asymptomatic. ICD therapy can be deactivated with affecting pacing.

The depletion of a device battery should always allow reassessment of the continuing need for device therapy.

7.3) National data collection

National audit data collected by the national pacemaker and ICD database (www.devicesurvey.com) has demonstrated significant disparity in ICD and CRT implantation rates across the UK which cannot be explained by disease prevalence. The cause of this apparent inequality of access is unknown and requires further research.

We suggest that NICE guidance should require each implanting centre to submit complete and timely audit data to the national database with a minimum data set including aetiology, NYHA functional class, left ventricular ejection fraction, QRS duration, history of ventricular arrhythmias (primary or secondary prevention) and complication rates.

Expected implant rates for ICD and CRT have been very helpful in planning services and we would welcome revised rates in the new guidance.

7.4) Reassessment

When a patient is assessed and found not to fulfil NICE guidance criteria for device implantation, we recommend reassessment at annual review or when there is a clinical event or other change in symptoms or treatment.

7.6) Implantation and follow-up

The implantation of ICD and CRT devices is complex and can be time consuming. The complication rates are significantly higher than for bradycardia pacemakers. Device follow-up is complex and time consuming with a requirement for individualisation of programming to optimise response and minimise the risk of inappropriate therapy. This includes the requirement for optimisation of programming in CRT devices with echocardiographic assessments, particularly in those who do not initially improve following implantation. In addition, patients with indications for ICD and CRT are complex and most have heart failure and other co-morbidity. They require frequent and expert clinical review to optimise symptoms and prevent decompensation and sudden death. Because of the effects of their underlying disease and treatment, many patients require psychological assessment and support. Implant and follow-up centres also need robust databases and protocols to deal with device complications and advisories with 24-hour cover for emergencies.

It is Heart Rhythm UK's view that to maintain clinical the cost-effectiveness seen in the clinical trials, these devices should be implanted by high-volume operators in high-volume centres.

8) Conclusions

8.1) Evolution of guidance on the use of ICD and CRT

- 1) Clinical guidance has evolved in its format and content
- 2) Whilst guidance could never encompass every conceivable situation, nor will there ever be complete evidence on which to base such guidance, nevertheless this formal process of evaluating evidence is important in setting standards of clinical practice
- 3) Guidance will always follow trial evidence so requires periodic re-evaluation
- 4) The inclusion and exclusion criteria adopted in clinical trials are always a compromise between generalisability and power calculations required to achieve statistical significance
- 5) Meta-analyses have been very helpful in defining treatment effects in subgroups
- 6) Whilst guidance can be written which reproduces trial inclusion and exclusion criteria, this can result in long, complex and potentially contradictory recommendations
- 7) Heart Rhythm UK's goal is to offer device therapy to all patients for whom there is evidence that they are likely to benefit
- 8) Device implantation in the UK is far lower than in other developed countries
- 9) The complexity of guidance may be contributing to under provision because of lack of knowledge and the perceived time and financial costs of screening tests
- 10) We recommend a pragmatic approach with simple, clear, easily memorable guidance which identifies areas where the evidence is clear and others where there is uncertainty. In small groups of patients with complex cardiovascular diseases, guidance should defer to the best evidence available at the time.

8.2) Key points in the current analysis

- 1) All patients should receive optimal pharmacological and other therapies.
- 2) All patients with cardiovascular disease should be fully assessed in order to identify patients who would benefit from device therapy.
- 3) Patients who are found not to have a device indication should be reassessed annually or sooner if there is a change in their clinical status.
- 4) The advantages and disadvantages of device therapy should be discussed with all patients to allow them to come to a fully informed decision.
- 5) ICD implantation reduces the risk of sudden cardiac death in patients resuscitated from cardiac arrest or haemodynamic compromise due to ventricular tachycardia.
- 6) Patients with a high risk cardiac condition and a history of syncope are at similar risk of sudden cardiac death as those resuscitated from cardiac arrest and benefit from ICD implantation.
- 7) Patients with severe left ventricular impairment (LVEF $\leq 35\%$), whether this is due to ischaemic or non-ischaemic heart disease, are at high risk of sudden death and benefit from ICD implantation.
- 8) There are no large randomised controlled trials of primary prevention ICD therapy in patients with rare high risk cardiac conditions. The best available contemporary evidence of risk factors should be used to guide therapy.
- 9) CRT implantation improves heart failure symptoms and reduces hospitalisation and mortality in patients with LVEF $\leq 35\%$ and QRS duration ≥ 120 ms.
- 10) Benefit from CRT is seen in patients from all NYHA functional classes. There is less evidence of long-term benefit in those with mild symptoms (NYHA I and II) but improvements in symptoms and mortality are consistent and statistically significant.

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- 11) Currently available indices of mechanical dyssynchrony derived from imaging are insufficiently sensitive and specific to be clinically useful.
- 12) Further stratification of benefit in patients with QRS 120-150ms can be derived from the presence of left bundle branch block.
- 13) Patients with QRS prolongation caused by necessary right ventricular pacing benefit from up-grade to a CRT device.
- 14) Patients with a bradycardia pacing indication and impaired ventricular function benefit from CRT.
- 15) The benefit of CRT shown in patients in atrial fibrillation is similar to sinus rhythm providing a high proportion of beats are biventricularly paced. This may require pharmacological treatment or ablation.

8.2) Summary recommendations

These key points can be summarised in the recommendations below. The over-lap in the criteria for ICD and CRT appear complex, but this combination would improve clinical utility.

- 1) All patients should undergo appropriate diagnostic tests to establish the aetiology and optimal management of their heart condition. It is essential to identify patients with conditions which can be cured with ablation therapy such as fascicular tachycardia or right ventricular outflow tract tachycardia.
- 2) All patients should receive optimal pharmacological therapy for their condition.
- 3) Patients should undergo revascularisation when indicated (NICE clinical guideline 126 – Management of Stable Angina. July 2011. <http://guidance.nice.org.uk/CG126>).
- 4) All patients should be assessed for relative and absolute contraindications to device therapy and co-morbidity which increases the risk of treatment or reduces its efficacy. These include myocardial infarction or revascularisation within 4 weeks unless the patient has had a secondary prevention ICD indication. This should be explained to the patient and weighed in decision making.
- 5) All patients should have their condition and its management options discussed with them to make a fully informed decision.
- 6) If a decision is made not to implant a device, this should be reviewed at least annually or when there is a significant change in the patient's condition.

Based on the currently available data, we recommend that in the absence of a fully reversible cause (including an arrhythmia which can be prevented by ablation therapy), patients on optimal pharmacological therapy, with expectation of life expectancy of ≥ 1 year and with a quality of life acceptable to the patient:

Patients with LVEF $\leq 35\%$ (regardless of aetiology) should routinely be considered for a device based on their symptoms (NYHA functional class) and QRS duration:

	NYHA I	NYHA II	NYHA III	ambulant NYHA IV
QRS < 120 ms	ICD	ICD	ICD	OPT
120-149 no LBBB	ICD	ICD	CRT-D	CRT-D
120-149 + LBBB	CRT-D	CRT-D	CRT-D	CRT-D
≥ 150 ms	CRT-D	CRT-D	CRT-D	CRT-D

CRT-P (pacemaker) implantation should be offered in place of CRT-D (defibrillator) when ICD therapy is contraindicated or declined by the patient.

- 3) **Patients with LVEF $> 35\%$** (without NYHA IV symptoms):
 - with spontaneous sustained ventricular arrhythmias
 - or**
 - with inherited conditions with high risk features for sudden cardiac death according to the best available evidence

should routinely be considered for: ICD

- 4) ICD implantation should not be performed within 4 weeks of a myocardial infarction or revascularisation unless the patient has a secondary prevention indication.

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Multiple Technology Appraisal (MTA)

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure

(review of TA95 and TA120) [ID481]

ASSESSMENT REPORT FOR CONSULTATION

Clinical Specialist Statement as nominated by Royal College of Nursing.

**Healthcare clinical expert [REDACTED] RN, EN(G), MSc in cardiology,
Cert Ed, Dip N. BHF Arrhythmia Specialist Nurse, ABMU Health Board, Swansea.**

Whilst it is appreciated that the appraisal focuses on the efficacy of the cardiac devices within various populations, the following comments are related to the practical issues encountered by clinicians. There is no or very limited evidence supporting these points, however if the appraisal was able to address or make recommendations for change these would be of great use for both patients and front line health care professionals.

ICDs –

1. Prior to implantation, patients and their carer / NOK must be counselled and fully informed about the risks / benefits of living with an ICD. They must also be made aware that they have a choice as to whether or not they agree to have the device implanted.
2. Patients who have received an ICD for secondary prevention, or have experienced multiple defibrillator shocks require access to cardiac rehabilitation services. Sadly, many cardiac rehabilitation services are not funded or do not have the capacity for patients with ICD implants.
3. Patients who have experienced multiple defibrillator shocks or are experiencing psychological distress following a cardiac arrest or syncope (despite having an ICD) require prompt access and treatment by counselling / psychological services.
4. There is an urgent need for education programmes for healthcare professionals in primary, secondary, tertiary care and paramedic services about deactivating (temporarily turning off) the ICD if a patient experiences multiple shocks for ongoing arrhythmia or device/lead failure.

5. There is an urgent need for education programmes for healthcare professionals in primary, secondary, tertiary care and palliative care about the importance of :-

(a) Early discussions about deactivating (permanently turning off) the ICD in end of life care (EoLC). For example when a patient has a terminal illness or advanced stages of a chronic condition such as heart failure, chronic obstructive airways disease or renal failure.

(b) Deactivation of the ICD in EoLC should be accompanied by an authorised Do Not Attempt Resuscitation order (DNAR).

(c) Deactivation of the ICD in EoLC does not equate to "instant death". It is important the patients and their relatives understand that deactivation allows a natural, peaceful death.

6. ICD services must provide a package of care which covers pre ICD counselling, implantation, follow up AND deactivation in end of life care. Deactivation in end of life care MUST be funded and authorised regardless whether the patient is at home, in a residential / nursing home, district general hospital or a hospice.

7. For the safety of allied professions there is a need for greater awareness about the importance of deactivating ICDs prior to post mortem or removal of the device prior to cremation.

CRT

1. Prior to implantation, patients and their relatives must understand there is a chance their symptoms may not improve despite the CRT device.

2. Post CRT implantation patients should have access to cardiac rehabilitation services. Many cardiac rehabilitation services are not funded for or do not have the capacity for patients diagnosed with heart failure +/- CRT devices.

CRT – D

All the above points apply, plus;

1. There is a need for education programmes for healthcare professionals in primary, secondary, tertiary care and palliative care, and patients and their family that deactivating the ICD (permanently turning off) in end of life care does not include the CRT settings.

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA 120)

Personal perspective: [REDACTED]

22nd April 2013

An update and amalgamation of the two technology appraisals is somewhat timely. In particular, the lack of guidance on patients with non-ischaemic cardiomyopathies was always a glaring omission in the previous TA95, and should be addressed in this current review.

Since the 2-volume, 654-page, tome landed on my desk a week ago, it has proven a challenge to get through it all in the short time allowed. However, although it is clear that a lot of work has gone into this document, there are number of fundamental issues:

- i) I find this document very repetitive and poorly written in places. The heart failure sections in particular are an example of the latter. There are also a large number of typographical errors
- ii) The categorisation of the patient populations into the 3 groups is not clinically helpful and is somewhat artificial. This is a fundamental flaw. I would have preferred to categorise patients with severe LVSD (LVEF \leq 35%) into:
 - a. Ischaemic/non-ischaemic aetiology
 - b. NYHA class
 - c. LBBB and Non-LBBB, with appropriate cut-offs for QRS duration
 - d. Presence or absence of atrial fibrillation (particularly for CRT)
- iii) The repeated use of the term “cardiac dyssynchrony”, rather than “the presence of left bundle branch block”. Echo assessment of dyssynchrony has largely been discredited (Hawkins NM. J Am Coll Cardiol. 2009 May 26;53(21):1944-59. Selecting patients for cardiac resynchronization therapy: the fallacy of echocardiographic dyssynchrony.). The vast majority of CRT trials recruited on the basis of QRS duration/LBBB
- iv) What clinicians *want* to know is:
 - a. Who should I implant an ICD in?
 - b. Who should I not implant an ICD in?
 - c. Should I implant CRT-P or CRT-D?
 - d. Does CRT work in non-LBBB?
 - e. Above what QRS duration is CRT effective?
 - f. Does CRT work in atrial fibrillation?
 - g. Which NYHA classes of patient should be considered for CRT?
 - h. What about broad paced rhythms – should they be *upgraded* to CRT?
 - i. Which is more cost effective – CRT-P or CRT-D?

