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 (review of TA95 and TA120)

Assessment Report

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

Produced by Southampton Health Technology Assessments Centre

Authors
JL Colquitt, Senior Research Fellow
D Mendes, Research Fellow
AJ Clegg, Professor / Director of SHTAC
P Harris, Research Fellow
K Cooper, Senoir Research Fellow
J Picot, Research Fellow
J Bryant, Principal Research Fellow

Correspondence to
Corresponding author:
Dr Jill Colquitt
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science Park
Southampton, SO16 7NS, UK.
Tel: +44(0)23 8059 5590
Fax:+44(0)23 8059 5639
email: j.colquitt@soton.ac.uk

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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.

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Contribution of authors

JL Colquitt (Senior Research Fellow) co-ordinated the project, developed the research protocol, assisted in the development of the search strategy, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, and drafted and edited the final report. D Mendes (Research Fellow, Health Economics) developed the protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, developed the economic evaluation, and drafted the report. AJ Clegg (Professor of Health Services Research / Director of SHTAC) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, drafted and edited the final report, and acted as guarantor for the project. P Harris (Research Fellow) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, and drafted the report. K Cooper (Senior Research Fellow, Health Economics) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, developed the economic evaluation, and drafted the report. J Picot (Senior Research Fellow) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, and contributed to the background section. J Bryant (Principal Research Fellow) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence and drafted the report.

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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, NHYA 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 threating 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 ≥ 120ms 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 influent 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]

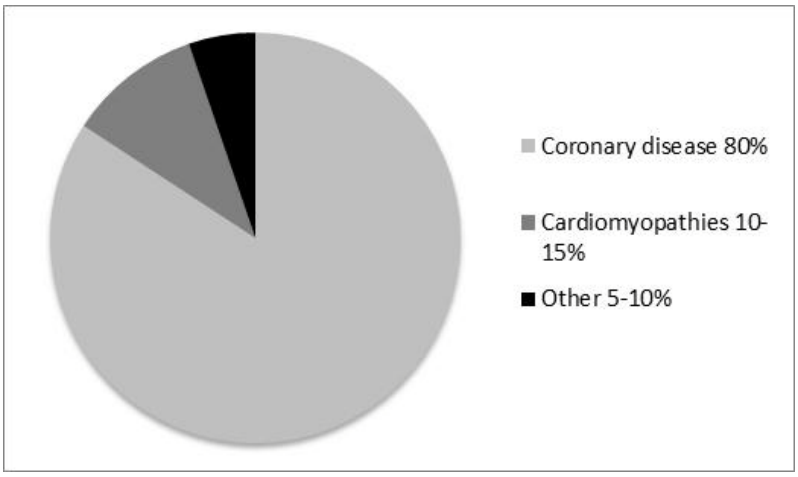


Figure 1: Proportions of SCD by different aetiologies[3]

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 [a 13]	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-wide[15] 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 appraisal[1] 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 GPRD[29] 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 USA[40] 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 inflation[44]) 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 device[41]) 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 arrhythmias[45] 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 America[49] 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 guidance[45] (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 hypertropy, 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.

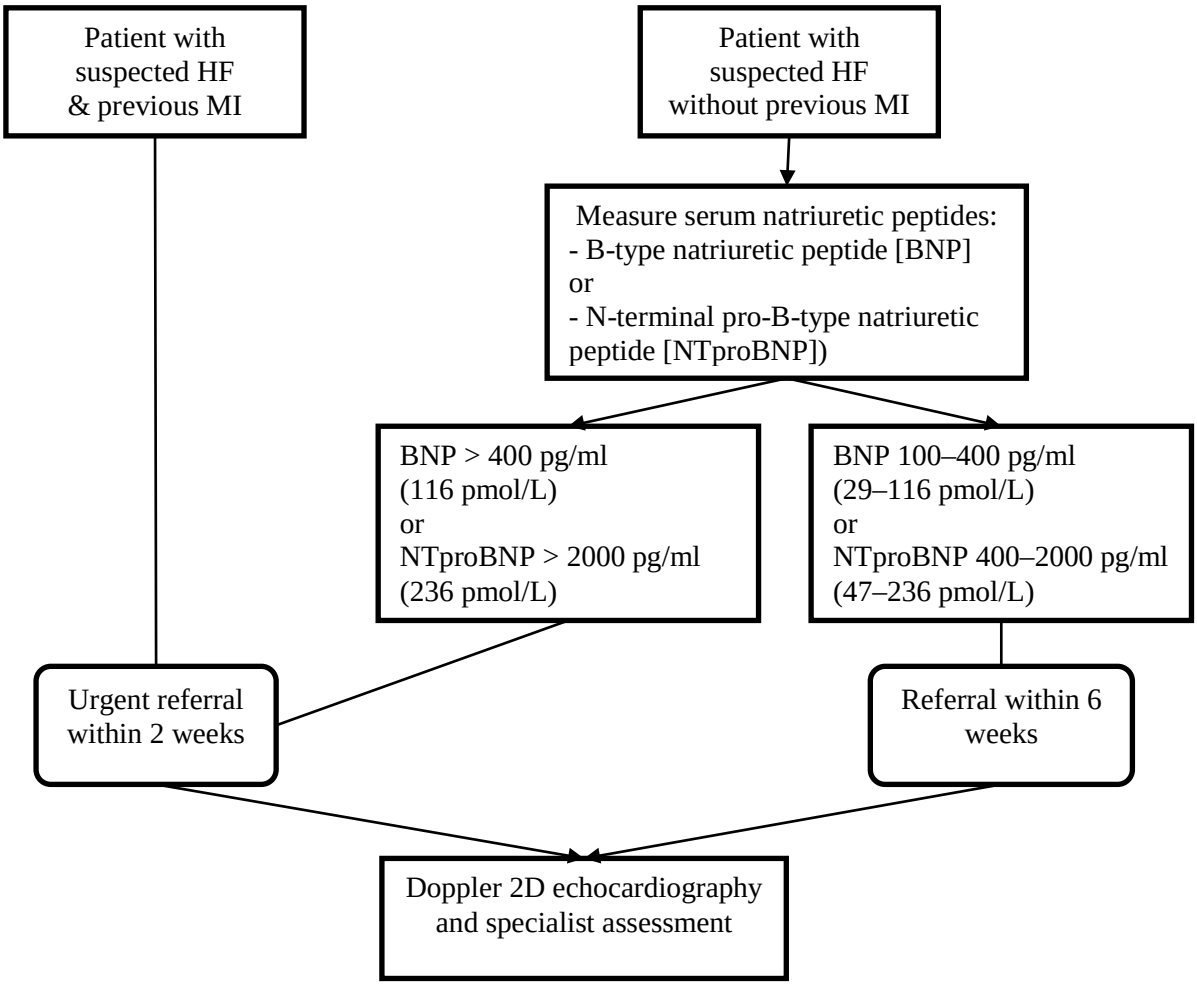


Figure 2: Key elements in the NICE Heart Failure Guideline diagnostic pathway[55]

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 failure[47] (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 failure[55] 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 ≤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 2011[61] 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 publication[59]). 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 proposed[58] 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 audit[58] 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 England[60] 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 targets[58]

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 audit[58] 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 Audit[58] 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 audit[59] 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 Europe[58] 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 2000[66]) 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-P, 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-of 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 scope[64] 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 case[69] and the suggested guideline for good practice in decision analytic modelling by Philips and colleagues[70] (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 Chi^2 and degrees of freedom (df), and I^2 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

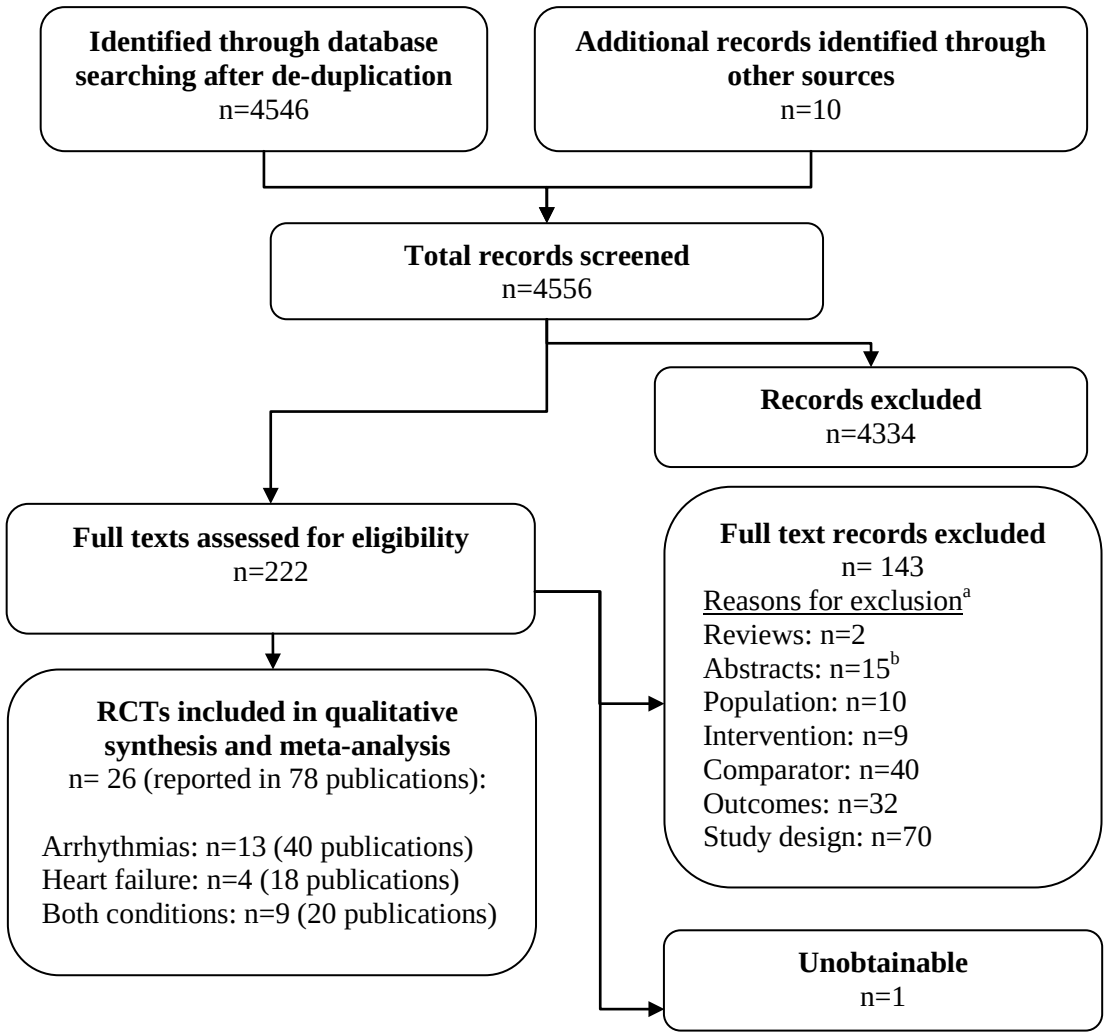
4.1 Overall quantity of evidence identified

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)
People at increased risk of sudden cardiac death as a result of ventricular arrhythmias	
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]
People with heart failure as a result of LVSD and cardiac dyssynchrony	
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 at.*, 2003[126]
MUSTIC	**Cazeau *et al.*, 2001**[127]
People with both conditions described above	
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 *et al.*, 2004**[138]
Piccirillo 2006	**Piccirillo *et al.*, 2006**[139]
Pinter 2009	**Pinter *et al.*, 2009**[140]
RAFT	**Tang *et al.*, 2010;**[141] Tang *et al.*, 2009[142]
RethinQ	**Beshai *et al.*, 2007;**[143] Beshai & Grimm, 2007[144]
RHYTHM ICD	**Summary of Safety and Effectiveness, 2004**[145] and 2005[146]