- v) **Heart failure.** It is clear that the author(s) are not aware of modern heart failure management, nor are they familiar with cardiac physiology. Examples include:
- a. Inotropes and “short term VADs” are not relevant in this patient population.
 - b. Statins have been shown in 2 large RCT’s not to alter outcome in patients with heart failure.
 - c. Aldosterone antagonists (now termed mineralocorticoid receptor antagonists – MRA’s) are not “for people resistant to other drug therapy” (p33). They have replaced ARBs as 3rd line treatments (after ACE inhibitors and beta-blockers). They are indicated in NYHA II-IV heart failure.
 - d. ACE inhibitors “should not be initiated in haemodynamically significant valve disease”. What about mitral regurgitation?? Presumably the authors refer to critical aortic stenosis. (p37)
 - e. Milrinone and enoximone??? (p37). Phosphodiesterase inhibitors have been shown to increase mortality in CHF!
 - f. Amiodarone is not part of “optimal medical therapy” for heart failure. SCD-HeFT – the largest amiodarone study in heart failure – showed no impact on mortality
 - g. There is no evidence for the use of aspirin in CHF
 - h. The UK does not use the term “congestive heart failure”
 - i. Calcium antagonists (except amlodipine) are contra-indicated in heart failure
 - j. “Other causes of heart failure include LVSD...” the LVSD is a consequence of the underlying aetiology
 - k. “Other causes of heart failure include....cardiomyopathy (either hypertrophic or restrictive)”. What about dilated cardiomyopathy? Or ARVC? As far as I am aware there is no large RCT of device therapy in restrictive cardiomyopathy!
 - l. cardiac catheterisation is not performed “if blood samples from the heart are required” (p32)
- vi) **Arrhythmias and device therapy.** The sections on arrhythmias and device therapy are similarly flawed. Examples include:
- a. A lack of understanding of the terms “pacing”, “cardioversion” and “defibrillation”
 - b. “Modern ICDs provide the functionality of standard pacemaker”. I am not aware of ICDs that do not, except of course for S-ICDs. This is not highlighted here (p28)
 - c. “CRT-P is appropriate for patients with less serious cardiac arrhythmias” (p29) – what on earth does that mean?
 - d. I cannot imagine when a “CRT-P would be ... upgraded to an ICD”
 - e. S-ICDs are not pectoral devices
 - f. Modern devices do not deliver resynchronisation shocks
 - g. ICDs do not “provide cardioversion and/or defibrillationfor asystole”!!! (p28)
- vii) Patients with congenital heart disease are not included in this document

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

**Implantable cardioverter defibrillators for the treatment of arrhythmias
and cardiac resynchronisation therapy for the treatment of heart failure
(review of TA95 and TA120)**

(name), Technology Appraisal Administrator
Email: TACommb@nice.org.uk

Fax: +44 (0)20 7061 9721

Post: 1st Floor, 10 Spring Gardens, London, SW1A 2BU

I confirm that:

- I agree with the content of the statement submitted by **Arrhythmia Alliance** and consequently I will not be submitting a personal statement.

Name

Signature

Date:

12/04/13

Appendix K – Expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

**Implantable cardioverter defibrillators for the treatment of arrhythmias
and cardiac resynchronisation therapy for the treatment of heart failure
(review of TA95 and TA120)**

Expert statement declaration form

Please sign and return by email to:
TACommB@nice.org.uk

If email is not possible, please return by fax to Jeremy Powell, Project
Manager
on 020 7061 9761

or by post to: NICE, 1st Floor, 10 Spring Gardens, London, SW1A 2BU

I confirm that:

- I agree with the content of the statement submitted by **Heart Rhythm UK** and consequently I will not be submitting a personal statement.

Name:

Signed:

Date: 25th November 2013

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120) [ID481]

Specification of further work following the Appraisal Committee meeting on 23 April 2013

Suggested presentation of analyses

- Please combine the ischaemic and non-ischaemic patient groups together, therefore presenting results for 24 subgroups rather than 48 in the original submission. For these subgroups, for each of the different scenarios presented, please present tables with fully incremental cost-effectiveness results as previously presented in tables 70-71 of the submission.
- Please also present a summary of the most optimal strategies at different cost-effectiveness thresholds, for example, at £20,000, £25,000 and £30,000 per QALY gained.

Specification of further work

1. The manufacturers' base case assumes a constant duration of effect of 7.5 years for all-cause mortality, followed by linear tapering over 20 years. Sensitivity analyses were also provided assuming life-long constant treatment effects without any tapering (MS page 194) as a more optimistic scenario, and assuming a constant duration of effect for 5 years as a more conservative scenario (Appendix 15 page 72-73). Please provide these analyses for the 24 subgroups outlined above, combining the ischaemic and non-ischaemic patient groups.

In addition, please also provide a sensitivity analysis assuming a constant duration of effect up to the *average* duration of follow up in the trials, followed by linear tapering thereafter?

2. The effect of CRT-D devices on all-cause hospitalisation for NYHA III and IV class patients estimated in the IPD network meta analysis (HR; [REDACTED]) was not incorporated in the model and the value estimated for CRT-P ([REDACTED] for NYH III and [REDACTED] for NYHA IV) was used instead. The manufacturers' stated that it is unlikely that the use of CRT-D will result in a smaller treatment effect than the use of CRT-P in a given patient group, as both include CRT therapy.

However, the Committee would like to see the effect on the ICERs of a more conservative estimate of effect of CRT D for all cause hospitalisation estimated in the IPD network meta-analysis (that is, HR [REDACTED])?

3. The Committee heard that defibrillating devices can increase anxiety in some patients. The manufacturers' model does not account for any additional cost of counselling apart from the bi-annual device related outpatient visits for ICD patients and quarterly visits for CRT (CRT-D or CRT-P) patients.

Given the feedback from experts on the importance of counselling, particularly for patients receiving defibrillator devices, what is the impact of this additional resource use on the ICERs?

4. The manufacturer's model excludes the possibility of crossover or device upgrades, which are possible in clinical practice. Please comment on the likelihood of device upgrades in clinical practice.

In particular, the Committee heard that there may be a subgroup of people indicated for CRT-P who are also likely to need a defibrillator in the near future, so that cardiologists would choose to implant a CRT-D in which the ICD function could be switched on when needed, rather than to implant a CRT-P device which would have to be upgraded to CRT-D at full cost at a later date. Please provide comment on experience with this situation in clinical practice, and on identification of a subgroup of patients for which this situation applies.

5. The Committee considered that further deterministic sensitivity analyses were required for resource use and cost parameters. Please provide such sensitivity analyses, as implementable within the current model structure.

**Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)
[ID481]**

Manufacturer's response to specification for further work following the appraisal committee meeting on 23rd April 2013

Executive Summary

Background

This document describes further analyses of a cost-effectiveness model developed by the ABHI group to meet a request made by NICE in their correspondence of 19th June 2013.

The original ABHI analysis included individual patient data from over 12,000 patients, representing 95% of the relevant randomised controlled trial evidence for the devices under evaluation. Analyses of this data set for the all-cause mortality endpoint demonstrated strong and statistically significant impacts of each device on all-cause mortality.

These results do not imply that every heart failure patient should receive an implantable device. The heart failure population that would be eligible for a device, be that CRT-P, CRT-D or ICD, and that is therefore considered in this appraisal, is a highly selected sub-population of heart failure patients. For all devices the potential patient population includes only those on optimal medical therapy, whom have undergone an echocardiography examination and been found to have ejection fraction (EF) < 35%. Furthermore, to be eligible for CRT patients must have wide QRS (>120 ms); and additionally the NYHA classification system would be applied to exclude NYHA IV patients from ICD devices.

New analyses

The analyses requested were:

- Aggregate ischaemic and non-ischaemic sub-groups and present summary tables at £30,000, £25,000 and £20,000 per QALY thresholds.
- Explore different durations of mortality treatment effect.
- Implement a treatment effect of 0.696 for CRT-D on hospitalisation.
- Include counselling costs.
- Conduct sensitivity analyses on cost parameters.
- Comment on device crossover/upgrade

Clinical experts confirmed that device crossover/upgrade was rare and its inclusion in the model would not be reflective of routine UK practice. Inclusion of counselling costs did not change the base case conclusions at any of the three thresholds considered. Further inspection of the model showed that a treatment effect of 0.696 for CRT-D on hospitalisation had in fact been used in the original base case submission. Cost parameter sensitivity analysis had minimal effect on the ICERs.

Combining ischaemic and non-ischaemic groups yields conclusions regarding the most cost-effective technologies that are consistent with summary tables presented at the first Committee meeting. Combining these groups has also increased the precision around the results, as each subgroup is now made up of a larger number of patients. Cost-effective interventions at the three requested thresholds are summarised in Table 1-3.

Table 1: Cost-effective interventions (threshold value = £30,000 per QALY gained)

NYHA	QRS <120ms	QRS ≥120-<150ms	QRS ≥150ms
I/II	ICD	ICD (no LBBB) CRT-D (with LBBB)	CRT-D (both LBBB groups)
III	ICD	CRT-D (both LBBB groups)	CRT-D (both LBBB groups)
IV	OPT	CRT-P (both LBBB groups)	CRT-P (both LBBB groups)

Table 2: Cost-effective interventions (threshold value = £25,000 per QALY gained)

NYHA	QRS <120ms	QRS ≥120-<150ms	QRS ≥150ms
I/II	ICD	ICD (no LBBB) CRT-D (with LBBB)	CRT-D (both LBBB groups)
III	OPT	CRT-D (both LBBB groups)	CRT-P (both LBBB groups)
IV	OPT	CRT-P (both LBBB groups)	CRT-P (both LBBB groups)

Table 31: Cost-effective interventions (threshold value = £20,000 per QALY gained)

NYHA	QRS <120ms	QRS ≥120-<150ms	QRS ≥150ms
I/II	OPT	ICD (no LBBB) OPT (with LBBB)	OPT (no LBBB) CRT-D (with LBBB)
III/IV	OPT	OPT (no LBBB) CRT-P (with LBBB)	CRT-P (both LBBB groups)

We would ask the Committee to note that in some cases, the ICERs are very close to threshold values, with the potential impact that very small differences in ICERs could change threshold-based decisions. The ICERs for all technologies will not be static and would be expected to decrease over time. As presented in ABHI original submission, real term prices (adjusted to 2011 equivalents) have fallen by 17% for CRT-P, 10.4% for CRT-D and 8% for ICD between 2006 and 2011. There is no Pharmaceutical Price Regulation Scheme (PPRS) for medical devices and historically market forces have driven acquisition costs down over time. Over the lifetime of this appraisal – all things being equal - the ICERs would therefore be expected to reduce.

Reducing the constant mortality benefit to 5 years (from the base case 7.5 years), followed by linear tapering to 20 years resulted in treatment choices as per the base case using the £30,000/QALY threshold with the exception of only one of the 24 subgroups:

- NYHA III patients with QRS ≥ 150 ms and LBBB, the cost-effective option switches from CRT-D to CRT-P when the treatment effect duration is reduced to 5 years (ICER for CRT-D vs. CRT-P = £30,548/QALY)

Reducing the constant mortality benefit to 5 years (from the base case 7.5 years), followed by linear tapering to 20 years resulted in treatment choices as per the base case using the mid-point threshold value of £25,000/QALY. Exceptions occurred in only four of the 24 subgroups:

- NYHA I/II patients with QRS duration < 120 ms, ICD becomes cost-ineffective if the treatment effect duration is reduced to 5 years (ICER for ICD vs. OPT = £25,714/QALY and £26,181/QALY in NYHA I and II respectively)
- NYHA II patients with QRS ≥ 150 ms and without LBBB, CRT-D becomes cost-ineffective if the treatment duration is reduced to 5 years, and ICD becomes the optimal treatment (ICER for CRT-D vs. ICD = £25,267/QALY)
- NYHA III patients with QRS ≥ 120 ms and < 150 ms and LBBB, the cost-effective option switches from CRT-D to CRT-P when the treatment effect duration is reduced to 5 years (ICER for CRT-D vs. CRT-P = £26,192/QALY)

In each case, although the optimal decision at a threshold of £25,000/QALY changed, the ICERs for the base case preferred treatment option remained under £26,200/QALY.

The base case analysis assumes that the mortality benefit is constant for 7.5 years followed by a linear tapering until year 20. The duration of effect is based on the longest available follow-up from the individual patient data analysis. Longer term analyses of the post-protocol period have been presented for two large trials, CARE-HF and MADIT-II. These analyses support that strong treatment effects for devices are maintained at 4.2-7.6 years average follow-up despite high degrees of cross-over from the control to the active trial arms. Analyses testing the validity of the proportional hazards assumption within the individual patient database found no evidence to suggest that treatment effects waned over time, supporting the use of a 7.5-year mortality benefit.

End of Executive Summary

Base case results combining ischemic and non-ischemic patient groups

As per the specification document, we have generated results for 24 rather than 48 subgroups using the same format as in the original submission. The results for patients without Left Bundle Branch Block (LBBB) are presented in Table 2 and for patients with LBBB in Table 3. These tables are to be interpreted in the same way to the results tables in the original submission: the “CE sequence” section ranks the treatments in terms of incremental benefit and the “ICERs” section reports the fully incremental cost-effectiveness ratios compared to the next most effective intervention on the frontier (dominance/ extended dominance also reported).

Table 2: Original cost-effectiveness results (pooled ischemic and non-ischemic) for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,074	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,253	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,102	£21,759	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,465	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,813	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,602	£23,738	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,826	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,178	Ext Dominated	£23,349	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,930	£25,200	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,578	£40,052	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,175	£35,811	N/A	CRTP	CRTP	CRTP

Table 3: Original cost-effectiveness results (pooled ischemic and non-ischemic) for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,677	£21,672	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,470	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,704	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,664	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,215	£24,875	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,496	£28,646	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,664	£37,104	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,500	£40,449	N/A	CRTP	CRTP	CRTP

N/A values indicate where a device is not evaluated in a specific population. The rationale for these exclusions is detailed in the original submission.