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 (MUSTT[147]) were included in the 2005 TAR,[65] as can be seen in Table 7. One further RCT (MAVERIC[148]) was noted in the 2005 TAR[65] as in progress at that time. The interventions in the MUSTT[147] and MAVERIC[148] 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] CIDS[86] and DEBUT[91] included people who had previous ventricular arrhythmia or had been resuscitated from cardiac arrest. Four studies included people with either a recent MI (DINAMIT[97] and IRIS[99]) or MI more than 3 to 4 weeks prior to study entry (MADIT I,[101] MADIT II[103]). AMIOVIRT,[71] CAT[84] and DEFINITE[92] included people with cardiomyopathy. CABG Patch[77] 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 TAR[65] (reason for exclusion)	Present TAR (participants)	Publication (bold text indicated primary or key publication)
Secondary prevention			
AVID	Included	Included (cardiac arrest)	**AVID investigators, 1997[73]** and 1999;[74] Hallstrom 1995;[75] Schron *et al.*, 2002[76]
CASH	Included	Included (cardiac arrest)	**Kuck *et al.*, 2000[83]**
CIDS	Included	Included (cardiac arrest)	**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	Excluded (participants)	Included (SUDS)	**Nademanee *et al.*, 2003[91]**
Primary prevention			
MADIT I	Included	Included (remote from MI)	**Moss *et al.*, 1996;[101]** MADIT executive Committee, 1991[102]
MADIT II	Included	Included (remote from MI)	**Moss *et al.*, 2002;[103]** and 1999;[104] Greenberg *et al.*, 2004;[105] Noyles *et al.*, 2007;[106]
DINAMIT	In progress	Included (early post MI)	**Hohnloser *et al.*, 2004;[97]** Hohnloser *et al.*, 2000[98]
IRIS	New	Included (early post MI)	**Steinbeck *et al.*, 2009;[99]** Steinbeck, 2004[100]
AMIOVIRT	Excluded (participants)	Included (cardiomyopathy)	**Strickberger *et al.*, 2003;[71]** Wijetunga and Strickberger, 2003[72]
CAT	Included	Included (cardiomyopathy)	**Bänsch *et al.*, 2002;[84]** The German dilated cardiomyopathy study investigators, 1992[85]
DEFINITE	Excluded (participants)	Included (cardiomyopathy)	**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]
CABG Patch	Included	Included (need for CABG)	**Bigger *et al.*, 1997;[77]** and 1993;[78]1998;[79] 1999;[80] Spotnitz *et al.*,1998;[81] Namerow *et al.*, 1999[82]

MUSTT	Included	Excluded due to intervention	**Buxton *et al.*, 1999;**[147] Lee *et al.*, 2002[149]
SCD-Heft	In progress, in NICE TA	Included (heart failure)	**Bardy *et al.*, 2005;**[107] Mitchell *et al.*, 2008;[108] Mark *et al.*, 2008;[109] Packer *et al.*, 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) (AVID[73]), amiodarone or beta-blocker (metoprolol) in separate groups (CASH[83]) or amiodarone (CIDS[86]), or with beta-blockers (propranalol, DEBUT[91]). Use of other medication was permitted in these trials. AVID[73] permitted use of aspirin, beta-blockers and ACE inhibitors where clinically appropriate in both groups. CASH[83] reported concurrent therapies at discharge (see below). CIDS[86] 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. DEBUT[91] 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] DINAMIT[97]) 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 (AMIOVIRT[71]), or ICD plus OPT versus OPT (CAT,[84] DEFINITE[92]). Pharmacological therapy received by the participants is discussed in further detail below.

CABG Patch[77] 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-HEFT[107] 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 <80mm 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 ≥150bpm causing presyncope or angina in a patient with a LVEF ≤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 (≤ 31days) and predefined markers of elevated risk.	Previous MI and LV dysfunction.	High risk cardiac patients with prior MI and advanced LVdysfunction.
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 ≤ 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 ≤0.35; asymptomatic NSVT; NYHA class I to III.	LVEF ≤ 30%; aged 18-70 years; symptomatic DCM ≤ 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 ≤ 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 trial[91] differed notably from the other three trials (AVID,[73] CASH[83] and CIDS[86]) of people resuscitated from cardiac arrest, as participants in DEBUT[91] 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 study[91] 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] CASH[83] and CIDS[86] had ischaemic heart disease (70 to 83%). A small proportion of those in CASH[83] and CIDS[86] had dilated cardiomyopathy. Two thirds of participants in AVID[73] and around three quarters of those in CIDS[86] had a previous MI.

All participants in CASH[83] and DEBUT,[91] 90% in CIDs[86] and 60% in AVID[73] had congestive heart failure. The majority (approximately 87%) of people in CASH[83] had NYHA Class I or Class II heart failure, whereas about half those in AVID[73] and CIDS[86] fell into these categories. Almost 40% of participants in CIDS[86] had moderate to severe heart failure (NYHA Class III and IV), compared with 10% of people in AVID[73] and 16% (all NYHA Class III) of people in CASH.[83] Mean LVEF was higher in CASH[83] (46%) than in AVID[73] (32%) or CIDS[86] (34%), suggesting there may have been disproportionate representation of relatively healthy participants in CASH.[83] Mean QT interval ranged from 387 msec (DEBUT[91]) to 445 msec (AVID).[73]

The people in DEBUT[91] 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 DEBUT[91] (mean LVEF 66-69%) than in AVID,[73] CASH[83] and CIDS,[86] and QT interval slightly lower.

Myocardial infarction (MI)

MADIT I[101] and MADIT II[103] included people with MI more than three weeks or one month previously. Participants in MADIT I[101] were also required to have a LVEF of 35% or less, whereas MADIT II[103] required advanced left ventricular dysfunction (LVEF ≤ 30%). DINAMIT[97] and IRIS[99] recruited people with recent MI (within 6 to 40 days and 5 to 31 days, respectively). DINAMIT[97] required participants to have a LVEF of 35% or less and standard deviation of normal-to normal RR intervals of ≤70 msec or a mean RR interval of ≤750 msec (heart rate ≥ 80 beats per minute) over 24 hours. IRIS[99] 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.

DINAMIT[97] had the greatest majority of participants in NYHA class I or II (around 70%), compared with 88% of participants in IRIS[99] 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 II[103]) to 35% (IRIS[99]), reflecting the different inclusion criteria of the studies.

The mean age of the participants in these trials was similar, ranging from 61.5 (DINAMIT[97]) to 65 (MADIT II[103]) years. The majority of participants (76% DINAMIT[97] to 92% MADIT I[101]) were men.

Cardiomyopathy

AMIOVIRT[71] and DEFINITE[92] recruited people with non-ischaemic dilated cardiomyopathy, non-sustained ventricular tachycardia, and LVEF of 35% or less. CAT[84] 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. AMIOVIRT[71] (13-18%) and DEFINITE[92] (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 (CAT[84] 24-25%, AMIOVIRT[71] 22-23%, DEFINITE[92] 21-22%). Mean QRS interval was similar between CAT[84] (ICD: 102 (SD 29), OPT 114 (SD 29) msec) and DEFINITE[92] (115, range 78-196), although the measures of variance suggest that some participants had cardiac dyssynchrony.

Participants in CAT[84] had a median duration of symptoms of just 3 months, compared to around 3 years in AMIOVIRT[71] and DEFINITE.[92] The participants in CAT[84] were also slightly younger (mean age 52 years) than in AMIOVIRT[71] (mean age 59 years) or DEFINITE[92] (mean age 58 years). The majority of participants (approximately 71% AMIOVIRT[71] and DEFINITE[92] to 80% CAT[84]) were men.

CABG surgery

Participants in CABG Patch[77] 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-HeFT[107] 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 ≥ 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

	Cardiomyopathy						CABG surgery		Heart failure		
Parameter	**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		

	Cardiomyopathy						CABG surgery		Heart failure		
Parameter	**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

[a]1 majory epicardial coronary artery with a 70% or greater stenosis. [b] Duration of heart failure, p=0.04. PVCs = premature ventricular complexes. [c] Median plus inter-quartile range.

Pharmacological therapy

Table 14 and Table 15 displays medication at hospital discharge.

Cardiac arrest

Two thirds of participants in AVID[73] 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 AVID[73] 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 AVID[73] 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 AVID[73] 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 CASH[83] 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 CASH[83] 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 CASH[83] 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 CIDS[86] 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 solatol (33.5% vs 21.4%), and digoxin (29.6% vs 22.7%). No other drugs were reported. The pharmacological therapy provided in CIDS[86] 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 DINAMIT[97] 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. IRIS[99] 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 DINAMIT[97] and IRIS.[99]

MADIT[101] 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 antiarrythmics 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 MADIT[101] would not be considered optimal by current standards.

MADIT II[103] 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 II[103] would be considered optimal by current standards.

Cardiomyopathy

AMIOVIRT[71] 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 DEFINITE[92] 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 antiarrythmics 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 Patch[77] 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-HeFT[107] 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-HeFT[107] 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-HeFT[107] would be considered optimal by current standards.

Table 14: Medication at discharge: cardiac arrest/MI

	Cardiac arrest (secondary prevention)							Recent MI				Remote MI			
Medication, %	**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

	Cardiac arrest (secondary prevention)							Recent MI				Remote MI			
Medication, %	**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

	Cardiomyopathy						CABG surgery		Heart failure		
Medication, %	**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

	Cardiomyopathy						CABG surgery		Heart failure		
Medication, %	**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

AVID[73] CASH[83] and CIDS[86] were multicentre studies; with the majority of centres in USA (AVID[73]) or Canada (CIDS[86]) or in Germany only (CASH[83]). DEBUT[91] was conducted in Thailand but the number of centres was not reported. The number of participants ranged from 66 (DEBUT main study[91]) to 1016 (AVID[73]). DEBUT[91] 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 AVID[73] to 57 months (SD 34) in CASH.[83]

DINAMIT,[97] IRIS,[99] MADIT I[101] and MADIT II[103]were multicentre studies. The majority of centres for DINAMIT[97] were in Canada, Germany and Europe (4 UK centres) and IRIS[99]was conducted in Europe (not UK) and Russia. The majority of centres for MADIT I[101] and MADIT II[103] were in the USA. Sample size ranged from 196 (MADIT I[101]) to 1232 (MADIT II).[103] Mean follow-up ranged from 20 months in MADIT II[103] to 37 months in IRIS.[99]

AMIOVIRT[71] and DEFINITE[92] were multi-centre studies with the majority of centres in USA, whereas CAT[84] was a multi-centre study conducted in Germany. Sample size was relatively small in AMIOVIRT[71] and CAT[84] (103 and 104 participants randomised, respectively); CAT[84] was designed as a pilot study. DEFINITE[92] randomised 458 participants. The trials had similar lengths of follow-up; mean follow-up was 2 years in AMIOVIRT[71] and CAT,[84] and 2.4 years in DEFINITE.[92]

CABG Patch[77] was a multicentre study conducted primarily in USA, with 900 participants randomised. Mean follow-up was 32 months.

SCD-HeFT[107] 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 Patch[77]) 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] IRIS[99]), and unclear in three trials (CIDS,[86] DEBUT,[91] CAT[84]). In AVID,[73] CABG Patch[77] 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-HeFT[107]). Five studies listed outcomes in a protocol or methods section that were not reported (CIDS,[86] CAT,[84] DEFINITE,[92] DINAMIT,[97] IRIS[99]). Risk of selective reporting bias was unclear in two studies (MADIT II,[103] CABG Patch[77]).

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 CASH[83] 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 Patch[77]), 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]	AVID[73]	CASH[83]	CIDS[86]	DEBUT[91]	IRIS[99]	DINAMIT[97]	MADIT I[101]	MADIT II[103]	CAT[84]	AMIOVIRT[71]	DEFINITE[92]	CABG Patch[77]	SCD-Heft[107]
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 IRIS[99] 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 CAT[84] trial found a higher occurrence of bradycardias among the OPT group (18.8%) than the ICD group (2.1%, p=0.015). The DEFINITE[92] 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

CASH[83] was designed as a 4 arm trial (ICD, amiodarone, metoprolol, propafenone), however the propafenone arm was terminated early due to interim analysis. DEBUT[91] 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 I[101] note that this altered the type of patient referred for entry to the trial.

Funding

AVID[73] and CIDS[86] 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 AVID[73] (ICDs 15.8%, AAD 24.0%, p<0.012, follow-up 18.2 months) and the main DEBUT[91] (ICDs 0%, AAD 14.0%, p<0.02, follow-up 3 years) trials found statistically significant differences. A separate pilot study for the DEBUT trial[91] 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 trial[83] reported all-cause mortality rates of 36.4% for the ICDs group compared with 44.4% for the AAD group (p=not stated, follow-up 57 months). The CIDS trial[86] 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 study[91]) 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 (Chi^2=5.89, df =4, 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 I[101] and MADIT II[103] on people remote from their MI and the SCD-HeFT[107] on people with heart failure. In the MADIT I trial[101] 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 trial[103] 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 II[103] 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 (Chi^2=3.54, df =1, I^2=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 trial[71] 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 trial[84] 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 trial[92] 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 (Chi^2=1.73, df =2, I^2=0%) (see Figure 4). The effect of combining the three cardiomyopathy trials with the non-ischaemic congestive heart failure subgroup of SCD-Heft[107] was assessed in section 4.2.2.12. The DINAMIT[97] and IRIS[99] trials assessed the effects of ICDs plus OPT compared with OPT in people who were in the early period post MI. The DINAMIT trial[97] 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 trial[99] 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 DINAMIT[97] and IRIS[99] 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 (Chi^2=0.19, df =1, I^2=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).