The specification document also requested summaries of optimal strategies at cost-effectiveness threshold values of £20,000, £25,000 and £30,000 per QALY gained. These are reported in Table 4, Table 5 and Table 6.

Table 4: Cost-effective interventions (original analysis, threshold value = £30,000 per QALY gained)

NYHA	QRS <120ms	QRS ≥120-<150ms	QRS ≥150ms
I/II	ICD	ICD (no LBBB) CRT-D (with LBBB)	CRT-D (both LBBB groups)
III	ICD	CRT-D (both LBBB groups)	CRT-D (both LBBB groups)
IV	OPT	CRT-P (both LBBB groups)	CRT-P (both LBBB groups)

Table 5: Cost-effective interventions (original analysis, threshold value = £25,000 per QALY gained)

NYHA	QRS <120ms	QRS ≥120-<150ms	QRS ≥150ms
I/II	ICD	ICD (no LBBB) CRT-D (with LBBB)	CRT-D (both LBBB groups)
III	OPT	CRT-D (both LBBB groups)	CRT-P (both LBBB groups)
IV	OPT	CRT-P (both LBBB groups)	CRT-P (both LBBB groups)

Table 6: Cost-effective interventions (original analysis, threshold value = £20,000 per QALY gained)

NYHA	QRS <120ms	QRS ≥120-<150ms	QRS ≥150ms
I/II	OPT	ICD (no LBBB) OPT (with LBBB)	OPT (no LBBB) CRT-D (with LBBB)
III/IV	OPT	OPT (no LBBB) CRT-P (with LBBB)	CRT-P (both LBBB groups)

We request that the committee review specific ICERs as well as the summary tables, as in a number of cases the ICERs are very close to the threshold values used (see, for example, CRT-P vs. OPT in non-LBBB, NYHA III, QRS ≥120 and <150ms: £20,178/QALY and CRT-D vs. OPT in LBBB, NYHA II, QRS between 120 and 150ms: £20,704). In order to facilitate this we have provided Figure 1 and Figure 2 which show the cost-effective treatment option according to a continuous display of the threshold.

Figure 1: Graphic display of cost-effective option across cost-effectiveness threshold values for patients without LBBB

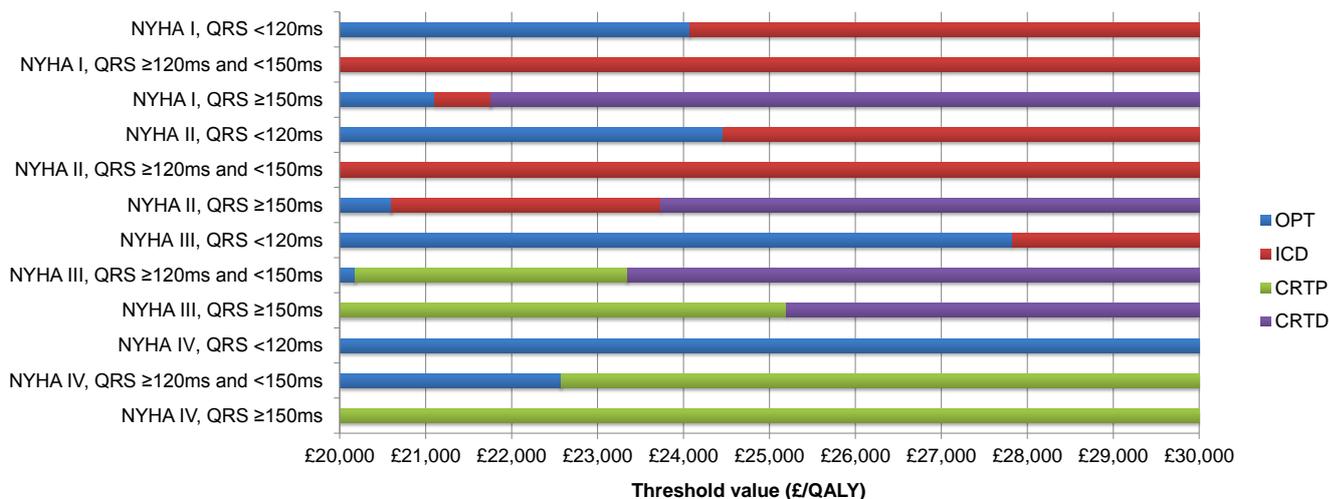


Figure 2: Graphic display of cost-effective option across cost-effectiveness threshold values for patients with LBBB



Requested scenario analyses

1) Duration of mortality treatment effects

The base case analysis assumes a constant duration of effect of 7.5 years for all-cause mortality followed by linear tapering up to year 20. In addition, sensitivity analyses using a life-long constant treatment effect and a five year treatment effect followed by linear tapering to year 20 were provided in the original ABHI submission. As requested, these sensitivity analyses are presented below using the revised presentation with 24 subgroups.

An additional analysis assuming that the duration of treatment effect is as per the average duration of follow-up in the trial database has also been run. As requested this scenario retains the tapering effects used in the base case (tapering until year 20). Mean follow-up was calculated using all patients included in the network meta-analysis. The analysis

comprised of using a Kaplan Meier analysis and calculating the restricted mean survival time¹. The survival analysis was run with all loss to follow-up occurrences considered as events and all deaths considered as occurrences of censoring.

The results for each scenario are presented below, followed by a narrative and tabular summary.

a) Life-long constant mortality treatment effect

The results using the life-long constant treatment effects are presented as Table 7 and Table 8.

Table 7: Sensitivity analyses - constant life-long mortality treatment effect for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£18,321	N/A	N/A	ICD	ICD	ICD
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,153	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£17,588	£18,558	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	ICD	N/A	N/A	Referent	£17,807	N/A	N/A	ICD	ICD	ICD
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£13,374	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£16,782	£19,748	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	ICD	N/A	N/A	Referent	£24,153	N/A	N/A	ICD	ICD	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£19,807	Ext Dominated	£21,438	CRTD	CRTD	CRTP
III	>150ms	OPT	CRTP	ICD	CRTD	Referent	£13,453	Ext Dominated	£22,217	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,500	£39,290	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,047	£34,627	N/A	CRTP	CRTP	CRTP

Table 8: Sensitivity analyses - constant life-long mortality treatment effect for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£16,692	£17,267	N/A	CRTD	CRTD	CRTD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£14,044	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,302	N/A	CRTD	CRTD	CRTD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£13,497	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,664	£21,786	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£9,928	£23,891	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,472	£35,479	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,334	£38,283	N/A	CRTP	CRTP	CRTP

b) Constant mortality treatment effect for five years

The results using a five-year constant treatment effect followed by tapering until year 20 are presented as Table 9 and Table 10.

¹ This analysis is equivalent to calculating the area under the Kaplan Meier curve. In this case the Kaplan Meier curve is complete by definition; as all non-dead patients must be lost to follow-up/subject to administrative censoring.

Table 9: Sensitivity analyses - constant mortality treatment effect for five years for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£25,714	N/A	N/A	ICD	OPT	OPT
I	>=120, <150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,295	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£22,366	£23,168	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£26,181	N/A	N/A	ICD	OPT	OPT
II	>=120, <150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,909	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,888	£25,267	N/A	CRTD	ICD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£29,309	N/A	N/A	ICD	OPT	OPT
III	>=120, <150ms	OPT	CRTP	ICD	CRTD	Referent	£20,421	Ext Dominated	£24,311	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,203	£26,586	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150ms	OPT	CRTP	CRTD	N/A	Referent	£22,702	£40,899	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,330	£36,934	N/A	CRTP	CRTP	CRTP

Table 10: Sensitivity analyses - constant mortality treatment effect for five years for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150ms	OPT	ICD	CRTD	N/A	Referent	£21,985	£23,080	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,615	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,049	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,879	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,489	£26,192	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,769	£30,548	CRTP	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150ms	OPT	CRTP	CRTD	N/A	Referent	£18,817	£38,202	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,666	£42,039	N/A	CRTP	CRTP	CRTP

c) Constant mortality treatment effect for average duration of follow up in trial database

The average (mean) follow up in the trial database was 2.54 years. The impact on cost-effectiveness of using this value for the fixed treatment effect period and tapering the treatment effect until year 20 is presented in Table 11 and Table 12.

Table 11: Sensitivity analyses - constant mortality treatment effect for mean trial follow up in patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£27,936	N/A	N/A	ICD	OPT	OPT
I	>=120, <150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£18,768	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£24,196	£25,155	N/A	CRTD	ICD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£28,463	N/A	N/A	ICD	OPT	OPT
II	>=120, <150ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£19,442	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£23,714	£27,389	N/A	CRTD	ICD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£31,573	N/A	N/A	OPT	OPT	OPT
III	>=120, <150ms	OPT	CRTP	ICD	CRTD	Referent	£20,864	Ext Dominated	£25,873	CRTD	CRTP	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,657	£28,735	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150ms	OPT	CRTP	CRTD	N/A	Referent	£23,041	£42,813	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,683	£39,155	N/A	CRTP	CRTP	CRTP

Table 12: Sensitivity analyses - constant mortality treatment effect for mean trial follow up in patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150ms	OPT	ICD	CRTD	N/A	Referent	£23,830	£24,982	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,218	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£23,897	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,534	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,937	£28,244	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£11,207	£33,410	CRTP	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150ms	OPT	CRTP	CRTD	N/A	Referent	£19,164	£40,371	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£15,035	£45,049	N/A	CRTP	CRTP	CRTP

The impact of different treatment effect durations on treatment choice at the £30,000, £25,000 and £20,000 per QALY thresholds is shown in Table 13, Table 14 and Table 15.

At the £30,000 per QALY threshold the model is insensitive to the treatment effect duration. The duration of treatment effect alters the preferred treatment choice in only two subgroups. In patients with NYHA III, QRS<120ms and no LBBB use of the most conservative treatment effect duration switches the preferred treatment option from ICD to OPT. In patients with NYHA III, QRS≥150ms and LBBB use of a five-year treatment effect duration switches the preferred treatment option from CRT-D to CRT-P.

Table 13: Impact of duration of treatment effect on treatment choice using £30,000 per QALY threshold

Subgroup	Duration of mortality treatment effect			
	Lifetime	7.5 years (base case)	5 years	Mean f/up
<i>Individuals without LBBB</i>				
NYHA I, QRS <120ms	ICD	ICD	ICD	ICD
NYHA I, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD
NYHA I, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA II, QRS <120ms	ICD	ICD	ICD	ICD
NYHA II, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD
NYHA II, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA III, QRS <120ms	ICD	ICD	ICD	OPT
NYHA III, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA III, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA IV, QRS <120ms	OPT	OPT	OPT	OPT
NYHA IV, QRS ≥120ms and <150ms	CRTP	CRTP	CRTP	CRTP
NYHA IV, QRS ≥150ms	CRTP	CRTP	CRTP	CRTP
<i>Individuals with LBBB</i>				
NYHA I, QRS <120ms	OPT	OPT	OPT	OPT
NYHA I, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA I, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA II, QRS <120ms	OPT	OPT	OPT	OPT
NYHA II, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA II, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA III, QRS <120ms	OPT	OPT	OPT	OPT
NYHA III, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA III, QRS ≥150ms	CRTD	CRTD	CRTP	CRTP
NYHA IV, QRS <120ms	OPT	OPT	OPT	OPT
NYHA IV, QRS ≥120ms and <150ms	CRTP	CRTP	CRTP	CRTP
NYHA IV, QRS ≥150ms	CRTP	CRTP	CRTP	CRTP

At the £25,000 per QALY threshold the model is sensitive to the treatment effect duration being increased in three subgroups, and is sensitive to it being decreased in six subgroups. Use of a lifetime treatment effect switches the treatment choice from OPT to ICD in patients with NYHA III, QRS<120ms; switches the treatment choice from CRT-P to CRT-D in patients with NYHA III, QRS≥150ms for both the no LBBB and LBBB subgroups.

Use of a 5-year time horizon switches the treatment choice from ICD to OPT in patients with NYHA I and II with QRS<120ms; switches the treatment choice from CRT-D to ICD in patients with NYHA II and QRS≥150ms and no LBBB and switches the treatment choice from CRT-D to CRT-P in patients with NYHA III and QRS≥120ms and <150ms with LBBB.

Use of the most conservative assumption switches the treatment choice from CRT-D to ICD in patients with NYHA I, QRS≥150ms and without LBBB and from CRT-D to CRT-P in patients with NYHA III, QRS≥120ms and <150ms and no LBBB.

Table 14: Impact of duration of treatment effect on treatment choice using £25,000 per QALY threshold

Subgroup	Duration of mortality treatment effect			
	Lifetime	7.5 years (base case)	5 years	Mean f/up
<i>Individuals without LBBB</i>				
NYHA I, QRS <120ms	ICD	ICD	OPT	OPT
NYHA I, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD
NYHA I, QRS ≥150ms	CRTD	CRTD	CRTD	ICD
NYHA II, QRS <120ms	ICD	ICD	OPT	OPT
NYHA II, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD
NYHA II, QRS ≥150ms	CRTD	CRTD	ICD	ICD
NYHA III, QRS <120ms	ICD	OPT	OPT	OPT
NYHA III, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA III, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA IV, QRS <120ms	OPT	OPT	OPT	OPT
NYHA IV, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA IV, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
<i>Individuals with LBBB</i>				
NYHA I, QRS <120ms	OPT	OPT	OPT	OPT
NYHA I, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA I, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA II, QRS <120ms	OPT	OPT	OPT	OPT
NYHA II, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA II, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA III, QRS <120ms	OPT	OPT	OPT	OPT
NYHA III, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA III, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD
NYHA IV, QRS <120ms	OPT	OPT	OPT	OPT
NYHA IV, QRS ≥120ms and <150ms	CRTD	CRTD	CRTD	CRTD
NYHA IV, QRS ≥150ms	CRTD	CRTD	CRTD	CRTD

At the £20,000 per QALY threshold the model is sensitive to the treatment effect duration increasing in seven subgroups. This is because many of the ICERs lie just above £20,000 per QALY in the base case. Using of more conservative treatment effect durations alters the treatment choice in only two subgroups; patients with NYHA I or II with QRS≥150ms and LBBB switch from CRT-D to OPT only when the most conservative treatment effect duration is used.

Table 15: Impact of duration of treatment effect on treatment choice using £20,000 per QALY threshold

Subgroup	Duration of mortality treatment effect			
	Lifetime	7.5 years (base case)	5 years	Mean f/up
<i>Individuals without LBBB</i>				
NYHA I, QRS <120ms	ICD	OPT	OPT	OPT
NYHA I, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD
NYHA I, QRS ≥150ms	CRTD	OPT	OPT	OPT
NYHA II, QRS <120ms	ICD	OPT	OPT	OPT
NYHA II, QRS ≥120ms and <150ms	ICD	ICD	ICD	ICD
NYHA II, QRS ≥150ms	CRTD	OPT	OPT	OPT
NYHA III, QRS <120ms	OPT	OPT	OPT	OPT
NYHA III, QRS ≥120ms and <150ms	C RTP	OPT	OPT	OPT
NYHA III, QRS ≥150ms	C RTP	C RTP	C RTP	C RTP
NYHA IV, QRS <120ms	OPT	OPT	OPT	OPT
NYHA IV, QRS ≥120ms and <150ms	OPT	OPT	OPT	OPT
NYHA IV, QRS ≥150ms	C RTP	C RTP	C RTP	C RTP
<i>Individuals with LBBB</i>				
NYHA I, QRS <120ms	OPT	OPT	OPT	OPT
NYHA I, QRS ≥120ms and <150ms	C RTD	OPT	OPT	OPT
NYHA I, QRS ≥150ms	C RTD	C RTD	C RTD	OPT
NYHA II, QRS <120ms	OPT	OPT	OPT	OPT
NYHA II, QRS ≥120ms and <150ms	C RTD	OPT	OPT	OPT
NYHA II, QRS ≥150ms	C RTD	C RTD	C RTD	OPT
NYHA III, QRS <120ms	OPT	OPT	OPT	OPT
NYHA III, QRS ≥120ms and <150ms	C RTP	C RTP	C RTP	C RTP
NYHA III, QRS ≥150ms	C RTP	C RTP	C RTP	C RTP
NYHA IV, QRS <120ms	OPT	OPT	OPT	OPT
NYHA IV, QRS ≥120ms and <150ms	C RTP	C RTP	C RTP	C RTP
NYHA IV, QRS ≥150ms	C RTP	C RTP	C RTP	C RTP

The following evidence supports the assumption that treatment effects are maintained over the long term, and that the use of a 7.5 year constant treatment effect may be reasonable:

- The original data lock for the CARE-HF study found that at a mean follow-up of 29.4 months the hazard ratio for all cause-mortality was 0.64 [95% CI 0.48, 0.85] for CRT-P vs. OPT². Long-term follow up recently published for CARE-HF³ found that at a

² Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *New England Journal of Medicine* 2005; 352(15):1539-1549.

mean follow-up of 56 (50) months in the CRT-P (OPT) arms the hazard ratio for all cause-mortality was 0.77 [0.63, 0.93], this is despite the fact that 156/404 (39%) of control patients crossed-over to a CRT device during follow-up.

- The original data lock for MADIT-II study found that at an average follow-up of 20 months, the hazard ratio for all cause-mortality was 0.69 [0.51, 0.93]⁴. Long-term follow-up found that at a median follow-up of 7.6 years the hazard ratio for all cause-mortality was 0.77 [0.65, 0.91], this is despite the fact that 167/490 (34%) of control patients crossed-over to a device during follow-up⁵. Attempts to adjust for cross-over by censoring patients at the time of cross-over and including treatment as a time-dependent covariable provided treatment effect estimates of 0.67 [0.56, 0.80] and 0.66 [0.56, 0.78] respectively.
- As reported in the original submission (Section 4.5.3), there is no evidence from the overall IPD analysis that hazard ratios describing the device treatment effects on all-cause mortality vary over time. A test of the validity of the proportional hazards assumption which looks for any correlation between the scaled Schoenfeld residuals and survival time produced a global p-value for device terms of [REDACTED] (a p-value of less than 0.05 is considered to indicate violation of the proportionality assumption). The p-values for individual treatment coefficients were CRT-P: [REDACTED]; CRT-D: [REDACTED] and ICD: [REDACTED]; again suggesting no evidence of time-dependence in the treatment effects.

2) Effect of CRT-D on hospitalisation in NYHA III/IV patients

On review of the model inputs, the estimated [REDACTED] treatment effect for CRT-D in patients with NYHA III/IV was implemented in the base case and the reporting of this was inaccurate. A comparison of reported and used treatment effects are presented in Table 16. Small differences occurred for two of the CRT-D treatment effects.

³ Cleland JGF, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. *Eur J Heart Fail.* 14[6], 628-634. 2012.

⁴ Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *New England Journal of Medicine.* 2002; 346(12):877-883.

⁵ Goldenberg I, Gillespie J, Moss A, Hall J, Klein H, McNitt S, Brown M et al. Long-Term Benefit of Primary Prevention With an Implantable Cardioverter-Defibrillator: An Extended 8-Year Follow-Up Study of the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation.* 2010;122:1265-1271.

Table 16: Comparison between reported and actual all-cause hospitalisation treatment effects in the ABHI model

	Reported as used in ABHI model			Actually used in ABHI model		
	NYHA I/II	NYHA III	NYHA IV	NYHA I/II	NYHA III	NYHA IV
ICD	■	■	■	■	■	■
CRT-P	■	■	■	■	■	■
CRT-D	■	■	■	■	■	■

We have therefore run a scenario using the approach reported in the submission i.e. using the values for CRT-P in NYHA III and IV patients to model the treatment effects for CRT-D in these groups. The impact of this scenario is presented in Table 17 and Table 18. This has a marginal impact on the ICERs and none of the treatment options at £20,000, £25,000 or £30,000 per QALY change from the base case.

Table 17: Sensitivity analyses – all-cause hospitalisation treatment effect for CRT-D set equal to CRT-P for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,074	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,253	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,102	£21,759	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,465	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,813	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,602	£23,738	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,826	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,178	Ext Dominated	£23,207	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,930	£25,050	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,578	£38,459	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,175	£34,245	N/A	CRTP	CRTP	CRTP

Table 18: Sensitivity analyses - all-cause hospitalisation treatment effect for CRT-D set equal to CRT-P for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,677	£21,672	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,470	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,704	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,664	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,215	£24,707	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,496	£28,467	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,664	£35,384	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,500	£38,722	N/A	CRTP	CRTP	CRTP

3) Inclusion of counselling costs

Heart Rhythm UK note in their statement on “Standards for the implantation and follow up of cardiac rhythm management devices in adults” that psychological support and counselling

service for ICD and CRT-D patients is a necessary part of device follow up⁶. They then go on to say that “*counselling prior to implant is essential and further counselling as and when required should be made available if a patient is having problems*”.

Input from our clinical advisors indicated that the initial counselling session would be delivered by a member of the support team, typically an arrhythmia nurse and that long term a small proportion of patients would require psychiatric support (cognitive behavioural therapy, CBT). The following typical lifetime counselling protocol was provided by our clinical advisors:

1 x arrhythmic nurse consultation (incurred by 100% of patients)

1 x full psychiatry visit (incurred by 0.5% of patients)

4 x CBT sessions (incurred by 0.5% of patients)

All input data used in the model were taken from the latest version of the PSSRU⁷. Based on the unit cost of a specialist nurse consultation (£22, Table 10.7), a counselling consultation (£59, Table 2.7) and the per-person-per-session cost of CBT (£15, Table 2.6) the overall expected per-patient cost of counselling used in the model is £27.95. For simplicity, this value is applied in the first model cycle. Based on feedback from the committee, the Heart Rhythm UK statement and feedback from the clinical advisors this is applied to those receiving defibrillator therapy (CRT-D or ICD) and not to patients who receive CRT-P.

The results from this sensitivity analysis are presented in Table 19 and

Table 20. The overall impact on the ICERs in all subgroups was negligible with no changes to optional treatment choice at £20,000, £25,000 or £30,000 per QALY gained.

Table 19: sensitivity analysis – inclusion of counselling costs for patients without LBBB

⁶ <http://heartrhythmuk.org.uk/files/file/Docs/Position%20Statements/121214-1-Heart%20Rhythm%20UK%20standards%20for%20CRM%20devices%20in%20adults%202013.pdf>

⁷ <http://www.pssru.ac.uk/project-pages/unit-costs/2012/>

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,105	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,275	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,131	£21,759	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,497	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,835	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,630	£23,738	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,865	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,178	Ext Dominated	£23,394	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,930	£25,248	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,578	£40,138	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,175	£35,883	N/A	CRTP	CRTP	CRTP

Table 20: sensitivity analysis – inclusion of counselling costs for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,705	£21,672	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,488	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,724	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,681	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,215	£24,922	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,496	£28,701	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,664	£37,179	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,500	£40,532	N/A	CRTP	CRTP	CRTP

4) Device crossover or upgrade in clinical practice

(a) Likelihood

Information on crossover or upgrade rates in routine clinical practice is sparse. The latest UK devices survey⁸ did not collect this information and recorded “upgrades” as new implants. Information is available from the Swedish annual ICD and pacemaker register prepared annually by the Karolinska Hospital department of cardiology⁹. In this document, the annual rate of upgrade to CRT (type unspecified) in ICD explant patients was 0.5%. Information on the rate of upgrades from CRT-P to CRT-D was not reported in this document.

A recent retrospective observational study from the UK¹⁰ concluded that 3.8% of patients upgraded from ICD to CRT-D during a mean follow up period of 48 months. Data were again not reported for the proportion of CRT-P patients who upgrade to CRT-D.

The clinical experts consulted for this appraisal also confirmed that cross-overs or device upgrades are rare in UK clinical practice. They explained that upgrade procedures are complex and associated with increased lead and infective complications; and that they are also considered to be a waste of resources.

(b) Upgrade from CRT-P to CRT-D

We discussed the possibility of using CRT-D in patients currently indicated for a CRT-P on the basis that they may require defibrillation in the future with the clinical experts consulted for this appraisal. They both viewed that it was implausible that a patient with a CRT-P indication would be implanted with a CRT-D on the basis that they may develop a life-threatening arrhythmia at some point in the future but that defibrillation would not be switched on initially.

5) Deterministic sensitivity analyses for resource use and cost parameters

In response to the committee request for further deterministic sensitivity analyses for resource use and cost parameters we have run the following additional analyses:

- +/-25% change to HRG EA12Z (related to ICD/CRT-D based therapy) - used to model non-purchase costs in patients who get an ICD or CRT-D device.

⁸[https://nicor5.nicor.org.uk/CRM/device.nsf/65153b7e3756850e80256aff003a2c78/\\$FILE/CRM%20National%20Annual%20Report%202011%20final%20release%20revised.pdf](https://nicor5.nicor.org.uk/CRM/device.nsf/65153b7e3756850e80256aff003a2c78/$FILE/CRM%20National%20Annual%20Report%202011%20final%20release%20revised.pdf)

⁹<https://www.pacemakerregistret.se/icdpmr/start.do>

¹⁰Scott et al. Pacing Clin Electrophysiol. 2012 Jan;35(1):73-80

- +/-25% change to HRG EA07Z (CRT-P based therapy) – unlike for CRT-D and ICD, a relevant tariff existed for CRT-P and this was used to cover all up front implant costs.
- +/-25% change to HRG EA39Z - this tariff value was applied to battery replacements for ICD and CRT-D therapy.
- Upper/lower quartile HF and non-HF Hospitalisation costs
- +/-25% change to cost of an outpatient visit

The raw cost-effectiveness results for all analyses are presented as Appendix 1 with a summary of where the preferred treatment option changes from those in the base case presented below. Where the results differ from the base case, three pieces of information are provided: the subgroup where the change occurs, the nature of the change ('from option X to option Y') and the respective absolute ICER that has driven the change in the optimal treatment choice at a given threshold.