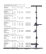
Table 17: All-cause mortality

Study	Follow-up	ICD, n/N (%) [rate/yr %]	OPT, n/N (%) [rate/yr %]	Effect	95% CI , p value
Cardiac arrest					
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
Early post MI					
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
Remote from MI					
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
Cardiomyopathy					
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
Scheduled for CABG					
CABG Patch[80]	mean 32 months (SD 16)	102/446 (22.9)	96/454 (21.2)		
Heart Failure					
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] CASH[83] and SCD-Heft[107] 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 16.5.4[67]) (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 AVID[74] and CIDS[86] 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 trial [86] 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 (Chi^2=0.84, df =1, 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 trial[105] on people remote from MI (ICD plus OPT 10.6%, OPT 16.3%, p<0.01) and the SCD-Heft trial[110] 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 trial[101] 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 I[101] and II[105] 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 (Chi^2=1.3, df =1, I^2=23%) (see Figure 5).

The DINAMIT[97] (ICD plus OPT 13.9%, OPT 14.3%, p=not stated) and IRIS[99] (ICD plus OPT 21.4%, OPT 21.9%, p=not stated) trials on those with a recent MI, the AMIOVIRT trial[71] on those with cardiomyopathy (ICD plus OPT 8%, amiodarone plus OPT 10%, p=not stated) and the CABG Patch trial[80] 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 trial[84] 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 DINAMIT[97] and IRIS[99] 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 (Chi^2=0, df =1, I^2=0%) (see Figure 5).The meta-analysis of the AMIOVIRT[71] and CAT[84] 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 (Chi^2=2.59, df =1, 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
Cardiac arrest					
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
Early post MI					
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)		
Remote from MI					
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
Cardiomyopathy					
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)		
Scheduled for CABG					
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
Heart Failure					
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 CASH[83] (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 DEBUT[91] (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 trial[83] showed a statistically significant difference. Similarly, the AVID[74] and CIDS[86] 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%; CIDS[86]: ICDs 9.2%, AAD 13.1%,), although neither demonstrated a statistically significant difference. The CIDS trial[86] 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 (Chi^2=5.47, df =4, I^2=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 DINAMIT[97] and IRIS[99] 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 (Chi^2=0.03, df =1, I^2=0%) (see Figure 6).

The MADIT I[101] (ICD plus OPT 3.2%, OPT 12.9%, p=not stated) and MADIT II[105] (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 (Chi^2=0.42, df =1, I^2=0%)(see Figure 6).

The AMIOVIRT,[71] CAT[84] and DEFINITE[92] trials in people with cardiomyopathy reported differing outcomes. The DEFINITE trial[92] 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 trial[71] 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 trial[84] 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 (Chi^2=0.41, df =1, I^2=0%) (Figure 6).

The CABG Patch trial[80] 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 trial[110] found significantly lower sudden cardiac or arrhythmic mortality in the group receiving ICD plus OPT (4.6%) compared with the group receiving amiadarone 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
Cardiac arrest					
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)		
Early post MI					
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
Remote from MI					
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
Cardiomyopathy					
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
Scheduled for CABG					
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
Heart Failure					
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 AVID[74] and CIDS[86] 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 (AVID[74]: ICDs 7.7%, AAD 7.7%; CIDS[86]: ICDs 11.3%, AAD 12.1%) (Table 20). The CIDS trial[86] 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 (Chi^2=0.06, 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 DINAMIT[97] and IRIS trials[99] 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 (Chi^2=0, 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 I[101] and MADIT II[105] 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; Chi^2=2.77, 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 AMIOVIRT[71] (ICDs plus OPT 5.9%, amiodarone plus OPT 5.8%), CAT[84] (ICDs plus OPT 8%, OPT 0%) and DEFINITE[92] (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; Chi^2=2.71, df =2, I^2=26%) (Figure 7). Similarly the CABG Patch trial[80] in those who were scheduled for CABG surgery (RR 1.26, 95% CI, 0.87, 1.82; p=0.21) and SCD-Heft trial[110] 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
Early post MI					
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
Remote from MI					
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)		
Cardiomyopathy					
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)		
Scheduled for CABG					
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
Heart failure					
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 AVID[74] and CIDS[86] 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; Chi^2=1.51, df =1, I^2=34%) (Figure 8). The CIDS trial[86] 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 DINAMIT[97] and IRIS[99] trials in people with a recent MI (RR 1.39, 95% CI, 0.86 to 2.27; p=0.18; Chi^2=0.70, df =1, I^2=0%), the MADIT I[101] and MADIT II[105] trials in people remote from MI (RR 1.06, 95% CI, 0.58 to 1.95; p=0.84; Chi^2=0.55, df =1, I^2=0%), and the AMIOVIRT[71] and CAT[84] trials in people with cardiomyopathy (RR 0.65, 95% CI, 0.13 to 3.29; p=0.60; Chi^2=0.75, df =1, I^2=0%) all found no statistically significant effects (Figure 8). Similarly the CABG Patch trial[80] in people who were scheduled for CABG surgery (RR 1.50, 95% CI, 0.82 to 2.73; p=0.19) and the SCD-Heft[110] 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
Cardiac arrest					
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
Early post MI					
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
Remote from MI					
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)		
Cardiomyopathy					
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)		
Scheduled for CABG					

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)		
Heart Failure					
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 trial[99] 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 trial[92] 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 trial[107] 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 trial[77] 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 CASH[83] 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 trial[83] 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 trial[83] 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 trial[91] reported mean survival times for the AAD group of 26.2 (SEM 1.4) months (no deaths in the ICDs group).

Only the AMIOVIRT[71] and CAT[84] trials in people with cardiomyopathy reported survival (Table 23). The AMIOVIRT trial[71]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 trial[84] 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 study[73] 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 trial[103] 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 CAT[84] and AMIOVIRT[71] 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 trial[84] and 3.9% of ICD plus OPT and 5.8% of amiodarone plus OPT patients had syncope in the AMIOVIRT study[71] (see Table 25). The MADIT II trial[105] 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
Cardiac arrest				
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 - 5 year event rate	0.289	Amiodarone plus OPT: 0.340	
			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
Cardiac arrest					
AVID[73]	Overall survival, mean 18.2 months (SD 12.2) - 1 year, % - 2 year, % - 3 year, %	 89.3 81.6 75.4	AAD 82.3 74.7 64.1		<0.02
	Survival free of cardiac death[a 74] - at 1 year - at 2 years	90.9% 85.0%	85.1% 81.2%		0.0042
	Survival to arrhythmic death[b74] - at 1 year - at 2 years	96.6% 94.2%	91.9% 89.1%		0.0002
	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)		
Cardiomyopathy					

Study	Outcome, follow-up	ICD, n/N (%)	OPT, n/N (%)	Effect	95% CI , p value
AMIOVIRT[71]	Survival rates %, - 1 year - 3 year	96% 88%	Amiodarone plus OPT: 90% Amiodarone plus OPT: 87%		 0.8[d]
	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
Cardiac arrest					
AVID[73]	% of patients re-hospitalised (patients at risk n=1011) - at 1 year - at 2 years - at 3 years	 59.5 74.8 83.3	 55.6 64.7 75.5		0.04
Remote from MI					
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
Cardiomyopathy					
CAT[84]	Syncope during VTS	6/50 (12)			
AMIOVIRT[71]	Syncope	3.9% [a]	5.8%	0.7	
Remote from MI					
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 AVID[76] and CIDS[89] trials, reported results from sub-studies using a range of generic and condition-specific measures of quality of life (QoL) (Table 26). The AVID trial[76] 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 trial[76] 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 trial[89] 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 trial[89] 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 trial[106] 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 significantly 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 study[71] 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 trial[96] 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 trial[82] 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 trial[82] 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 trial[109] 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
Cardiac arrest (secondary prevention)				
AVID [76]	1 year follow-up	(n=416)	AAD (n=384)	
	SF-36 PCS score, mean (SD) - baseline - 12 months	37.4 (10.9) 40 (10.5)[a]	36.5 (11.2) 38 (17)[a]	0.3
	SF-36 MCS score, mean (SD) - baseline - 12 months	45.9 (11.8) 49 (16.5)[a]	47.5 (11.5) 48 (17)[a]	0.006
	Patient concerns checklist- baseline - follow-up	15.9 (8.6) nr	16.2 (8.9) nr	0.06 0.1
	QL index – baseline	22.1 (4.9)	21.9 (5.0)	
	Impact of adverse symptoms on QoL[b] - SF-36 PCS score - SF-36 MCS score - Patient concerns	 -2.25 (-3.32, -1.18) p<0.001 -2.32 (-3.76, -0.88) p=0.002 1.84 (0.91, 2.76) p<0.001	 -1.64 (-2.89, -0.41) p=0.009 -0.51 (-1.97, 0.94) p=0.5 0.91 (0.07, 1.75) p=0.03	
	Impact of ICD shocks on QoL - SF-36 PCS score - SF-36 MCS score - Patient concerns	 -1.45 (-2.74, -0.18) p=0.03 -1.82 (-3.56, -0.08) p=0.04 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]	*ICDs* no shocks (n=66)	*ICDs* 1-4 shocks (n=27)	*ICDs* ≥5 shocks (n=15)	Amiodarone (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)	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		
	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 mobitity[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		
Remote from MI						
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	
Cardiomyopathy				
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
CABG				
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 Enguage 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 heath 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 trial[91] and the AVID[73] and CASH[83] trials respectively. The DEBUT trial[91] reported that 30% of the ICDs group and 14% of the AAD group suffered adverse events (p not stated). The AVID trial[73] 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 trial[83] 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 superventricular 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 trial[86] 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 trial[86] included skin discolouration (6.3%) and pulmonary infiltrate (5.7%). In the CASH trial[83] 10% of people receiving amiodarone (9.8%) or metoprolol (10.3%) had to discontinue drug treatment. The AVID trial[73] reported that 5% of the AAD group had suspected pulmonary toxicity at two years. Other adverse events reported by the AVID,[73] CASH[83] and DEBUT[91] 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 IRIS[99] and CABG-Patch[77] trials respectively. Deaths among those receiving the comparator treatments were only reported in the CABG-Patch trial[77] 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 I[101] and SCD-Heft[77] trials only syncope (5%) and hypothyroidism (6%) affected ≥5% of people in the comparator groups. The CABG-Patch trial[77] 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 trial[77] reported event rates ≥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 ≥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
Cardiac arrest (secondary prevention)					
AVID[73]	Non-fatal torsade-de-pointes ventricular tachycardia		1/509 (0.2)		
	Suspected pulmonary toxicity, % - at 1 year - at 2 years		3 5		
	Death due to pulmonary toxicity		1/509 (0.2)		
	Thyroid replacement medication, % - at 1 year - at 2 years	1 1	10 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	Meto-prolol	
	- 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)	Meto-prolol 0/0 (0)	
	Other complications - Infection - Haematoma or seroma - Pericardial effusion - Pleural effusion - Pneumothorax - Dislodgement or migration of system leads - Device dysfunction	3/99 (3.0) (explantation required for 2) 6/99 (6.1) 1/99 (1.0) 3/99 (3.0) 1/99 (1.0) 3/99 (3.0) 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) - in patients with non-thoracotomy lead system (n=277)	 1/33 (3.0) 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]	Operative mortality	0/0 (0)		
-main study	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 - T-wave oversensing	 7/37 (19.0) 3/37 (8.1)		
	Pocket erosion requiring removal of ICD	1/37 (2.7)		
	Side-effects in B-Blocker group: - Impotence / decrease in libido - Fatigue - Profound bradycardia - Hypotension plus central nervous system side effect		1/29 (3.4) 1/29 (3.4) 1/29 (3.4) 1/29 (3.4)	
Early post MI				
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)		
Remote from MI				
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)		
Cardiomyopathy				
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 - device dislocation & bleeding requiring revision - electrode dislocation requiring revision	 0/50 (0) 2/50 (4) 2/50 (4)		
	Complications in 24 months of follow-up - electrode dislocation & sensing/isolation defects - infection with total device replacement - perforation	10 in 7 patients 7/50 (14) 2/50 (4) 1/50 (2)		
DEFINITE[92]	Complications during implantation of ICD - hemothorax - pneumothorax - cardiac tamponade	3/229 (1.3) 1/229 (0.4) 1/229 (0.4) 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)		
Scheduled for CABG				
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)	
	- deep sternal-wound infection	12 [b]/446 (2.7)	2 [b]/454 (0.4)	0.01<p<0.05
	- infection at wound or catheter site	55 [b]/446 (12.3)	27 [b]/454 (5.9)	0.01<p<0.05
	- pneumonia	38 [b]/446 (8.5)	18 [b]/454 (4.0)	0.01<p<0.05
	- 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			
	- angina pectoris	120[b]/446 (27.0)	125 [b]/454 (27.5)	
	- myocardial infarction	2 [b]/446 (0.5)	19 [b]/454 (4.2)	0.01<p<0.05
	- 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)		
Heart Failure				
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 - later in the course of follow-up	 5% 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%	

[a] Or 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 trial[73] 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 ≤ 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 trial[105] 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 ≥20% (favoured ICD, data in figure only).