In terms of absolute changes to all ICERs, the model was robust to all alterations, with none of the analyses having a dramatic impact. However, the analyses do highlight the fact that small changes to cost parameters can impact on the choice of treatment in a subset of the 24 patient groups. These groups are primarily those with NYHA I to III HF and very wide QRS duration ($\geq 150\text{ms}$) or NYHA III and wide QRS duration ($\geq 120\text{ms}$ and $< 150\text{ms}$). The results arise due to the base case ICERs being very close to the threshold values, and in particular the £25,000/QALY threshold in some subgroups. As such, the results in these tables should be read in conjunction with the relevant model outputs presented in Appendix 1.

Table 21: summary of additional deterministic sensitivity analyses for patients without LBBB

Analysis	Cost-effectiveness threshold (per QALY gained)		
	£30,000	£25,000	£20,000
		<i>Alteration to HRG EA12Z (ICD / CRT-D non-purchase, £5,556)</i>	
Increased by 25%	None	NYHA I, QRS <120ms, ICD → OPT, £24,074 → £25,645 NYHA II, QRS <120ms, ICD → OPT, ICD: £24,465 → £26,027 NYHA III, QRS ≥120ms and <150ms, CRT-D → CRT-P, CRT-D: £23,349 → £25,611	None
Decreased by 25%	None	NYHA III, QRS ≥150ms, CRT-P → CRT-D, CRT-D: £25,200 → £22,806	NYHA I, QRS ≥150ms, OPT → ICD, ICD: £21,102 → £19,668 NYHA II, QRS ≥150ms, OPT → ICD, ICD: £20,602 → £19,231
		<i>Alteration to HRG EA07Z (total CRT-P implant cost, £8,281)</i>	
Increased by 25%	NYHA IV, QRS ≥150ms, CRT-P → CRT-D, CRT-D: £35,811 → £29,881	NYHA III, QRS ≥150ms, CRT-P → CRT-D, CRT-D: £25,200 → £20,927 NYHA IV, QRS ≥120ms and <150ms CRT-P → OPT, CRT-P: £22,578 → £28,516	NYHA IV, QRS ≥150ms CRT-P → OPT, CRT-P: £17,175 → £21,618
Decreased by 25%	None	NYHA III, QRS ≥120ms and <150ms, CRT-D → CRT-P, CRT-D: £23,349 → £27,276	NYHA III, QRS ≥120ms and <150ms, OPT → CRT-P, CRT-P: £20,178 → £15,182
		<i>Alteration to HRG EA39Z (ICD/CRT-D battery replacement cost, £2,748)</i>	
Increased by 25%	None	None	None
Decreased by 25%	None	NYHA III, QRS ≥150ms, CRT-P → CRT-D, CRT-D: £25,200 → £24,747	None
		<i>HF and non-HF Hospitalisation costs (£2,295 and £2,448 respectively)</i>	
Use of upper quartile data	None	None	NYHA III, QRS ≥120ms and <150ms, OPT → CRT-P, CRT-P: £20,178 → £19,724
Use of lower quartile data	None	NYHA III, QRS ≥150ms, CRT-P → CRT-D, CRT-D: £25,200 → £24,990	None
		<i>Cost of an outpatient visit (£110)</i>	
Increased by 25%	None	NYHA II, QRS ≥150ms, CRT-D → ICD, CRT-D: £23,768 → £25,403	None
Decreased by 25%	None	None	NYHA III, QRS ≥120ms and <150ms, OPT → CRT-P, CRT-P: £20,178 → £19,635

Table 22: summary of additional deterministic sensitivity analyses for patients with LBBB

Analysis	Cost-effectiveness threshold (per QALY gained)		
	£30,000	£25,000	£20,000
<i>Alteration to HRG EA12Z (ICD / CRT-D non-purchase, £5,556)</i>			
Increased by 25%	NYHA III, QRS ≥150ms, CRT-D → CRT-P, CRT-D: £28,646 → £31,356	NYHA III, QRS ≥120ms and <150ms, CRT-D → CRT-P, CRT-D: £24,875 → £27,232	None
Decreased by 25%	None	None	NYHA I, QRS ≥120ms and <150ms OPT → ICD, ICD: £20,677 → £19,303 NYHA II, QRS ≥120ms and <150ms, OPT → CRT-D, CRT-D: £20,704 → £19,683
<i>Alteration to HRG EA07Z (total CRT-P implant cost, £8,281)</i>			
Increased by 25%	None	NYHA III, QRS ≥150ms, CRT-P → CRT-D, CRT-D: £28,646 → £23,709	NYHA IV, QRS ≥120 and <150ms CRT-P → OPT, CRT-P: £18,664 → £23,546
Decreased by 25%	NYHA III, QRS ≥150ms, CRT-D → CRT-P, CRT-D: £28,646 → £33,583	NYHA III, QRS ≥120ms and <150ms, CRT-D → CRT-P, CRT-D: £24,875 → £29,070	None
<i>Alteration to HRG EA39Z (ICD/CRT-D battery replacement cost, £2,748)</i>			
Increased by 25%	None	NYHA III, QRS ≥120ms and <150ms, CRT-D → CRT-P, CRT-D: £24,875 → £25,313	None
Decreased by 25%	None	None	None
<i>HF and non-HF Hospitalisation costs (£2,295 and £2,448 respectively)</i>			
Use of upper quartile data	None	NYHA III, QRS ≥120ms and <150ms, CRT-D → CRT-P, CRT-D: £24,875 → £25,100	None
Use of lower quartile data	None	None	None
<i>Cost of an outpatient visit (£110)</i>			
Increased by 25%	None	NYHA III, QRS ≥120ms and <150ms, CRT-D → CRT-P, CRT-D: £24,875 → £25,037	None
Decreased by 25%	None	None	None

Appendix 1

HRG tariff EA12Z (ICD/CRT non-purchase costs tariff)

Lower value for HRG tariff

Table 23: Sensitivity analyses – a reduction in tariff EA12Z for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	ICD	N/A	N/A	Referent	£22,502	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,189	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£19,668	£21,756	N/A	CRTD	CRTD	ICD
II	<120ms	OPT	ICD	N/A	N/A	Referent	£22,904	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£15,728	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£19,231	£23,735	N/A	CRTD	CRTD	ICD
III	<120ms	OPT	ICD	N/A	N/A	Referent	£25,864	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,178	Ext Dominated	£21,087	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,930	£22,806	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,578	£35,752	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,175	£32,215	N/A	CRTP	CRTP	CRTP

Table 24: Sensitivity analyses – a reduction in tariff EA12Z for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£19,303	£21,669	N/A	CRTD	CRTD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,603	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£19,683	N/A	CRTD	CRTD	CRTD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£16,817	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,215	£22,517	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,496	£25,937	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,664	£33,311	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,500	£36,291	N/A	CRTP	CRTP	CRTP

Upper value for HRG tariff

Table 25: Sensitivity analyses – an increase in tariff EA12Z for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	ICD	N/A	N/A	Referent	£25,645	N/A	N/A	ICD	OPT	OPT
I	>=120, <150 ms	OPT	CRTP	ICD	N/A	Referent	Dominated	£17,318	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£22,354	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£26,027	N/A	N/A	ICD	OPT	OPT
II	>=120, <150 ms	OPT	CRTP	ICD	N/A	Referent	Dominated	£17,898	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,973	£23,741	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£29,787	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,178	Ext Dominated	£25,611	CRTD	CRTP	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,930	£27,594	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,578	£44,353	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,175	£39,407	N/A	CRTP	CRTP	CRTP

Table 26: Sensitivity analyses – an increase in tariff EA12Z for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below	Highest ICER	Highest ICER
		1st	2nd	3rd	4th	1st	2nd	3rd	4th	£30k/QALY	below £25k/QALY	below £20k/QALY
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,964	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,337	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,725	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,511	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,215	£27,232	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,496	£31,356	CRTP	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,664	£40,896	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,500	£44,608	N/A	CRTP	CRTP	CRTP

HRG tariff EA07Z (CRT-P tariff)

Lower value for HRG tariff

Table 27: Sensitivity analyses – a reduction in tariff EA07Z for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,074	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,253	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,102	£21,759	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,465	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,813	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,602	£23,738	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,826	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£15,182	Ext Dominated	£27,276	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,667	£29,473	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£16,640	£46,934	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£12,732	£41,740	N/A	CRTP	CRTP	CRTP

Table 28: Sensitivity analyses – a reduction in tariff EA07Z for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,677	£21,672	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,470	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,704	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,664	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,848	£29,070	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£8,177	£33,583	CRTP	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£13,783	£43,283	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£11,028	£47,296	N/A	CRTP	CRTP	CRTP

Upper value for HRG tariff

Table 29: Sensitivity analyses – an increase in tariff EA07Z for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,074	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,253	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,102	£21,759	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,465	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,813	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,602	£23,738	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,826	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	Ext Dominated	Ext Dominated	£21,954	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£17,193	£20,927	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£28,516	£33,170	N/A	CRTP	OPT	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£21,618	£29,881	N/A	CRTD	CRTP	OPT

Table 30: Sensitivity analyses – an increase in tariff EA07Z for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,677	£21,672	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,470	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,704	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,664	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£17,582	£20,679	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£12,816	£23,709	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£23,546	£30,924	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,973	£33,602	N/A	CRTP	CRTP	CRTP

HRG tariff EA39Z (battery replacement for ICD/CRT-D)

Lower value for HRG tariff

Table 31: Sensitivity analyses – a reduction in tariff EA39Z for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£23,690	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,020	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,817	£21,572	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,056	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,566	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,312	£23,544	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,493	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,178	Ext Dominated	£22,971	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,930	£24,747	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,578	£39,687	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,175	£35,389	N/A	CRTP	CRTP	CRTP

Table 32: Sensitivity analyses – a reduction in tariff EA39Z for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,375	£21,495	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,244	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,428	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,424	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,215	£24,437	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,496	£28,098	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,664	£36,713	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,500	£39,986	N/A	CRTP	CRTP	CRTP

Upper value for HRG tariff

Table 33: Sensitivity analyses – an increase in tariff EA39Z for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,457	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,487	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,388	£21,947	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,874	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£17,061	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,893	£23,932	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£28,158	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,178	Ext Dominated	£23,727	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,930	£25,654	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,578	£40,418	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,175	£36,233	N/A	CRTP	CRTP	CRTP

Table 34: Sensitivity analyses – an increase in tariff EA39Z for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,979	£21,850	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,697	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,980	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,904	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,215	£25,313	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,496	£29,194	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,664	£37,494	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,500	£40,913	N/A	CRTP	CRTP	CRTP

Hospitalisation costs (HF related and non-HF related)

For the purpose of this sensitivity analyses, the derived lower estimates for HF related and non-HF related hospitalisations are £1,804 and £1,859 respectively with the corresponding upper values being £2,804 and £2,941. These were derived by taking a weighted average of the lower and upper quartiles, weighting by activity.

Lower value for all NHS tariffs

Table 35: Sensitivity analyses – a reduction in all hospitalisation costs for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,147	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,250	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,126	£21,898	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,552	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,819	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,628	£23,907	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,875	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,669	Ext Dominated	£23,123	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,168	£24,990	CRTD	CRTD	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£23,298	£39,283	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,745	£35,081	N/A	CRTP	CRTP	CRTP

Table 36: Sensitivity analyses – a reduction in all hospitalisation costs for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,714	£21,853	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,498	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	>=120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,777	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,704	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	>=120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,492	£24,632	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,600	£28,429	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£19,303	£36,281	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,750	£39,679	N/A	CRTP	CRTP	CRTP

Upper value for all NHS tariffs

Table 37: Sensitivity analyses – an increase in all hospitalisation costs for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,007	N/A	N/A	ICD	ICD	OPT
I	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,257	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,081	£21,630	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,386	N/A	N/A	ICD	ICD	OPT
II	>=120, <150 ms	OPT	CRTD	ICD	N/A	Referent	Dominated	£16,809	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,579	£23,581	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,781	N/A	N/A	ICD	OPT	OPT
III	>=120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£19,724	Ext Dominated	£23,559	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,710	£25,396	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	>=120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£21,912	£40,767	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£16,647	£36,489	N/A	CRTP	CRTP	CRTP

Table 38: Sensitivity analyses –an increase in all hospitalisation costs for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	≥120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,644	£21,505	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,444	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	≥120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,636	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,627	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	≥120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,958	£25,100	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,400	£28,849	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	≥120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,073	£37,868	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,270	£41,165	N/A	CRTP	CRTP	CRTP

Outpatient costs

Lower value

Table 39: Sensitivity analyses –a reduction in outpatient costs for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,005	N/A	N/A	ICD	ICD	OPT
I	≥120, <150 ms	OPT	CRTP	ICD	N/A	Referent	Dominated	£16,182	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,855	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,397	N/A	N/A	ICD	ICD	OPT
II	≥120, <150 ms	OPT	CRTP	ICD	N/A	Referent	Dominated	£16,742	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,532	£22,074	N/A	CRTD	CRTD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,742	N/A	N/A	ICD	OPT	OPT
III	≥120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£19,635	Ext Dominated	£23,190	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,510	£25,040	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	≥120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£22,148	£39,864	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£16,769	£35,625	N/A	CRTP	CRTP	CRTP