The CABG Patch trial in people who were scheduled for a CABG[77] 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 mortality[107] and cause of death[110] according to cause of congestive heart failure (ischaemic or nonischaemic) and NYHA class (class II or III), and also according to race[108] 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 death[110] (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-Heft[107] non-ischaemic congestive heart failure subgroup with data from the three cardiomyopathy trials (AMIOVIRT,[71] CAT,[84] DEFINITE[92]) was considered appropriate by clinical experts. SCD-Heft[107] 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 characteristic 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 caddiac 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 threating 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 (COMPANION[118]).

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 at. 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 MIRACLE[123] and MUSTIC,[127] all participants were implanted with a CRT-P device, and pacing was inactivated in the control group. Participants in CARE-HF[111] and COMPANION[118] 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-HF [111]) to 100% (MUSTIC[127])]. All the trials included participants with LVEF ≤ 35%; average LVEF was about 22% in MIRACLE[123] and COMPANION,[118] and 25% in CARE-HF.[111]

The trials differed in their eligibility criteria for the QRS interval, with CARE-HF[111] and COMPANION[118] requiring a QRS interval ≥120 ms, MIRACLE[123] ≥130 ms and MUSTIC[127] ≥150ms. 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-HF [111]) to 59% (COMPANION[118]).

The mean age of the participants in the studies was similar, ranging from around 64 years in MIRACLE[123] and MUSTIC[127] to 68 years in COMPANION[118] (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 cardio-myopathy 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]	160b	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-HF[111] used diuretics, which was around 94% in the other studies. Both CARE-HF[111] and MUSTIC[127] reported that less than half of the participants used digoxin, while around a third of the participants in MUSTIC[127] 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 MIRACLE[123] and MUSTIC[127] 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, COMPANION[118] and MUSTIC[127] reported total cardiac death, while both CARE-HF[111] and COMPANION[118] reported death due to heart failure. Heart failure hospitalisation was reported by all four trials. CARE-HF,[111] MIRACLE[123] and MUSTIC[127] reported details on worsening heart failure, while arrhythmias were reported by CARE-HF[111] and MUSTIC.[127] All trials except MUSTIC[127] reported change in NYHA class, but only CARE-HF[111] and MIRACLE[123] 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 (Spirololactone)	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	

[a] N=67 enrolled, n =58 randomised.

Setting

All four studies were multicentre trials, ranging from 15 (MUSTIC [127]) to 128 (COMPANION[118]) centres. CARE-HF[111] and MUSTIC[127] were undertaken in Europe, both including centres in the UK. The COMPANION study[118] was undertaken in the USA, while MIRACLE[123] had centres in the USA and Canada.

The MUSTIC study[127] 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 study[123] was 6 months. Mean length of follow-up in the CARE-HF study[111] was 29.4 months, plus an 8 months extension (total mean follow-up 37.4 months). COMPANION[118] 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] MIRACLE[123] and MUSTIC[127] was unclear. Risk of selection bias was low in CARE-HF.[111]

MIRACLE[123] 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). MUSTIC[127]was at high risk of performance and detection bias, with only participants blinded to the treatment order (CRT-P on or off). Both CARE-HF[111] and COMPANION,[118] were unblinded trials, placing them at high risk of performance bias. For detection bias, CARE-HF[111] 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 COMPANION[118] was low, with a steering committee and endpoints committee unaware of treatment assignment.

Both COMPANION[118] and MUSTIC[127] were at low risk of attrition bias. MUSTIC[127] reported both numbers and reasons for withdrawals, while COMPANION[118] censored data in their ITT analysis for

participants who withdrew and data could not be obtained. CARE-HF[111] 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 study[123] 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-HF[111] and COMPANION study[118] 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, MIRACLE[123] and MUSTIC[127] were at high risk of selective reporting bias. MIRACLE[123] assessed change in NYHA class but failed to report the data and MUSTIC[127] included the SF-36 in the study protocol,[124] but did not report the data.

There was an additional risk of bias in MUSTIC[127] 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] MIRACLE[123] and MUSTIC[127] appeared to be adequately powered to detect a difference in the relevant primary outcome measures. MUSTIC[127] randomised 58 participants, MIRACLE[123] randomised 453 participants and CARE-HF randomised 813 participants. COMPANION[118] 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 . MIRACLE[123] reported that 4% of participants crossed over from OPT to CRT-P, but reported no details for the CRT-P treatment group. COMPANION[122] reported that out of 78 cardiac procedures in the OPT group, 33 (42%) were for CRT implants. In addition, COMPANION[120] 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 study[111] baseline measures were taken prior to randomisation and implantation, while in the COMPANION study[118] randomisation was prior to implantation, but baseline measures were taken one week after successful implantation. The remaining two studies (MIRACLE[123] and MUSTIC[127]) randomised participants after implantation. In the MIRACLE study[123] baseline measures were taken before implantation and randomisation, while in the MUSTIC study[127] 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.

MUSTIC[127] 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 trial[118] 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-HF[111] reported conflicts of interests, as some/all authors were consultants or investigators for, or employees of, the company providing the funding. Both CARE-HF[111] and COMPANION[118] stated that sponsors had no role in data analysis, while MIRACLE[123] 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-HF[111] 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, MIRACLE[123] 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 COMPANION[118] 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). MUSTIC[127] 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, 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 trial[127] from the meta-analysis has little effect (RR 0.73, 95% CI, 0.60 to 0.89 p=0.002).

CRT-D vs OPT

COMPANION[118] 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

COMPANION[118] 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	1st period: 1/29 (3.4[b]) 2nd period: 2/29 (6.9[b])	1st period: 0/29 (0) 2nd 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 COMPANION[121] and MUSTIC[127] reported total cardiac deaths.

CRT-P vs OPT

COMPANION[121] 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 MUSTIC[127] 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

COMPANION[121] 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 COMPANION[121] 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	1st period: 1/29 (3.4[a]) 2nd period: 2/29 (6.9[a])	1st period 0/29 (0) 2nd 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 trial[111] and the COMPANION[121] reported mortality due to HF.

CRT-P vs OPT

CARE-HF[111] 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. COMPANION[121] 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 (Chi^2 0.99, df=1, I^2=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

COMPANION[121] 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 COMPANION[121] 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] Per annum	38/409 (8.8) 3.0%	64/404 (15.8) 5.1%	HR 0.55	0.37 to 0.82, 0.003
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] % of deaths	52/595 (8.7) 49.5	34/308 (11.0) 44.2	HR 0.73	0.47 to 1.11, 0.143
		CRT-P, n/N (%)	**CRT-D, n/N (%)**		
	CRT-P 16.5, CRT-D 16.0[a] % of deaths	53/617 (8.6) 40.5	52/595 (8.7) 49.5	RR 0.98[b]	0.68 to 1.42, 0.93[b]

[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-HF[111] 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 (Chi^2 7.22, df=2, I^2=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 report[125] associated with MIRACLE reported SCD (CRT-P n=7, OPT n=5) at 9 months follow-up (the main publication reported outcomes at 6 months[123]), 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

COMPANION[121] 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 COMPANION[121] (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

COMPANION[121] 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	1st crossover: 1/29 (3.4[b]) 2nd crossover:1/29 (3.4[b])	1st crossover: 0/29 (0) 2nd 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-HF[111] 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 MIRACLE[123] 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 COMPANION[118] 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, MUSTIC[127] reported data for the first crossover period only. There was evidence of substantial statistical heterogeneity between the studies (Chi^2 8.50, 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 CTR-D and 11.9 months for those with OPT.

CRT-P vs CRT-D

COMPANION[118] 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. COMPANION[118] 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] COMPANION[122] and MIRACLE[123] reported events and/or number of days of hospitalisations due to heart failure. CARE-HF[111] reported the number unplanned hospitalisation of patients worsening heart failure. COMPANION[122] reported the number of admissions, the percentage of total admissions and the number of average admission per patient year of follow-up, while MIRACLE[123] 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, MIRACLE[123] 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 (Chi^2 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

COMPANION[122] 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. COMPANION[118] 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 trial[111] reported atrial arrhythmias or ectopy, while MUSTIC trial[127] 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 trial[127] (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% s 10.7% OPT; HR 0.51, 95% CI, 0.26 to 1.00, p=0.05), vasodilators or positive intropic 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). MUSTIC[127] 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	1st period: 0/29 2nd period: 0/29	1st period: 1/29 (3.4) 2nd 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 intropic 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	1st period: 0/29 (0) 2nd period: 0/29 (0)	1st period: 1/29 (3.4) 2nd 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] COMPANION[118] and MIRACLE[123] reported improvement in NYHA class. The three trials included people in NYHA class III and IV at baseline. CARE-HF[111] reported NYHA class at 18 months and mean NYHA class at 90 days, MIRACLE[123]reported improvements in NYHA class at 6 months, and COMPANION[118] 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-HF[111] 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, 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. MIRACLE[123] 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

MIRACLE[123] 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

COMPANION[118] reported the mean increase in 6-minute walk at 3 and 6 months, while MIRACLE[123] 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. MUSTIC[127] reported mean distance walked in 6 minutes at 3 months. Only CARE-HF[111] did not report 6-minute walk distance. Only two trials reported change in peak oxygen consumption. The MIRACLE trial[123] reported median change in VO_2 and MUSTIC[127] reported mean VO_2 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 MUSTIC[127] (Chi^2 2.93, 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).

MIRACLE[123] 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 Group 2 (CRT-P OFF, CRT-P ON) n=24 Both groups n=46	 384.1 (78.9) 412.9 (116.9) 399.2 (100.5)	 336.1 (128.3) 316.2 (141.8) 325.7 (134.4)		 <0.001
COMPANION[118]	Change in 6-minute walk, m, mean change (SD) 3 months 6 months	 33 (99) (n=422) 40 (96) (n=373)	 9 (84) (n=170) 1 (93) (n=142)		 <0.001 <0.001
		CRT-D	**OPT**		
	Change in 6-minute walk, m, mean change (SD) 3 months 6 months	 44 (109) (n=420) 46 (98) (n=378)	 9 (84) (n=170) 1 (93) (n=142)		 <0.001 <0.001
		CRT-P	**CRT-D**		
	Change in 6-minute walk, m, mean change (SD) 3 months 6 months	 33 (99) (n=422) 40 (96) (n=373)	 44 (109) (n=420) 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-HF[115] 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. COMPANION[118] and MIRACLE[123] reported mean change from baseline for MLWHFQ scores, while CARE-HF[115]and MUSTIC[127] reported final mean values. MUSTIC[127] 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, 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-HF[115] 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 COMPANION[118] 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 MIRACLE[123] and MUSTIC[127] 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 MIRACLE[123] 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-HF[111] and COMPANION[118] randomised participants to receive either a CRT-P (or CRT-D) device or OPT only (Table 48). However, CARE-HF[111] limited reporting of adverse events to device-related complications. Only COMPANION[118] 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 COMPANION[118] 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-D[118] 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-HF[111] 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] Enrolled n=571 Successfully implanted n=528 Randomised n=453 CRT-P n=228 OPT n=225	*All participants undergoing implantation (n=571)*	
	Unsuccessful implantation	43/571 (7.5)
	Complete heart block requiring permanent cardiac pacing	2/571 (0.4)
	Death due to clinical events during implant procedure (progressive hypotension; asytole)	2/571 (0.4)
	Coronary-sinus dissection	23/571 (4.0)
	Cardiac vein or coronary-sinus perforation[a]	12/571 (2.1)
	Participants who had successful implantation (n=528)	
	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] Enrolled n=67 Randomised n=58 CRT-ON, CRT-P OFF n =29 CRT-P OFF, CRT-P ON n=29	Unsuccessful implantation	5/64 (7.8)
	Early lead dislodgement	8/58 (13.8)
	CRT-P-ON	
	Uncorrectable loss of left ventricular pacing efficacy	2/58 (3.4)
	Decompensation attributed to rapidly progressive aortic stenosis	1/58 (1.7)
	CRT-P-OFF	
	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-HF[111] 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		
		IHD, n=168	**non-IHD, n=197**	**IHD, n=135**	**non-IHD, n=235**	**p value**
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-CD[128]) was included in the 2007 TAR on CRT,[43] however participants in CONTAK-CD[128] 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 *et al.*, 2003[128],** Lozano *et al.*, 2000[130], FDA report[131], Saxon *et al.*, 1999[129]
MADIT-CRT	**Moss *et al.*, 2009, [132;133]**Solomon *et al.* 2010,[134] Goldenberg *et al.* 2011,[136;146]Arshad *et al.* 2011[152]
MIRACLE ICD	**Young *et al.*, 2003[137]**
MIRACLE ICD II	**Abraham *et al.*, 2004[138]**
Piccirillo 2006	**Piccirillo *et al.*, 2006[139]**
Pinter 2009	**Pinter *et al.*, 2009[140]**
RAFT	**Tang *et al.*, 2010;[141]** Tang *et al.*, 2009[142]
RethinQ	**Beshai *et al.*, 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). Piccirillo[139] states that the participants were undergoing prophylactic treatment with the ICD or CRT-D. Pinter[140] 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 II[138] and RAFT[141] were in NYHA class II; in CONTAK-CD, [128] MIRACLE ICD,[137] RethinQ[143] and RHYTHM ICD[145] the majority of participants were in NYHA class III; and the majority of participants in Piccirillo[139] 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% (RethinQ[143]) to 100% (Piccirillo[139]). RethinQ[143] enrolled people with ischemic or non-ischaemic cardiomyopathy and Piccirillo[139] enrolled people with ischemic dilated cardiomyopathy.