Table 40: Sensitivity analyses –a reduction in outpatient costs for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	≥120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,487	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,110	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	≥120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£20,273	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,279	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	≥120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£13,786	£24,713	CRTD	CRTD	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,153	£28,483	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	≥120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£18,253	£36,915	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,161	£40,260	N/A	CRTP	CRTP	CRTP

Upper value

Table 41: Sensitivity analyses –an increase in outpatient costs for patients without LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	ICD	N/A	N/A	Referent	£24,142	N/A	N/A	ICD	ICD	OPT
I	≥120, <150 ms	OPT	CRTP	ICD	N/A	Referent	Dominated	£16,324	N/A	ICD	ICD	ICD
I	>150ms	OPT	ICD	CRTD	N/A	Referent	£21,173	£23,236	N/A	CRTD	CRTD	OPT
II	<120ms	OPT	ICD	N/A	N/A	Referent	£24,534	N/A	N/A	ICD	ICD	OPT
II	≥120, <150 ms	OPT	CRTP	ICD	N/A	Referent	Dominated	£16,884	N/A	ICD	ICD	ICD
II	>150ms	OPT	ICD	CRTD	N/A	Referent	£20,673	£25,403	N/A	CRTD	ICD	OPT
III	<120ms	OPT	ICD	N/A	N/A	Referent	£27,909	N/A	N/A	ICD	OPT	OPT
III	≥120, <150 ms	OPT	CRTP	ICD	CRTD	Referent	£20,722	Ext Dominated	£23,508	CRTD	CRTD	OPT
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,349	£25,360	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	≥120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£23,007	£40,240	N/A	CRTP	CRTP	OPT
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£17,580	£35,997	N/A	CRTP	CRTP	CRTP

Table 42: Sensitivity analyses –an increase in outpatient costs for patients with LBBB

NYHA Class	QRS Duration	C-E Sequence				ICERs				Highest ICER below £30k/QALY	Highest ICER below £25k/QALY	Highest ICER below £20k/QALY
		1st	2nd	3rd	4th	1st	2nd	3rd	4th			
I	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
I	≥120, <150 ms	OPT	ICD	CRTD	N/A	Referent	£20,748	£23,247	N/A	CRTD	CRTD	OPT
I	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£17,830	N/A	CRTD	CRTD	CRTD
II	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
II	≥120, <150 ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£21,135	N/A	CRTD	CRTD	OPT
II	>150ms	OPT	ICD	CRTD	N/A	Referent	Ext Dominated	£18,049	N/A	CRTD	CRTD	CRTD
III	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
III	≥120, <150 ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£14,644	£25,037	CRTD	CRTP	CRTP
III	>150ms	OPT	ICD	CRTP	CRTD	Referent	Dominated	£10,840	£28,809	CRTD	CRTP	CRTP
IV	<120ms	OPT	N/A	N/A	N/A	Referent	N/A	N/A	N/A	OPT	OPT	OPT
IV	≥120, <150 ms	OPT	CRTP	CRTD	N/A	Referent	£19,076	£37,292	N/A	CRTP	CRTP	CRTP
IV	>150ms	OPT	CRTP	CRTD	N/A	Referent	£14,840	£40,639	N/A	CRTP	CRTP	CRTP

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA 120) [ID481]

SHTAC review of the manufacturer's response to the specification of further work following the Appraisal Committee meeting on 23rd April 2013

Southampton Health Technology Assessments Centre (SHTAC)

September 2013

Table of Contents

Summary	3
Introduction and methods	5
Suggested presentation of analyses	6
Specification of further work	7
1. Duration of mortality treatment effects	7
2. Effect of CRT-D devices on all-cause hospitalisation for NHYA III/IV	9
3. Inclusion of counselling costs.....	10
4. Device upgrade in clinical practice.....	11
5. Deterministic sensitivity analyses for resource use and cost parameters.....	12
6. AG further analyses.....	13

Summary

ABHI has undertaken the additional analyses as requested by the Appraisal Committee. The AG has checked the model structure and parameter inputs and has reproduced the updated results presented by the ABHI using their model. The AG considers that the new results are consistent with those in the original ABHI analyses. The ABHI have conducted all the required analyses specified by NICE and have presented these in the same format as the original submission with 24 rather than 48 subgroups. The ABHI have commented upon the impact of the changes to the model results with respect to any changes in the preferred treatment at the £20,000, £25,000 and £30,000 per QALY thresholds.

In the analysis the ABHI have not concluded which are the specific key drivers of the cost effectiveness results. The AG has undertaken additional sensitivity analyses to explore the impact of some of the parameters that may determine the ICERs. Given the complexity of interpreting the large number of subgroups in the model, the AG focused on three of the subgroups that contained the largest number of patients to illustrate the effects of changes to the different parameters.

Duration of mortality treatment effects

In the ABHI analyses, the model results were robust to changes to the model parameters for the duration of mortality treatment effects at the £30,000 per QALY threshold: for treatment duration the preferred treatment of choice alters in only two of the 24 subgroups (NYHA III, QRS <120 ms and no LBBB and NYHA III, QRS ≥ 150ms and LBBB. At lower thresholds (£20,000 and £25,000 per QALY) the model is more sensitive to changes in the duration of treatment effect, changing the most cost effective treatment in nine of the 24 subgroups.

The AG investigated other assumptions for the duration of the treatment effect (7.5 years treatment effect with no tapering effect, and 7.5 years treatment effect with tapering effect of 10 years) and the effect of changes to the mortality treatment effect (+/- 10%). Changes to these parameters were shown to result in changes to the model results, such that for two of the three subgroups analysed, the preferred treatment of choice alters at the £30,000 per QALY threshold. For the other subgroup the treatment of choice alters at the £20,000 per QALY threshold.

Effect of CRT-D on hospitalisation in NYHA III/IV patients

The AG confirmed that the treatment effect used in the original ABHI's submission was [REDACTED] and the reporting of this was inaccurate in the original submission. The AG completed sensitivity analyses for three selected subgroups and found changing the treatment effect for hospitalisation has only a small effect on cost effectiveness results.

Inclusion of counselling costs

ABHI reported that inclusion of counselling costs did not change the base case conclusions at any of the three thresholds considered. Sensitivity analyses undertaken by the AG for three selected subgroups confirmed that increasing these costs to a worst case scenario had little impact on the model results.

Device crossover or upgrade in clinical practice

Clinical experts contacted by the AG confirmed that device crossover/upgrade as described in the Specification document is rare in clinical practice.

Resource use and cost parameters

For the changes in device costs relating to the HRG tariff, the preferred treatment of choice alters in two of the 24 subgroups (NYHA III, QRS \geq 150ms, LBBB, and NYHA IV, QRS \geq 150 ms, without LBBB) in the ABHI analysis. For these subgroups, the base case ICERs were close to the £30,000 per QALY threshold.

The AG investigated the effect of changes to the manufacturers' device cost (not relating to the HRG tariff) in the three selected subgroups. These showed a similar impact to the model results as for changes to the HRG tariff.

Conclusions

The AG has checked the results for the base case using the ABHI model and considers that the new results are consistent with those in the original analyses. The AG has also checked the additional analyses submitted and replicated these by running the ABHI model. The ABHI analyses and those undertaken by the AG have shown that the ABHI model appears most sensitive to changes in parameter values for the assumptions surrounding the treatment effect of mortality and duration of treatment effect. The impact of the scenarios on the model differed for the different subgroups, but most remained under the £30,000 per QALY gained threshold. For the lower thresholds, some scenarios had the effect of changing the preferred treatment with only a small change in the ICER where the base case ICER was close to the threshold.

Introduction and methods

Following the Appraisal Committee Meeting on 23rd April 2013, the Committee requested that the manufacturers (ABHI) undertake additional analyses as detailed in the specification of further work (Appendix). This document summarises the review of these analyses by the SHTAC Assessment Group (AG).

The AG has checked the results of the ABHI additional analyses by re-running the ABHI model for each of the scenarios presented, and checking the submitted model (structure and parameters) against the original ABHI model. The AG has also used the ABHI model to run additional analyses to aid interpretation of the ABHI results. Given the large number of subgroups in the model, the AG focused on three of the 24 subgroups (Group 1: NYHA II, QRS \geq 150 ms, LBBB, Group 2: NYHA III, QRS \geq 150 ms, LBBB; and Group 3: NYHA II, QRS $<$ 120 ms, without LBBB). These subgroups were selected to reflect different patient characteristics and potential treatment options and for their larger sample size in the IPD analysis. However they are not necessarily representative of all the other subgroups. It should be noted that for first subgroup (NYHA II, QRS \geq 150 ms), CRT-P was excluded as a treatment option in the ABHI model as minimal IPD data were available from the clinical trials.

Clinical experts were asked by the AG to comment on the questions raised by the Appraisal Committee regarding device crossover or upgrade in clinical practice, and on assumptions made by ABHI for counselling costs.

Concerns previously raised by the AG in the assessment report regarding appropriateness of the 48 original subgroups and how these relate to the populations scoped by NICE have not been repeated here.

Suggested presentation of analyses

Please combine the ischaemic and non-ischaemic patient groups together, therefore presenting results for 24 subgroups rather than 48 in the original submission. For these subgroups, for each of the different scenarios presented, please present tables with fully incremental cost-effectiveness results as previously presented in tables 70-71 of the submission.

Please also present a summary of the most optimal strategies at different cost-effectiveness thresholds, for example, at £20,000, £25,000 and £30,000 per QALY gained.

The ABHI has provided the analyses as requested in terms of 24 subgroups rather than 48 in the original submission. The AG has checked the results for the base case using the ABHI model and considers that the new results are consistent with those in the original analyses. Although the results have changed by combining the ischaemic and non-ischaemic groups, there are no differences in the conclusions of the optimal treatment with regard to £30,000 per QALY cost effectiveness threshold for the aggregated results compared to the original results, except for subgroups with very small numbers in the IPD (such as NYHA I, non-ischaemic, QRS \geq 150 ms without LBBB). For the £25,000 and £20,000 thresholds, there are some differences in the preferred treatment by aggregating the analyses in terms of 24 subgroups rather than 48. For some subgroups, the ischaemic and non-ischaemic ICERs are either side of a threshold. However, for the majority of the subgroups, the ischaemic and non-ischaemic ICERs are similar and aggregating the results does not change the preferred treatment.

With respect to changing the cost-effectiveness threshold, ABHI has presented a summary of optimal strategies at cost-effectiveness threshold values of £30,000, £25,000 and £20,000 per QALY gained (ABHI Tables 4 to 6). Changing the threshold from £30,000 to £25,000 per QALY changes the optimal strategy in three of the 24 subgroups (NYHA III, QRS $<$ 120 ms; and NYHA III, QRS \geq 150 ms, both LBBB groups). Changing the threshold to £20,000 per QALY changes the optimal strategy in most subgroups. The ABHI requests that the committee note that the ICERs are very close to the threshold values, with the potential impact that very small differences in ICERs could change threshold-decisions. Furthermore, they would expect that the ICERs would fall as acquisition costs of the medical devices reduce over time.

Specification of further work

1. Duration of mortality treatment effects

The manufacturers' base case assumes a constant duration of effect of 7.5 years for all-cause mortality, followed by linear tapering over 20 years. Sensitivity analyses were also provided assuming life-long constant treatment effects without any tapering (MS page 194) as a more optimistic scenario, and assuming a constant duration of effect for 5 years as a more conservative scenario (Appendix 15 page 72-73). Please provide these analyses for the 24 subgroups outlined above, combining the ischaemic and non-ischaemic patient groups.

In addition, please also provide a sensitivity analysis assuming a constant duration of effect up to the average duration of follow up in the trials, followed by linear tapering thereafter?

The ABHI has provided the analyses requested, and the AG has replicated these results using the ABHI model. The results from the changes to the duration of the treatment effect are shown in the ABHI document (Tables 7-12). The ABHI has shown the impact of different treatment effect durations on treatment choice at £30,000, £25,000 and £20,000 per QALY thresholds (ABHI Tables 13- 15). At the £30,000 per QALY threshold the model results are insensitive to the treatment effect duration, and the preferred treatment of choice alters in only two of the 24 subgroups (NYHA III, QRS < 120 ms, without LBBB from ICD to OPT for the worst case scenario with 2.54 years treatment effect; and NYHA III, QRS ≥ 150 ms and LBBB from CRT-D to CRT-P with 5 year treatment effect). At lower thresholds (£20,000 and £25,000 per QALY) the model is more sensitive to changes in the duration of treatment effect, with regard to the most cost effective treatment, as the base case ICERs are close to the thresholds. For example, at the £25,000 threshold, the model is sensitive to the treatment duration being increased (best case scenario) in three of the 24 subgroups, and sensitive to it being decreased (worst case scenarios) in six subgroups (ABHI Table 14). At the £20,000 threshold, the model is sensitive to the treatment duration being increased (best case scenario) in seven of the 24 subgroups, and being decreased (worst case scenario) in two subgroups (Table 15).

The ABHI original submission justified the use of a treatment duration of 7.5 years as this was the maximum follow-up included in the network meta-analysis. Beyond this period, they assumed that the hazard ratio converges to 1 linearly over a 20 year period (linear tapering of the treatment effect). The original submission does not discuss or justify the use of this linear tapering.

The AG notes that alternative plausible assumptions would be that there is no linear tapering of the treatment effect after 7.5 years, or the linear tapering would be for a shorter time period than 20 years, such as 10 years. Another variable that might have had a significant impact on the model results is the treatment effect of the devices. The AG has completed these sensitivity analyses in the *AG further analyses* (see Tables 1 to 3) for three particular subgroups (Group 1: NYHA II, QRS ≥ 150 ms, LBBB, Group 2: NYHA III, QRS ≥ 150 ms, LBBB; and Group 3: NYHA II, QRS < 120 ms, without LBBB).

Subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

For the first subgroup, the cost effectiveness of CRT-D vs. OPT varied between £13,497 and £23,938 per QALY gained (Table 1), for life-long constant treatment effects and 7.5 years treatment effect with no tapering of the treatment effect, respectively (compared to a base case of £17,664 per QALY for this subgroup). The scenarios for a 2.54 year treatment effect (£20,534 per QALY gained) and 10 years with tapering effect (£21,796 per QALY gained) also produced ICERs between the £20,000 per QALY gained and £25,000 per QALY gained thresholds.

The cost effectiveness of CRT-D vs. OPT varied between £15,785 and £19,997 for changes to the mortality treatment effectiveness of CRT-D of +/-10% (Table 1).

Subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

For the second subgroup, the cost effectiveness of CRT-D vs. CRT-P varied between £23,891 and £36,142 per QALY gained (Table 2), for life-long constant treatment effects and 7.5 years treatment effect with no tapering of the treatment effect, respectively (compared to a base case of £28,646 per QALY for this subgroup). All treatment duration effect scenarios, other than the base case and best case scenarios, produced ICERs above the £30,000 per QALY threshold.

The cost effectiveness of CRT-D vs. CRT-P varied between £21,335 and £47,374 for changes to the mortality treatment effectiveness of CRT-D and CRT-P of +/- 10%, respectively (Table 2).

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup, the cost effectiveness of ICD vs. OPT varied between £17,807 and £34,268 per QALY gained (Table 3), for life-long constant treatment effects and 7.5 years treatment effect with no tapering of the treatment effect respectively, (compared to a base case of £24,465 per QALY for this subgroup). All other treatment effect scenarios were between the £20,000 per QALY gained and £30,000 per QALY gained thresholds, except for the scenario of 10 years tapering effect (£30,997 per QALY gained).

The cost effectiveness of ICD vs. OPT varied between £19,514 and £32,761 for changes to the mortality treatment effectiveness of ICD of +/- 10% (Table 3).

The sensitivity analyses undertaken by ABHI and the AG show that the assumptions on the duration of the treatment effect and the mortality treatment effect are the key drivers of the cost effectiveness results. However, the effect of these changes on the recommended treatment for each subgroup depends upon the base case results and the cost effectiveness threshold used. For two of the three subgroups shown above (subgroups 2 and 3), the model results were sensitive to the treatment duration and mortality treatment effect, switching the preferred treatment option at the £30,000 per QALY threshold, whilst for subgroup 1 the model results were insensitive to changes to these parameters. For subgroup 1, where the base case results were less than the £20,000 per QALY threshold, changes to the treatment duration switch the preferred treatment option at the £20,000 per QALY threshold.

2. Effect of CRT-D devices on all-cause hospitalisation for NYHA III/IV

The effect of CRT-D devices on all-cause hospitalisation for NYHA III and IV class patients estimated in the IPD network meta analysis (HR; [REDACTED]) was not incorporated in the model and the value estimated for CRT-P ([REDACTED] for NYH III and [REDACTED] for NYHA IV) was used instead. The manufacturers' stated that it is unlikely that the use of CRT-D will result in a smaller treatment effect than the use of CRT-P in a given patient group, as both include CRT therapy.

However, the Committee would like to see the effect on the ICERs of a more conservative estimate of effect of CRT D for all cause hospitalisation estimated in the IPD network meta-analysis (that is, HR [REDACTED])?

The ABHI reported that the estimated HR [REDACTED] treatment effect for CRT-D in patients with NYHA III/IV was implemented in the base case and the reporting of this was inaccurate. The AG has checked the model and agrees that this value is implemented in the base case of the original ABHI's submission.

The AG notes that the ABHI has not explored the sensitivity of the model results to changes in the all-cause hospitalisation rates for the devices. The AG explores these in sensitivity analyses in the AG *further analyses* (see Tables 1 to 3) by varying the treatment effect of the hospitalisation rate by +/- 25% for the three selected subgroups (NYHA II, QRS \geq 150 ms, LBBB; NYHA III, QRS \geq 150 ms, LBBB; NYHA II, QRS < 120 ms, no LBBB).

Subgroup 1: NYHA II, QRS \geq 150 ms, LBBB

For the first subgroup, the cost effectiveness of CRT-D vs. OPT varied between £17,300 and £18,028 per QALY gained, for an increase and reduction in the treatment effect on hospitalisation of 25%, respectively (compared to a base case of £17,664 per QALY for this subgroup).

Subgroup 2: NYHA III, QRS \geq 150 ms, LBBB

For the second subgroup, the cost effectiveness of CRT-D vs. CRT-P varied between £26,985 and £30,308 per QALY gained, for an increase and reduction in the treatment effect on hospitalisation of 25%, respectively (compared to a base case of £28,646 per QALY for this subgroup).

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup, the cost effectiveness of ICD vs. OPT varied between £23,691 and £25,239, for an increase and reduction in the treatment effect on hospitalisation of 25%, respectively (compared to a base case of £24,465 per QALY for this subgroup).

The results show that changing the treatment effect on hospitalisation has only a small effect on the cost effectiveness results. The effect of these changes on the recommended treatment for each subgroup depends upon the base case results and the cost effectiveness threshold. The base case results for subgroup 2 and 3 were close to the £30,000 and £25,000 thresholds, respectively, and small changes to the results cause the ICERs to exceed these thresholds. Subgroup 1 is close to the

£20,000 per QALY threshold but changes to all-cause hospitalisation do not cause the ICER for CRT-D vs. OPT to exceed this threshold.

3. Inclusion of counselling costs

The Committee heard that defibrillating devices can increase anxiety in some patients. The manufacturers' model does not account for any additional cost of counselling apart from the bi-annual device related outpatient visits for ICD patients and quarterly visits for CRT (CRT-D or CRT-P) patients.

Given the feedback from experts on the importance of counselling, particularly for patients receiving defibrillator devices, what is the impact of this additional resource use on the ICERs?

The submission presented a 'typical lifetime counselling protocol' as follows:

- 1 x arrhythmic nurse consultation (incurred by 100% of patients)
- 1 x full psychiatry visit (incurred by 0.5% of patients)
- 4 x CBT sessions (incurred by 0.5% of patients)

These estimates were thought to be conservative by our experts, as 'many patients need counselling pre and post implant'. It was thought that 2-3% of patients would require a psychology or psychiatry consultation and CBT, with a psychology consultation more common than psychiatry.

The AG is unable to replicate the cost of £27.95 per patient cost of counselling used in the model from the data provided by the ABHI. It is unclear whether the ABHI has made an error in the reporting or in the calculation of the counselling cost. Changing the estimates provided by the ABHI of 0.5% of patients attending full psychiatry visit and CBT sessions to 5% for both gives the reported cost of £27.95. These estimates are more in line with those suggested by our experts.

It may be that the cost of CBT is underestimated. The ABHI has based its costs upon group therapy with 10 people per session, but it may also be that some patients are referred to smaller group or individual CBT. In addition, CBT is often given for more than 4 sessions, sometimes as 6 or 12 sessions. In the case where CBT is given for 6 sessions on an individual basis, the per patient cost of counselling would be as much as £70 (i.e. per patient cost: CBT cost = £15 per session x 6 sessions x 10 individuals x 5% of patients receiving the intervention = £45; Nurse consultation = £22, Psychiatric visit cost £2.95. Total cost £69.95).

The AG has completed sensitivity analyses using this higher counselling cost in the *AG further analyses* (Tables 1 to 3) for the three selected subgroups (NYHA II, QRS ≥ 150 ms, LBBB; NYHA III, QRS ≥ 150 ms, LBBB; NYHA II, QRS < 120 ms, without LBBB). Including counselling costs and increasing these in sensitivity analyses has little impact on the model for the three subgroups shown below.

Subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

For the higher cost of counselling, the cost effectiveness of CRT-D vs. OPT increases only marginally to £17,706 per QALY, for the first subgroup (compared to a base case of £17,664 per QALY).

Subgroup 2: NYHA III, QRS \geq 150 ms, LBBB

For the second subgroup the cost effectiveness of CRT-D vs. CRT-P increases only marginally to £28,782 (compared to a base case of £28,646).

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup the cost effectiveness of ICD vs. OPT increases only marginally to £24,544 (compared to a base case of £24,465).

4. Device upgrade in clinical practice

The manufacturer's model excludes the possibility of crossover or device upgrades, which are possible in clinical practice. Please comment on the likelihood of device upgrades in clinical practice.

In particular, the Committee heard that there may be a subgroup of people indicated for CRT-P who are also likely to need a defibrillator in the near future, so that cardiologists would choose to implant a CRT-D in which the ICD function could be switched on when needed, rather than to implant a CRT-P device which would have to be upgraded to CRT-D at full cost at a later date. Please provide comment on experience with this situation in clinical practice, and on identification of a subgroup of patients for which this situation applies.

a) Likelihood of device upgrades in clinical practice

One AG clinical expert stated that in clinical practice upgrade from CRT-P to ICD is unlikely. CRT-D to ICD would be irrational and an upgrade would generally be CRT-P to CRT-D rather than ICD for technical and clinical reasons. The ICD to CRT-D upgrade rate sounds reasonable and would occur if someone with a pre-existing ICD develops a CRT indication (generally progressive heart failure and QRS prolongation). In view of this risk some authorities have argued in favour of implanting CRT-D rather than ICD in all cases but this view is not widely supported.

b) Upgrade from CRT-P to CRT-D

Two AG clinical experts agreed with the ABHI experts that it would be clinically implausible to implant CRT-D and not switch the defibrillator on. One expert stated that it is recognised that the indication for CRT implies a de-facto risk of arrhythmic death and most countries regard the need for CRT as indicative of a need for CRT-D. If a patient with a pre-existing CRT-P device had an episode of life threatening arrhythmia, they would be upgraded to CRT-D, but if that were anticipated prior to implantation of the initial device a CRT-D would have been implanted in the first place.

5. Deterministic sensitivity analyses for resource use and cost parameters

The Committee considered that further deterministic sensitivity analyses were required for resource use and cost parameters. Please provide such sensitivity analyses, as implementable within the current model structure.

The ABHI has run the following additional analyses:

- +/-25% change to HRG EA12Z (related to ICD/CRT-D based therapy) - used to model non-purchase costs in patients who get an ICD or CRT-D device.
- +/-25% change to HRG EA07Z (CRT-P based therapy) – unlike for CRT-D and ICD, a relevant tariff existed for CRT-P and this was used to cover all up front implant costs.
- +/-25% change to HRG EA39Z - this tariff value was applied to battery replacements for ICD and CRT-D therapy.
- Upper/lower quartile HF and non-HF Hospitalisation costs
- +/-25% change to cost of an outpatient visit

The AG has replicated these results using the ABHI model. The total cost relating to the device used in the model consists of the HRG tariff cost and the manufacturers' device cost. However, the AG notes that the ABHI varies only part of the cost of the devices, relating to the HRG tariff, and the manufacturers' device cost has not been varied. The AG has therefore also included sensitivity analyses varying the device cost by an arbitrary range of +/-10% to illustrate potential uncertainty for the three selected subgroups (see *AG further analyses*, Tables 1 to 3).

Subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

For the first subgroup, the changes to the resource use and cost parameters in the ABHI analyses only have a small effect on the results. The cost effectiveness varies between £16,817 and £18,511 per QALY for CRT-D for changes to the HRG cost for EA12Z (compared to a base case of £17,664 per QALY for this subgroup). Varying the device cost for CRT-D by +/- 10% changed the cost effectiveness results between £16,504 and £18,824 per QALY gained.

Subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

For the second subgroup, the changes to the resource use and cost parameters in the ABHI analyses have a more substantial effect on the model results. The cost effectiveness varies between £23,709 and £33,583 per QALY for CRT-D vs. CRT-P for changes to the HRG cost for EA072 (compared to a base case of £28,646 per QALY for this subgroup). Varying the device cost of CRT-D by +/- 10% changed the cost effectiveness results between £25,311 and £31,982 per QALY gained.

Subgroup 3: NYHA II, QRS < 120 ms, no LBBB

For the third subgroup, the changes to the resource use and cost parameters in the ABHI analyses only have a small effect on the results. The cost effectiveness varies between £22,904 and £26,027 per QALY for ICD vs. OPT for changes to the HRG cost for EA12Z (compared to a base case of £24,465 per QALY for this subgroup). Varying the device cost of ICD by +/- 10% changed the cost effectiveness results between £22,831 and £26,099 per QALY gained.