RethinQ[143] 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-CD[128]) to 169 ms (RHYTHM ICD[145]). Pinter[140] did not report baseline QRS duration, but required a minimum duration of 120 ms for study eligibility. MADIT-CRT[132] 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-CD[128]) to 26% (RethinQ[143]).

The mean age of the participants in the trials was similar, ranging from 63 (MIRACLE ICD II[138]) to 67 (MIRACLE ICD[137]) years. The majority [75% (MADIT-CRT[132]) to 90% (MIRACLE ICD II[138])] 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 ICD[137] and MIRACLE ICD II,[138] and around 80-95% of participants in MADIT-CRT,[132] Piccirillo,[139] RAFT,[141] RethinQ[143] and RHYTM 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 RethinQ[143] and around 7% in MADIT-CRT[132] 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 ≤	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 - mean (SD)	160 (27)	156 (26)			165 (22)	162 (22)	166 (25)	165 (23)	160 (4)	159 (8)	nr	nr	157 (23.6)	158.3 (24.0)	107 (12)	106 (13)	169 (16)	167 (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] Pinter[140]), sudden cardiac death (six trials: CONTAK CD,[128] MIRACLE ICD,[137] MIRACLE ICD II,[138] Piccirillo,[139] RethinQ,[143] Rhythm ICD[145]) and death from other causes (six trials: CONTAK CD,[128] MIRACLE ICD II,[138] Piccirillo,[139] Pinter,[140] RethinQ,[143] Rhythm ICD[145]). Three trials (CONTAK CD,[128] Piccirillo,[139] RAFT[141]) 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 ICD[145]), 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 ICD[145]). 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 Hearth Failure questionnaire (CONTAK CD,[128] MIRACLE ICD,[137] MIRACLE ICD II,[138] Pinter,[140] RethinQ,[143] Rhythm ICD[145]). 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-CRT[132]).

The number of participants randomised ranged from 31 (Piccirillo[139]) to 1820 (MADIT-CRT[132]). The length of follow-up was 6 months in CONTAK-CD,[128] MIRACE ICD,[137] MIRACLE ICD II,[138] Pinter[140] and RethinQ,[143] 12 months in Piccirillo and RHYTHM ICD,[145] and an average of 2.4 years in MADIT-CRT[132] 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 I[137] and II,[138] RethinQ[143]) were at low risk of selection bias. MADIT-CRT[132] 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. RethinQ[143] and RHYTHM ICD[145] 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 I[137] and II,[138] RAFT[141] and Pinter.[140]

Risk of attrition bias in CONTAK-CD [128] was low for the primary outcome, but high for other outcomes. MADIT-CRT[132] 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] RethinQ[143] 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] RHYTM ICD,[145] Pinter[140] and Piccirillo[139] had a low risk of attrition bias.

RAFT[141] 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 RHYTM 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 I[137] and II, Pinter,[140] Piccirillo[139] and RethinQ[143] 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 study[137] 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] Pinter[140] Piccirillo[139] and RethinQ[143] 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]
Selection bias									
Random sequence generation	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Allocation concealment	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Performance bias									
Blinding of participants & personnel	Low	High	Low	Low	High	Low	Low	Unclear	Unclear
Detection bias									
Blinding of outcome assessment	Low	High	Low	Low	High	Low	Low	Low	Unclear
Attrition bias									
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
Reporting bias									
Selective reporting	Low	Low	Low	Low	Low	Low	High	Low	Unclear
Other bias									
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 ICD[137] 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 VO_2 (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 ICD[137] (a difference in NYHA class of 0.75, QoL of 13 points, or 6MWT distance of 50 m), Pinter[140] (12% decrease in end-systolic volume), RAFT[141] (25% relative reduction in the composite outcome) and RethinQ[143] (difference of 23% in the proportion of patients who achieved the primary end point).

The actual event rate observed in CONTAK-CD[128] 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-CRT[132] 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 ICD[137] was not powered to detect a morbidity or mortality difference. Piccirillo[139] 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 II[138] and RHYTHM ICD[145] 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% (Pinter[140]) to 12.4% (MADIT-CRT[132]) of participants, the most common reason for crossover was heart failure events (Table 56). Crossover from CRT-D to ICD occurred in 0% (RethinQ[143]) to 7.5% (MADIT-CRT[132]) 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] Piccirillo[139] and RAFT[141] randomised participants before or at the time of implantation. CONTAK-CD[128] 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 I[137] and II,[138] Pinter,[140] RethinQ[143] and RHYTHM ICD[145]) randomised only those participants who were successfully implanted. In MIRACLE ICD[137] randomisation occurred within 7 days of successful implant, in Pinter[140] participants were randomly assigned following completion of baseline procedures 14-28 days post implant, and in RethinQ[143] and RHYTHM ICD[145] baseline evaluation occurred 14 days post implant, followed by randomisation.

The study design of CONTAK-CD[128] 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.

Piccarillo[139] 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.

RAFT[141] 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 ICD[145] 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 ICD[145] was the basis of an FDA report by St Jude Medical, Sunnvale, CA. Piccarillo 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] RAFT[141]) (see Table 57). MADIT-CRT[132] 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 RAFT[141] 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-CD[128] (CRT-D 4.5% vs ICD 6.5%, RR 0.69, 95% CI 0.33 to 1.45, p=0.33), MIRACLE ICD[137] (CRT-D 7.5% vs ICD 8.2%, RR 0.91, 95% CI 0.45 to 1.83, p=0.79), MIRACLE ICD II[138] (CRT-D 2.4% vs ICD 2.0%, RR 1.19, 95% CI 0.17 to 8.26, p=0.86), Piccirillo[139] (CRT-D 0% vs ICD 0%), Pinter[140] (CRT-D 2.8% vs ICD 2.8%, RR 1.00, 95% CI 0.07 to 15.38, p=1.00), RethinQ[143] (CRT-D 5.7% vs ICD 1.2%, RR 4.89, 95% CI 0.58 to 40.95, p=0.14) and RHYTHM ICD[145] (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-CRT[132] and 40 months in RAFT.[141]

The trials were considered sufficiently similar to combine in a random effects meta-analysis, and were grouped according the NYHA class of the majority of the participants in each trial. There was no evidence of significant statistical heterogeneity between the studies ($Chi^2 = 4.82$, df = 7, I^2=0%). Note that the Piccirillo study[139] 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 study[141] 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). RAFT[141] 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 (Chi^2 2.38, df 5, I^2 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] Calcualted 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 II[138] study of people with mild NYHA class II heart failure, or in the small Piccirillo study[139] 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 trial[143] 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] RethinQ[143] or RHYTHM ICD.[145] Combining the other three trials (MIRACLE ICD II,[138] CONTAK-CD,[131] MIRACLE ICD[137]) 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-CD[131] (CRT-D 0.8%, ICD 1.2%) and RHYTHM ICD[145] (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 Piccirillo[139] or Pinter[140] 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 ICD[137] (CRT-D 92.4% vs ICD 92.2%, p=0.96) or RethinQ[143] (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, RethinQ[143]) (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] Piccirillo[139] and RAFT[141] reported hospitalisations related to heart failure (Table 63); MIRACLE ICD,[137] Pinter[140] and RAFT[141] reported all-cause hospitalisations (Appendix 7). The RAFT study[141] 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-CD [128] 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 II[138] and RHYTHM ICD[145] 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 ICD[137] is not estimable (see Figure 25). A significantly greater proportion of the CRT-D group improved by one class or more in RethinQ[143] (54% vs 29%, p=0.006), and the majority (81% of participants) with CRT-D in the small Piccirillo study[139] 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-CD[128] 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 (Chi^2 8.57, df 2, I^2 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)	
	Improved 1 class	27[a]/109 (25)	35[a]/116 (30)	0.1
	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-CRT[132] 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 II[138]) 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 ICD[137], Pinter,[140] RethinQ[143]) trials reported no statistically significant difference between the groups in change from baseline (Table 66). Piccirillo[139] and RHYTHM ICD[145] 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 VO_2, 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-CD[128] found improvements in both peak VO_2 and distance walked in 6 minutes that were statistically significantly greater with CRT-D compared with ICD. MIRACLE ICD[137] and RHYTHM ICD[145] found statistically significant improvements in peak VO_2, but not distance walked in 6 minutes; MIRACLE ICD[137] also found significant improvements in exercise duration in favour of CRT-D. MIRACLE ICD II[138] (mild heart failure) found no statistically significant differences in change in peak VO_2 or exercise duration, but found a significant improvement in ventilatory response to exercise with CRT-D versus ICD. RethinQ[143] 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 VO_2. 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 VO_2 (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 ICD[137] and RethinQ[143]

report medians not means, the difference remains statistically significant when these studies are omitted.

Figure 28: Change in peak VO_2

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 (SD113.3)	(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). Pinter[140] 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)	ns
	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] Piccirillo[139] and RAFT[141]), 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- CRT[132] and RAFT[141] 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] RAFT[141] and RHYTHM ICD.[145] MIRACLE ICD[137] and MIRACLE ICD II[138] 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] RethinQ[143] and RHYTHM ICD[145]) reported adverse events for both interventions combined (Table 70). MIRACLE ICD[137] also reported events separately for CRT-ON and CRT-OFF (see Table 71), as did MADIT-CRT[132] and RAFT[141] for CRT-D versus ICD devices. Adverse events were not reported by Pinter;[140] and Piccirillo[139] 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 ICD[145]) clearly described the implantations as successful (83.3% to 91%) (Table 69).

Perioperative deaths occurred in between 0.1% (MADIT-CRT[132]) to 2.4% (RHYTHM ICD[145]) 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 ICD[137] and MIRACLE ICD II[138] 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-CRT[132] had the LV lead repositioned during the first 30 days.

The RAFT trial[141] 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-CRT[132] 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), 31events
	- 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

[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 1st 30 days	44/1089 (4.0)			
	Frequency of serious device-related adverse events during long-term follow-up after the 1st 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] Implanted n=1787 CRT-D n=888 ICD n=899		**CRT-D, n/N (%)**	**ICD, n/N (%)**		
	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-CRT[132] 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.

RAFT[141] 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).

RethinQ[143] 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 statisitically 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-CRT[132] 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 ≥150ms	147/645 225/1175	HR 1.06 HR 0.48	0.74 to 1.52 0.37 to 0.64, 0.001
LVEF ≤25% >25%	 101/646 271/1174	 HR 0.70[a] HR 0.60[a]	
LVEDV ≤240ml > 240ml	 184/828 184/969	 HR 0.70[a] HR 0.62[a]	
LVESV ≤170ml > 170ml	 190/835 178/962	 HR 0.66[a] HR 0.70[a]	
All patients	372/1820	HR 0.66	

[a] Hazard ratios estimated from figure by reviewer.

Table 73: MADIT-CRT[152] 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%)	
	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		<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 RAFT[141] 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: RAFT[141] 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: RethinQ [143] 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 $\geq$ 120ms 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 sub-set 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] DEBUT[91]). 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 [redacted] to limit the effects of trial cross-over at longest follow-up ([redacted]). Missing data for the covariables appeared limited [redacted], 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, Akaiko 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 utilities[153] 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

[redacted].

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]

[redacted] for ICDs. Hazard ratios were presented for CRT-D compared with CRT-P [redacted]) and for CRT-D compared with ICD [redacted]. The MS states that proportional hazards tests showed that the benefits were maintained over time (global p-value for device terms [redacted]).