The effect of changes to the resource use and cost parameters differs between the subgroups shown above. For subgroups 1 and 3, changes to these costs had only a small impact on model results with ICERs for all scenarios for group 1 remaining below £20,000 per QALY gained and those for group 3 equal to or below £26,000 per QALY gained. For subgroup 2, these changes had a larger effect and switch the preferred treatment option at the £30,000 per QALY threshold from CRT-D to CRT-P for changes to the device cost and HRG cost EA072 and EA12Z. In all other instances the ICERs were between £25,000 and £30,000 per QALY gained.

6. AG further analyses

The ABHI results are presented for 24 categories, which makes interpretation difficult. Whilst the ABHI has largely answered the questions asked for by the NICE committee, i.e. to examine various scenarios and sensitivity analyses, the analysis has not concluded which are the specific key drivers of the cost effectiveness results, and interpretation of this is not intuitive from the results presented.

To examine the relative impact of the input parameters on the cost effectiveness results, the AG has examined the impact of these changes on the model results for three particular subgroups (NYHA II, QRS \geq 150 ms, LBBB; NYHA III, QRS \geq 150 ms, LBBB, NYHA II, QRS $<$ 120 ms, no LBBB). These groups were chosen to reflect a range of patients and potential treatment options, and as they included the largest numbers of people in the IPD analyses. Sensitivity analyses are shown in Tables 1 to 3 for those parameters varied in the ABHI's addendum. We have also included other variables which had not been included but might have an impact on the model results, such as treatment effect on mortality rates, treatment effect on hospitalisation rates, device costs and utility values (new analyses completed by AG are shown in bold in Tables 1 to 3). The mortality treatment effect was varied in the AG sensitivity analyses by +/- 10%, as this was similar to the confidence intervals around the ICD treatment effect. The device costs were varied by +/- 10%, an arbitrary range chosen to be illustrative of the potential uncertainty associated with these costs.

The results of these analyses have been summarised in the earlier sections. Tables 1 to 3 show that the model is most sensitive, in terms of magnitude of change to the ICERs, to changes in parameter values for the assumptions surrounding the treatment effect on mortality and the duration of the treatment effect. These changes only impact on the preferred treatment where the base case results are close to the threshold value.

Table 1 Sensitivity analyses for subgroup 1: NYHA II, QRS ≥ 150 ms, LBBB

Scenario	ICER (£ / QALY)		% change
	ICD	CRT-D vs. OPT	CRT-D
Base case	Ext Dominated	£17,664	
<i>Treatment effect</i>			
Life-long constant treatment effects	Ext Dominated	£13,497	-23.6%
5 years treatment effect	Ext Dominated	£18,879	6.9%
2.54 years treatment effect	Ext Dominated	£20,534	16.2%
No tapering effect, 7.5 years treatment effect	Ext Dominated	£23,938	35.5%
Tapering effect 10 years	Ext Dominated	£21,796	23.4%
Mortality treatment effect ICD +10%	Ext Dominated	£17,664	0.0%
Mortality treatment effect ICD -10%	Ext Dominated	£17,664	0.0%
Mortality treatment effect CRT-D +10%	Ext Dominated	£15,785	-10.6%
Mortality treatment effect CRT-D -10%	Ext Dominated	£19,997	13.2%
<i>Hospitalisation treatment effect</i>			
All cause hospitalisation treatment effect CRT-D +25%	Ext Dominated	£17,300	-2.1%
All cause hospitalisation treatment effect CRT-D -25%	Ext Dominated	£18,028	2.1%
<i>Counselling costs</i>			
Including counselling costs	Ext Dominated	£17,681	0.1%
Increased counselling costs of £70 per patient	Ext Dominated	£17,706	0.2%
<i>Resource use and cost parameters</i>			
HRG EA12Z -25% (related to ICD/CRT-D)	Ext Dominated	£16,817	-4.8%
HRG EA12Z + 25% (related to ICD/CRT-D)	Ext Dominated	£18,511	4.8%
HRG EA072 - 25% (related to CRT-P)	Ext Dominated	£17,664	0.0%
HRG EA072 +25% (related to CRT-P)	Ext Dominated	£17,664	0.0%
HRG EA39Z -25% (related to ICD/CRT-D)	Ext Dominated	£17,424	-1.4%
HRG EA39Z +25% (related to ICD/CRT-D)	Ext Dominated	£17,904	1.4%
All hospitalisation costs lower estimate	Ext Dominated	£17,704	0.2%
All hospitalisation costs higher estimate	Ext Dominated	£17,627	-0.2%
Outpatient visit -25%	Ext Dominated	£17,279	-2.2%
Outpatient visit +25%	Ext Dominated	£18,049	2.2%
Device cost CRT-D +10%	Ext Dominated	£18,824	6.6%
Device cost CRT-D -10%	Ext Dominated	£16,504	-6.6%
<i>Utility</i>			
Utility gain CRT-D / CRT-P +25%	Ext Dominated	£17,572	-0.5%
Utility gain CRT-D / CRT-P -25%	Ext Dominated	£17,790	0.7%

Analyses in bold are those completed by the AG, not included within the ABHI additional analyses.

Table 2 Sensitivity analyses for subgroup 2: NYHA III, QRS ≥ 150 ms, LBBB

Scenario	ICER (£ / QALY)		% change from base case	
	CRT-P vs. ICD	CRT-D vs CRT-P	CRT-P	CRT-D
Base case	£10,496	£28,646		
<i>Treatment effect</i>				
Life-long constant treatment effects	£9,928	£23,891	5.41%	16.60%
5 years treatment effect	£10,769	£30,548	-2.60%	-6.64%
2.54 years treatment effect	£11,207	£33,410	-6.77%	-16.63%
No tapering effect, 7.5 years treatment effect	£11,530	£36,142	-9.85%	-26.17%
Tapering effect 10 years	£11,151	£33,435	-6.24%	-16.72%
Mortality treatment effect ICD +10%	£10,496	£28,646	0.00%	0.00%
Mortality treatment effect ICD -10%	£10,496	£28,646	0.00%	0.00%
Mortality treatment effect CRT-P +10%	£9,183	£47,374	12.51%	-65.38%
Mortality treatment effect CRT-P -10%	£12,220	£21,489	-16.43%	24.98%
Mortality treatment effect CRT-D +10%	£10,496	£21,335	0.00%	25.52%
Mortality treatment effect CRT-D -10%	£10,496	£43,706	0.00%	-52.57%
<i>Hospitalisation treatment effect</i>				
All cause hospitalisation treatment effect CRT-D +25%	£10,496	£26,985	0.00%	5.80%
All cause hospitalisation treatment effect CRT-D -25%	£10,496	£30,308	0.00%	-5.80%
<i>Counselling costs</i>				
Including counselling costs	£10,496	£28,701	0.00%	-0.19%
Increased counselling costs of £70 per patient	£10,496	£28,782	0.00%	-0.47%
<i>Resource use and cost parameters</i>				
HRG EA12Z -25% (related to ICD/CRT-D)	£10,496	£25,937	0.00%	9.46%
HRG EA12Z +25% (related to ICD/CRT-D)	£10,496	£31,356	0.00%	-9.46%
HRG EA072 -25% (related to CRT-P)	£8177	£33,583	22.09%	-17.23%
HRG EA072 +25% (related to CRT-P)	£12,816	£23,709	-22.10%	17.23%
HRG EA39Z -25% (related to ICD/CRT-D)	£10,496	£28,098	0.00%	1.91%
HRG EA39Z +25% (related to ICD/CRT-D)	£10,496	£29,194	0.00%	-1.91%
All hospitalisation costs lower estimate	£10,600	£28,429	-0.99%	0.76%
All hospitalisation costs higher estimate	£10,400	£28,849	0.91%	-0.71%
Outpatient visit -25%	£10,153	£28,483	3.27%	0.57%
Outpatient visit +25%	£10,840	£28,809	-3.28%	-0.57%
Device cost of CRT-D +10%	£10,496	£31,982	0.00%	-11.65%
Device cost of CRT-D -10%	£10,496	£25,311	0.00%	11.64%
<i>Utility</i>				
Utility gain CRT-D / CRT-P +25%	£9,855	£28,301	6.11%	1.20%
Utility gain CRT-D / CRT-P -25%	£11,367	£29,068	-8.30%	-1.47%

Analyses in bold are those completed by the AG, not included within the ABHI additional analyses.

Table 3 Sensitivity analyses for subgroup 3: NYHA II, QRS < 120 ms, no LBBB

	ICER (£ / QALY)	% change
Scenario	ICD	ICD
Base case	£24,465	
<i>Treatment effect</i>		
Life-long constant treatment effects	£17,807	27.2%
5 years treatment effect	£26,181	-7.0%
2.54 years treatment effect	£28,463	-16.3%
No tapering effect, 7.5 years treatment effect	£34,268	-40.1%
Tapering effect 10 years	£30,997	-26.7%
Mortality treatment effect ICD +10%	£19,514	20.2%
Mortality treatment effect ICD -10%	£32,761	-33.9%
<i>Hospitalisation treatment effect</i>		
All cause hospitalisation treatment effect ICD +25%	£23,691	3.2%
All cause hospitalisation treatment effect ICD -25%	£25,239	-3.2%
<i>Counselling costs</i>		
Including counselling costs	£24,497	-0.1%
Increased counselling costs of £70 per patient	£24,544	-0.3%
<i>Resource use and cost parameters</i>		
HRG EA12Z -25% (related to ICD/CRT-D)	£22,904	6.4%
HRG EA12Z + 25% (related to ICD/CRT-D)	£26,027	-6.4%
HRG EA072 - 25% (related to CRT-P)	£24,465	0.0%
HRG EA072 +25% (related to CRT-P)	£24,465	0.0%
HRG EA39Z -25% (related to ICD/CRT-D)	£24,056	1.7%
HRG EA39Z +25% (related to ICD/CRT-D)	£24,874	-1.7%
All hospitalisation costs lower estimate	£24,552	-0.4%
All hospitalisation costs higher estimate	£24,386	0.3%
Outpatient visit -25%	£24,397	0.3%
Outpatient visit +25%	£24,354	0.5%
Device cost of ICD +10%	£26,099	-6.7%
Device cost of ICD -10%	£22,831	6.7%
<i>Utility</i>		
Utility gain CRT-D / ICD +25%	£24,292	0.7%
Utility gain CRT-D / ICD -25%	£24,679	-0.9%

Analyses in bold are those completed by the AG, not included within the ABHI additional analyses.

Appendix

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120) [ID481]

Specification of further work following the Appraisal Committee meeting on 23 April 2013

Suggested presentation of analyses

- Please combine the ischaemic and non-ischaemic patient groups together, therefore presenting results for 24 subgroups rather than 48 in the original submission. For these subgroups, for each of the different scenarios presented, please present tables with fully incremental cost-effectiveness results as previously presented in tables 70-71 of the submission.
- Please also present a summary of the most optimal strategies at different cost-effectiveness thresholds, for example, at £20,000, £25,000 and £30,000 per QALY gained.

Specification of further work

1. The manufacturers' base case assumes a constant duration of effect of 7.5 years for all-cause mortality, followed by linear tapering over 20 years. Sensitivity analyses were also provided assuming life-long constant treatment effects without any tapering (MS page 194) as a more optimistic scenario, and assuming a constant duration of effect for 5 years as a more conservative scenario (Appendix 15 page 72-73). Please provide these analyses for the 24 subgroups outlined above, combining the ischaemic and non-ischaemic patient groups.

In addition, please also provide a sensitivity analysis assuming a constant duration of effect up to the *average* duration of follow up in the trials, followed by linear tapering thereafter?

2. The effect of CRT-D devices on all-cause hospitalisation for NYHA III and IV class patients estimated in the IPD network meta analysis (HR; [REDACTED]) was not incorporated in the model and the value estimated for CRT-P ([REDACTED] for NYH III and [REDACTED] for NYHA IV) was used instead. The manufacturers' stated that it is unlikely that the use of CRT-D will result in a smaller treatment effect than the use of CRT-P in a given patient group, as both include CRT therapy.

However, the Committee would like to see the effect on the ICERs of a more conservative estimate of effect of CRT D for all cause hospitalisation estimated in the IPD network meta-analysis (that is, HR [REDACTED])?

3. The Committee heard that defibrillating devices can increase anxiety in some patients. The manufacturers' model does not account for any additional cost of counselling apart from the bi-annual device related outpatient visits for ICD patients and quarterly visits for CRT (CRT-D or CRT-P) patients.

Given the feedback from experts on the importance of counselling, particularly for patients receiving defibrillator devices, what is the impact of this additional resource use on the ICERs?

4. The manufacturer's model excludes the possibility of crossover or device upgrades, which are possible in clinical practice. Please comment on the likelihood of device upgrades in clinical practice.

In particular, the Committee heard that there may be a subgroup of people indicated for CRT-P who are also likely to need a defibrillator in the near future, so that cardiologists would choose to implant a CRT-D in which the ICD function could be switched on when needed, rather than to implant a CRT-P device which would have to be upgraded to CRT-D at full cost at a later date. Please provide comment on experience with this situation in clinical practice, and on identification of a subgroup of patients for which this situation applies.

5. The Committee considered that further deterministic sensitivity analyses were required for resource use and cost parameters. Please provide such sensitivity analyses, as implementable within the current model structure.