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 ≥150ms 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 ≥150ms 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	[redacted]	[redacted]	[redacted]	[redacted]
≥120 to <150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]
≥150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]
LBBB					
QRS	**Device**	**Sex and Age Groups**			
		Male <60yrs	**Male ≥60yrs**	**Female <60yrs**	**Female ≥60yrs**
≥120 to <150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]
≥150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]

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	[redacted]	[redacted]	[redacted]
QRS 120-149ms	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]
Ischaemic aetiology			
QRS <120ms	[redacted]	[redacted]	[redacted]
QRS 120-149ms	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]

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	[redacted]	[redacted]	Results from IPD analysis clinically plausible
NYHA III	[redacted]	[redacted]	Results from IPD analysis clinically plausible
NYHA IV	[redacted]	[redacted]	Device not assessed in this patient group
CRT-P			
NYHA I/II	[redacted]	[redacted]	Device not assessed in this patient group
NYHA III	[redacted]	[redacted]	Results from IPD analysis clinically plausible
NYHA IV	[redacted]	[redacted]	Results from IPD analysis clinically plausible
CRT-D			
NYHA I/II	[redacted]	[redacted]	Results from IPD analysis clinically plausible
NYHA III	[redacted]	[redacted]	Results from IPD analysis not clinically plausible. Assumed same as CRT-P value given common component (CRT)
NYHA IV	[redacted]	[redacted]	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	[redacted]	[redacted]	N/A
QRS 120-149ms	[redacted]	[redacted]	N/A
QRS ≥150ms	[redacted]	[redacted]	N/A
Ischaemic aetiology			
QRS <120ms	[redacted]	[redacted]	N/A
QRS 120-149ms	[redacted]	[redacted]	N/A
QRS ≥150ms	[redacted]	[redacted]	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	[redacted]	[redacted]
QRS ≥150ms	N/A	[redacted]	[redacted]
Ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS 120-149ms	N/A	[redacted]	[redacted]
QRS ≥150ms	N/A	[redacted]	[redacted]

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	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]
Ischaemic aetiology			
QRS <120ms	N/A	N/A	N/A
QRS 120-149ms	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]

Source: MS, Tables 47, p145.

HRQoL

The negative binomial regression model (MS, Table 52, p152) for patients randomised to OPT was used to generate baseline results for the different sub-groups (Table 83). Given the limitations of the dataset used, the estimates were checked with population norms and with the mean values from the three trials included in the IPD. Although variations were evident, the MS felt that they were within acceptable tolerance levels. Treatment effects on HRQoL were estimated as mean change from baseline using the IPD (Table 84). As several estimates appeared counter-intuitive, reflecting the limited and skewed data available, the MS adjusted the values based on IPD analysis of MLWHF 6 month data and a systematic review (Table 84). As a result, the MS suggests that caution should be taken when interpreting the results. Validation of the adjusted values provided in the MS is difficult due to the lack of published evidence, as such the increments presented should viewed with caution.

[redacted] and so this was applied in the economic model presented in the MS.

Table 83 Comparison of indicative individuals with population equivalents

Non-Ischaemic aetiology				
NYHA	Gender	Decrements from unity		
		Pop Norm	Derived	Disease specific component[a]
I/II	Males	0.2100	[redacted]	[redacted]
I/II	Female	0.2098	[redacted]	[redacted]
III	Male	0.2100	[redacted]	[redacted]
III	Female	0.2098	[redacted]	[redacted]
IV	Male	0.2100	[redacted]	[redacted]
IV	Female	0.2098	[redacted]	[redacted]
Ischaemic aetiology				
NYHA	Gender	Decrements from unity		
		Pop Norm	Derived	Disease specific component[a]
I/II	Males	0.2100	[redacted]	[redacted]
I/II	Female	0.2098	[redacted]	[redacted]
III	Male	0.2100	[redacted]	[redacted]
III	Female	0.2098	[redacted]	[redacted]
IV	Male	0.2100	[redacted]	[redacted]
IV	Female	0.2098	[redacted]	[redacted]

[a] Corresponds to difference between population norm and derived value. To be interpreted as the impact of the disease above and beyond what would naturally occur. Assumed starting age 66 years
Source: MS, Tables 53 and 54, p153.

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	[redacted]	[redacted]	[redacted]	No clinical reason why person already on OPT would have a change in utility.
ICD	[redacted]	[redacted]	[redacted]	Value derived from IPD analysis [redacted]. Systematic review suggests ICDs have a positive impact.
CRT-P	[redacted]	[redacted]	[redacted]	Cost effectiveness results not generated for this treatment option.
CRT-D	[redacted]	[redacted]	[redacted]	Value derived from IPD analysis [redacted]. Systematic review and MLWHF suggests CRT-Ds have a positive impact.
NYHA III				
OPT	[redacted]	[redacted]	[redacted]	No clinical reason why person already on OPT would have a change in utility.
ICD	[redacted]	[redacted]	[redacted]	Results from IPD analysis not significantly different from zero. Literature review suggests ICDs have no benefit in this group.
CRT-P	[redacted]	[redacted]	[redacted]	Value derived from IPD analysis [redacted]. Literature review and MLWHF analysis suggests CRT-P has a benefit in this group.
CRT-D	[redacted]	[redacted]	[redacted]	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	[redacted]	[redacted]	[redacted]	No clinical reason why person already on OPT would have a change in utility.
ICD	[redacted]	[redacted]	[redacted]	Cost effectiveness results not generated for this treatment option

CRT-P	[redacted]	[redacted]	[redacted]	Not enough information available. Assumed same as for NYHA III. Analysis of MLWHF data supports this assumption.
CRT-D	[redacted]	[redacted]	[redacted]	Not enough information available. Assumed same as for NYHA III. Analysis of MLWHF data supports this assumption.

[a]Significant 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 CRD-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. iven 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.

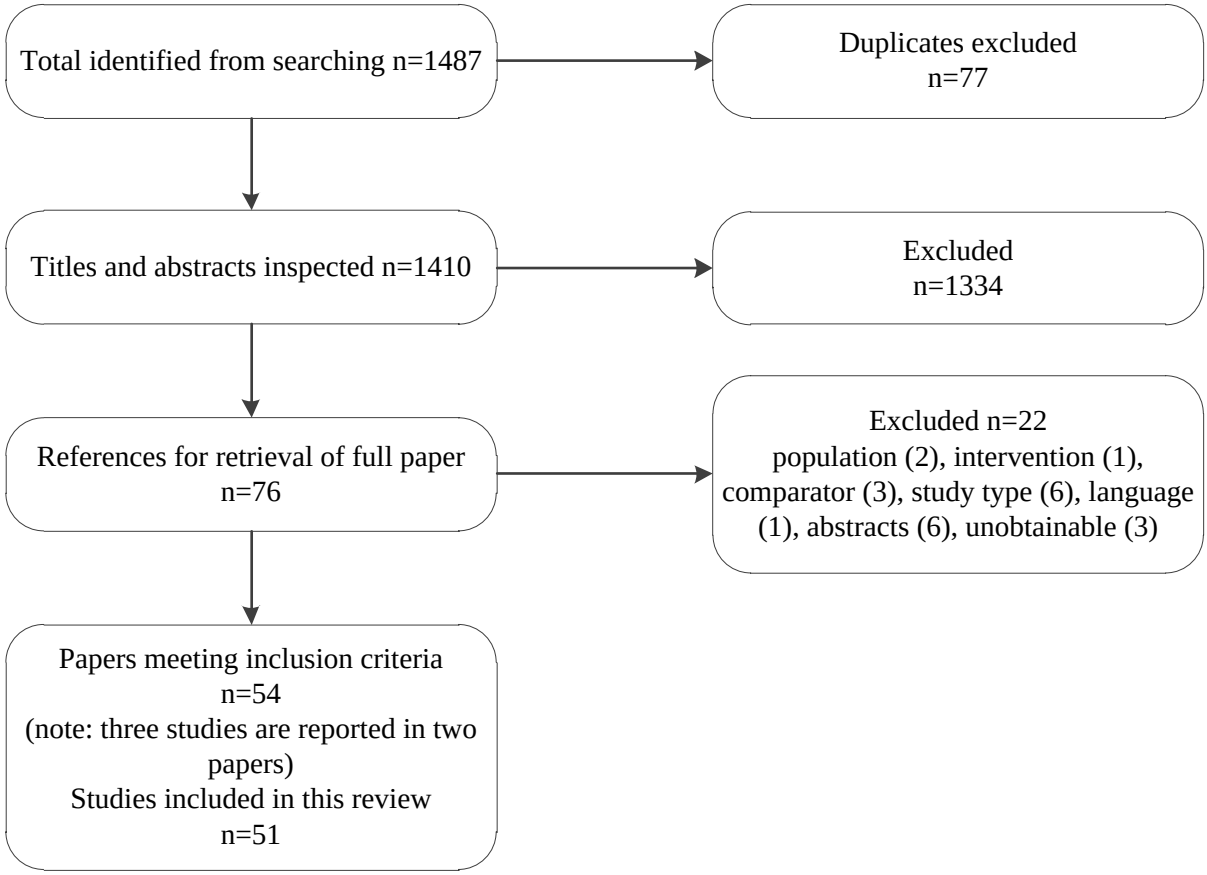
5.1.1 Quantity and quality of research available

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 colleagues[155] and MSAC[172]); 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 Australia[172] and Japan.[150] Two studies were conducted in two countries (one in UK and France[156] and one in Germany and USA[173]). 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 II[103] (6 studies[154;157;164;171;180;186]) and SCD-HeFT[107] (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 colleagues[42]). 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 *et al*., 2005[154]	USA	Adults with a history of MI and an LVEF ≤30%	Survival	MADIT II	Cost-effective ($50,500/LYG)
Bertoldi *et al*., 2011[155]	Brazil	HF NYHA II, III or IV, EF≤35%.	Markov	Meta-analysis of trials	Marginally cost-effective ($32,663/QALY)
Buxton *et al*., 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 *et al*., 2007[156]	UK and France	HF NYHA II or II, LV dysfunction ≤35%	DES	SCD-HeFT	Cost effective (Cost benefit ratio 0.17 UK)
Chan *et al*., 2006[157]	USA	Ischemic heart disease and LVEF ≤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 *et al*., 2009[158]	USA	Cardiomyopathy (EF ≤ 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 *et al*., 2009[160]	Belgium	LVEF ≤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 *et al*., 2009[161]	Canada	HF NYHA II or II, LV dysfunction ≤35%	DES	SCD-HeFT	Cost effective (Cost benefit ratio of 0.05)
Feingold *et al*., 2010[162]	USA	Children (10-15 years old) with dilated cardiomyopathy and HF	Markov	Paedriatric cardiology prospective studies	Not cost effective ($281,622/QALY)
Fillion *et al*., 2009[163]	Canada	Severe LV dysfunction at risk of SCD	Markov	Meta-analysis of trials	Not cost effective ($108,900/QALY)
Gandjour *et al*., 2011[164]	Germany	EF ≤ 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 *et al*., 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 *et al*., 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 *et al*., 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 *et al*., 1992[168]	USA	Patients with sustained VT/VF	Markov	Case series of ICD patients	Cost effective ($29,244/LYG)
Larsen *et al*., 2002[169]	USA	EF ≤ 40%. Sustained VT or resuscitated from CA	Trial	AVID	Moderately cost-effective ($66,677/LYG)
Mark *et al*., 2006[170]	USA	HF NYHA II or III, LV dysfunction ≤35%	Trial	SCD-HeFT	Cost effective ($41,530/QALY)
McGregor and Chen, 2004[171]	Canada	Adults with a history of MI and an LVEF ≤30%	Markov	MADIT II	Unclear ($47,458/LYG)
MSAC, 2006[172]	Australia	Adults with a history of MI and an LVEF ≤30%; or HF NYHA II or III, LV dysfunction ≤35%	Decision tree	SCD-HeFT, COMPANION	Cost-effective in patients with moderate to severe symptoms of CHF (ICD $39,885/LYG)
Mushlin *et al*., 1998[173]	Germany and USA	Adults with a history of MI and an LVEF ≤30%	Trial	MADIT	Cost-effective in selected high-risk patients ($27,000/LYG)
Neyt *et al*., 2008[174]	Belgium	HF NYHA II or II, LV dysfunction ≤35%	Markov	SCD-HeFT	Not cost effective (€132,100/QALY)
O'Brien *et al*., 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 *et al*., 1997[176]	USA	CA survivors at high risk of SCD	Markov	CASH, MADIT	Cost effective for high risk groups ($74,400/QALY)
Owens *et al*., 2002[177]	USA	Patients at risk of SCD (trial characteristics)	Markov	MADIT, AVID, CIDS, CASH, MUSTT, CABG-PATCH	Cost effective in high risk groups ($54,700/QALY)
Parkes *et al*., 2000[66]	UK	Patients at risk of SCD from arrhythmia.	Survival calculation	AVID	Unclear (£40,500 – 87,000/LYG)
Ribeiro *et al*., 2010[178;201]	Brazil	HF NYHA II and III, LVEF ≤ 35%	Markov	Several sources; scenario with MADIT I	Not cost effective (R$ 68,318/QALY)
Sanders *et al*., 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 *et al*., 2004[180]	USA	Adults with a history of MI and an LVEF ≤30%	Markov	MADIT II	Cost-effective ($50,900/QALY)
Sanders *et al*., 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 *et al*., 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 *et al.*, 2001[183] & O'Brien *et al*., 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 *et al*., 2008[150]	Japan	Brugada syndrome with abnormal hearts	Markov	Several trials including DEBUT	Cost-effective ($14,667/QALY)
Weiss *et al*., 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 *et al*., 2007[185]	Canada	Hypertrophic cardiomyopathy at risk of SCD (no previous CA)	Markov	ICD registries and cohort studies	Cost-effective ($19,400/QALY)
Zwanziger *et al*., 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 *et al*., 2005[154]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Bertoldi *et al*., 2011[155]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Buxton *et al*., 2006[42]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Caro *et al*., 2007[156]	Y	Y	Y	?	Y	N	N	Y	Y	Y
Chan *et al*., 2006[157]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Chan *et al*., 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 *et al*., 2009[160]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Deniz *et al*., 2009[161]	Y	N	Y	?	Y	N	N	Y	Y	Y
Feingold *et al*., 2010[162]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Fillion *et al*., 2009[163]	Y	N	Y	?	Y	Y	?	Y	Y	Y
Gandjour *et al*., 2011[164]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Goldenberg *et al*., 2005[165]	Y	N	?	?	N	Y	Y	Y	Y	Y
Kupersmith *et al*., 1995[167]	Y	N	Y	?	Y	N	Y	Y	Y	Y
Kuppermann *et al*., 1990[166]	Y	N	Y	N	N	N	N	Y	N	Y
Larsen *et al*., 1992[168]	Y	N	Y	?	Y	N	Y	Y	Y	Y
Larsen *et al*., 2002[169]	Y	N	Y	?	Y	N	?	Y	Y	Y
Mark *et al*., 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 *et al*., 1998[173]	Y	N	Y	N	?	N	?	Y	Y	Y
Neyt *et al*., 2008[174]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
O'Brien *et al*., 1992[175]	Y	Y	Y	N	?	N	Y	Y	N	Y
Owens *et al*., 1997[176]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Owens *et al*., 2002[177]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Parkes *et al*., 2000[66]	Y	Y	?	N	Y	Y	N	N	Y	Y
Ribeiro *et al*., 2010[178;201]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Sanders *et al*., 2001[179]	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Sanders *et al*., 2004[180]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Sanders *et al*., 2005[181]	Y	N	Y	?	N	Y	Y	Y	Y	Y
Sanders *et al*., 2010[182]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Sheldon *et al*., 2001[183] & O'Brien *et al*., 2001[202]	Y	N	Y	N	Y	N	?	Y	Y	Y
Wang *et al*., 2008[150]	Y	N	Y	?	N	Y	Y	Y	Y	Y
Weiss *et al*., 2002[184]	Y	N	Y	?	N	N	?	Y	Y	N
You *et al*., 2007[185]	Y	N	Y	?	?	Y	Y	Y	Y	Y
Zwanziger *et al*., 2006[186]	Y	N	Y	?	Y	N	?	Y	Y	Y

5.1.2.1 Buxton and colleagues[42]

Buxton and colleagues[42] 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 AVID[73]). 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 colleagues[42] collected resource and cost data for 211patients 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 colleagues[42] 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 study[42] 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 study[42] 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-effective[155] 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] Brazil[155] 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 USA[197] and Canada[194]) 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)
CRT-P vs OPT					
Banz, 2005[187]	Germany	Patients with HF	Markov	Several publications and expert opinion	Cost-effective (€36,600/QALY)
Bertoldi *et al.*, 2011[155]	Brazil	HF NYHA II, III or IV, EF≤35%.	Markov	Meta-analyses	Cost-effective (Int $15,723/QALY)
Blomstrom *et al.*, 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 *et al.*, 2009[203] Fox *et al.*, 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 *et al.*, 2010[188]	Spain	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective (€28,612/QALY)
Calvert *et al.*, 2005[189]	UK	HF NYHA III or IV, LVEF <35%	Trial-based	CARE-HF	Cost-effective (€19,319/QALY)
Caro *et al.*, 2006[190]	UK	HF NYHA III or IV, LVEF <35%	DES	CARE-HF	Cost effective (£15,247/QALY)
Feldman *et al.*, 2005[192]	USA	HF NYHA III or IV, LVEF ≤35%, QRS > 120ms	Survival	COMPANION	Cost-effective ($19,600/QALY)
Heerey *et al.*, 2006[193]	Ireland	HF NYHA III or IV and QRS interval of > 130 ms	Markov	Retrospective cohort study	Cost-effective (Dominant)
McAlister *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2012[200]	Argentina	HF NYHA I or II, LVEF ≤40% QRS ≥120ms	Markov	Meta-analysis of REVERSE, MADIT-CRT, RAFT	Cost-effective (Int $34,185/QALY)
Yao *et al.*, 2007[198]	UK	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective (€7,538/QALY)
CRT-D vs OPT					
Aidelsburger *et al.*, 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 *et al.*, 2005[192]	USA	HF NYHA III or IV, LVEF ≤35%, QRS > 120ms	Survival	COMPANION	Cost-effective ($43,000/QALY)
MSAC, 2006[172]	Australia	HF NYHA III or IV, LVEF ≤35%, QRS > 120ms	Decision tree	COMPANION	Cost-effective for patients with CHF NYHA III or IV, sinus rhythm, LVEF≤35% and a QRS duration ≥120ms despite OPT. (€22,944/LYG)
Yao *et al.*, 2007[198]	UK	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective at WTP of €44,100/QALY
CRT-D vs CRT-P					
Bertoldi *et al.*, 2011[155]	Brazil	HF NYHA II, III or IV, EF≤35%.	Markov	Meta-analyses	Non cost-effective (Int $84,345/QALY)
Bond *et al.*, 2009[203] Fox *et al.*, 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 *et al.*, 2010[188]	Spain	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Non cost-effective (€53,547/QALY)
Neyt *et al.*, 2011[196]	Belgium	HF NYHA III or IV, LVEF ≤35%, QRS > 120ms	Markov	COMPANION	Not cost effective (€57,000/QALY)
Yao *et al.*, 2007[198]	UK	HF NYHA III or IV, LVEF <35%	Markov	CARE-HF	Cost-effective (€18,017/QALY)
CRT-D vs ICD					
Bertoldi *et al.*, 2011[155]	Brazil	HF NYHA II, III or IV, EF≤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 colleagues[203]

Fox and colleagues[43] (also reported in Bond and colleagues[203]) 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 ≤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 colleagues[205]) and utility for hospitalisation with HF (0.57 from McAllister and colleagues[194]). 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 colleagues[43] 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
CRT-P vs OPT										
Banz, 2005[187]	Y	N	Y	Y	Y	Y	N	N	Y	Y
Bertoldi *et al.*, 2011[155]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Blomstrom *et al.*, 2008[191]	Y	N	Y	?	Y	Y	Y	Y	Y	Y
Bond *et al.*, 2009[203] Fox *et al.*, 2007[43]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Callejo *et al.*, 2010[188]	Y	?	Y	Y	Y	Y	Y	Y	Y	Y
Calvert *et al.*, 2005[189]	Y	Y	Y	?	Y	Y	Y	Y	Y	Y
Caro *et al.*, 2006[190]	Y	Y	Y	?	Y	Y	?	Y	Y	Y
Feldman *et al.*, 2005[192]	Y	N	Y	?	Y	Y	N	Y	Y	Y
Heerey *et al.*, 2006[193]	Y	N	Y	Y	?	Y	N	Y	Y	Y
McAlister *et al.*, 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 *et al.*, 2011[196]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Nichol *et al.*, 2004[197]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Poggia *et al.*, 2012[200]	?	N	Y	Y	Y	Y	Y	Y	Y	Y
Yao *et al.*, 2007[198]	Y	Y	Y	?	?	Y	Y	Y	Y	Y
CRT-D vs OPT										
Aidelsburger *et al.*, 2008[199]	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Feldman *et al.*, 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 *et al.*, 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
CRT-D vs CRT-P										
Bertoldi *et al.*, 2011[155]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Bond *et al.*, 2009[203] Fox *et al.*, 2007[43]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Callejo *et al.*, 2010[188]	Y	?	Y	Y	Y	Y	Y	Y	Y	Y
Neyt *et al.*, 2011[196]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Yao *et al.*, 2007[198]	Y	Y	Y	?	?	Y	Y	Y	Y	Y
CRT-D vs ICD										
Bertoldi *et al.*, 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 studies[43] 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 ≤35% and QRS direction >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, one[172] found CRT-D cost-effective compared with OPT and one found CRT-D marginally cost-effective compared with ICD.[155]

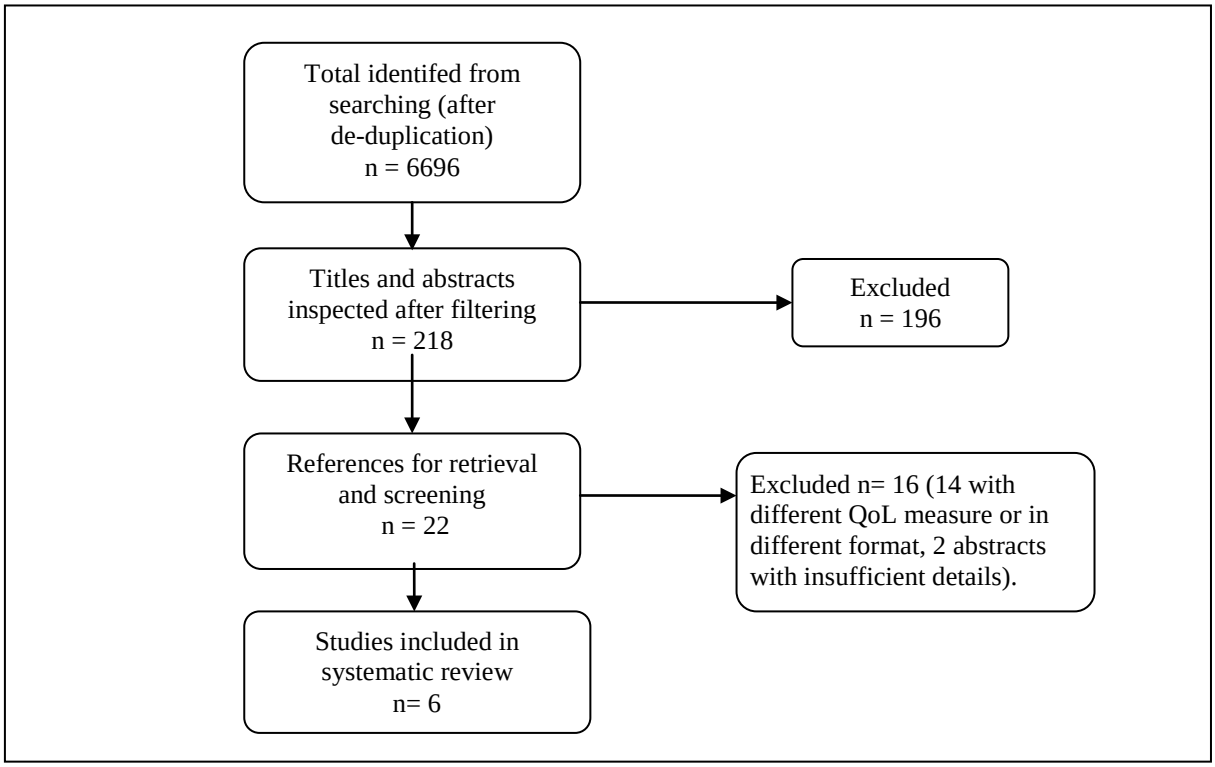
5.2 Systematic review of health-related quality of life studies

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-5D[206] 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-HF[205] and HeartMed RCT[209]).

Buxton and colleagues[42] 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 colleagues[210] 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 colleagues[205] 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 colleagues[207] 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 colleagues[208] estimated utilities for NYHA classification and number of cardiovascular rehospitalisations for patients with chronic heart failure after acute myocardial infarction in the EPHESUS RCT. The EPHESUS 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 colleagues[209] 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 USA[210]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 age[210] 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 study[209] 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 (0.60[205] and 0.66[207]). Three studies reported mean baseline EQ-5D score by NYHA class. Mean baseline EQ-5D score for NYHA Class III was 0.61,[205] 0.63[208] 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] 0.53[208] 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 Class[207] 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 ≤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 ≥150ms and all women with a QRS≥120 to <150ms and a marginally insignificant effect for all men QRS≥120 to <150ms. ICDs had a significant benefit for men aged <60 years and for men aged ≥60 years with a QRS ≥120 to <150ms and non-LBB. CRT-P had a significant benefit for women with QRS ≥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 requirements[69] 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 al[69]

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 colleagues[153] 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 0.1 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 al [42] and Fox et al [43]) 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 2002[177]). 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 CRT[43] 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 jointed 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 colleagues[43] 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 al [42] and Fox et al [43]) 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 2002[177]) 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 NICE[64]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 results 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.

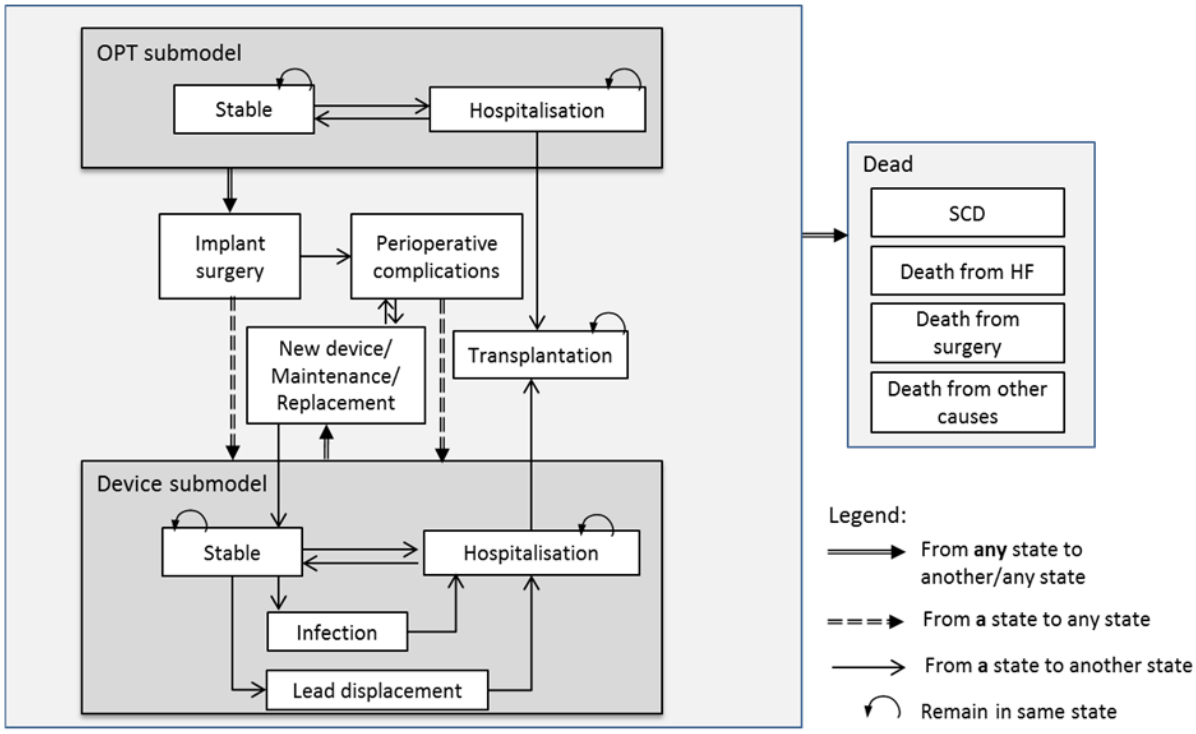
A Markov model developed in Microsoft Excel was used to simulate disease progression in a cohort of patients, who move between distinct health states over their lifetime. The probability of being in a given health state or moving to a different one (experiencing an event) is calculated repeatedly over 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 TA120[43] 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 scope[64] 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 scope[64] 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

	Comparisons	
Population	*Intervention*	*Comparator*
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 the 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 TA120[43] 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 TA120[43] 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 II[103] and SCD-HeFT[107]) 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, AVID[73] results were used for our base case analysis of patients at increased risk of SCD due to ventricular arrhythmia. MADIT II[103] 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-HeFT[107] 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-HeFT[107]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(λ)	-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(λ)+γ ln(t); S(t) = exp(-λ.t^γ)

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-HeFT[107] 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-Heft[107] non-ischaemic congestive heart failure subgroup and the three cardiomyopathy trials (AMIOVIRT,[71] CAT,[84] DEFINITE[92])).

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 colleagues[212] 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 colleagues[212] 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**
Peri-operative complications			
Mechanical complication	0.053	0.046	0.062
Post-operative complications			
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 colleagues[43] 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(λ)+γ ln(t); S(t) = exp(-λ.t^γ)

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-HF[111](252/404 events in 29.4 months), MIRACLE[123] (50/225 patients in 6 months), MUSTIC[127] (9/29 events in 3 months), and COMPANION[118] (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 colleagues[43], 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 colleagues[43] 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-HF[111] reported 1 death in 409 patients, MIRACLE[123] 1 in 571 patients, MUSTIC[127] 1 in 64 patients, and COMPANION[118] 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

COMPANION[118] 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-HF[111] (19/409), MIRACLE[123] (43/571), MUSTIC[127] (5/64), and COMPANION[118] (78/617). COMPANION[118] 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 colleagues[43] 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-HF[111](24/409), MIRACLE[123](30/571) and MUSTIC[127] (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-HF[111] (3/409 in 29.4 months) and MIRACLE[123](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-CD[128](7/517 in 6 months), RETHINQ[143] (6/172 in 6 months), RHYTHM ICD[145] (4/205 in 15.1 months), MADIT-CRT[132] (12/1089 in 28.8 months), and RAFT[141] (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-HF[113] 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 colleagues[43] who derived the distribution of patients per NYHA class at baseline and 90 days from the CARE-HF trial[111] 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.*, 2003[214] 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-CRT[132] and RAFT[141]) 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-CRT[132] 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
RAFT			
ICD-CRT arm (R^2 = 0.9894)			
ln(λ)	-6.334	-6.467	-6.202
γ	1.243	1.20	1.27
MADIT –CRT			
Men CRT-D arm (R^2 = 0.989)			
ln(λ)	-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 RAFT[141] 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-CD[128] reported 32 of 245 patients in the CRT-D arm were hospitalised, Piccirillo [139] reported none of 16 patients followed for 12 months, and RAFT[141] 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-CD[128], Piccirillo[139], and RAFT.[141]

The COMPANION trial[118] 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 trial[118] 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 ICD[137](42/187), MICACLE ICD II[138] (19/85), CONTAK-CD[128] (36/245), and Pinter[140](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

RAFT[141] 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				
		Mean	SE	LL	UL	Distribution
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 Audit[217] 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 colleagues[218] 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 colleagues[123] report 2 heart transplants in 532 participants from the MIRACLE trial. As Fox and colleagues[43], 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 colleagues[208]) 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 colleagues[209]) was also found in the systematic review. Holland and colleagues[209] 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 colleagues[219] as used in Fox and colleagues[43] 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 colleagues[42]) 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 colleagues[42] 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 colleagues[208](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 colleagues[208] (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 (£)
Whole system			
CRT-P	3,411	2,742	4,080
CRT-D	12,293	9,884	14,702
ICD	9,692	7,792	11,592
Leads[a]			
CRT-P	811	652	970
CRT-D	541	435	647
ICD	543	437	649
Battery			
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=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
ICD			
ln(λ)	-15.784	-16.182	-15.385
γ	1.943	1.889	1.996
Device longevity (years)	8.20	12.76	5.40
CRT-P			
ln(λ)	-14.222	-13.747	-14.697
γ	1.677	1.613	1.74
Device longevity (years)	11.81	22.22	6.58
CRT-D			
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 Costs[222] 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				
Implantation, Reimplantation, and Lead displacement/ replacement				
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
Explant				
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
Battery failure/ device replacement				
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 Costs[222] 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 colleagues[43] 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
Infection Total Cost (£)[a]				
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 colleagues[43] 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 colleagues[43] 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
Total	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

AVID[73] 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.

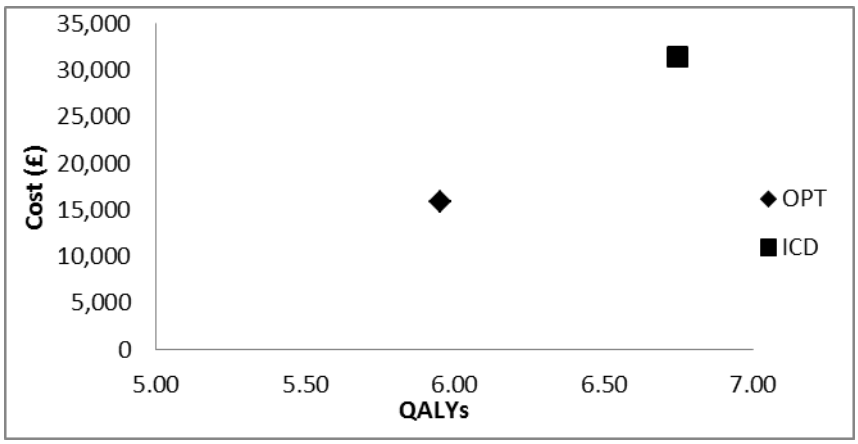
Table 114: Population 1 base case results for 65-year old patients from AVID trial

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 Coalition[216] 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 II[103] 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-HeFT[107] 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-HeFT[107]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-HeFT[107]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
Structural parameters					
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
Survival and HRs					
Baseline all-cause mortality, ln(λ), 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
Event probabilities					
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(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

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

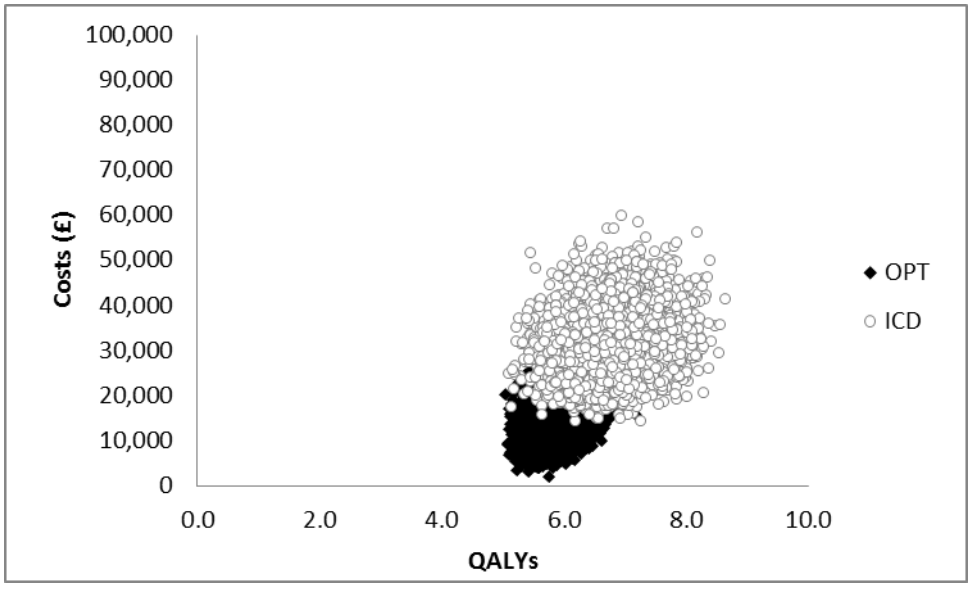
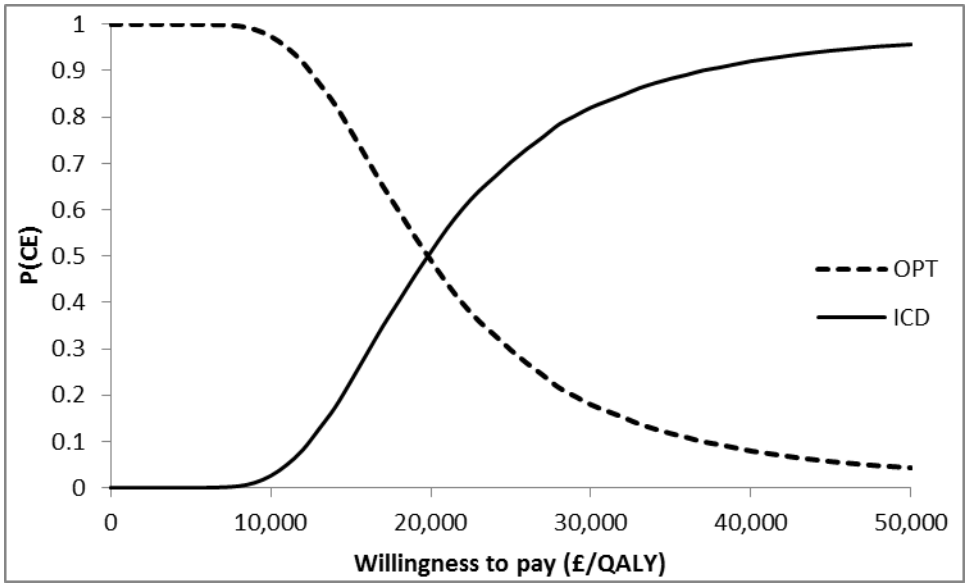


Figure 36 shows the variation of the probability of cost-effectiveness for both interventions as the willingness to pay increases from £0 to £50,000 per QALY gained. The addition of ICD to OPT for SCD secondary prevention has a 51% probability of being cost-effective at a willingness-to-pay threshold 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 scope[64] (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

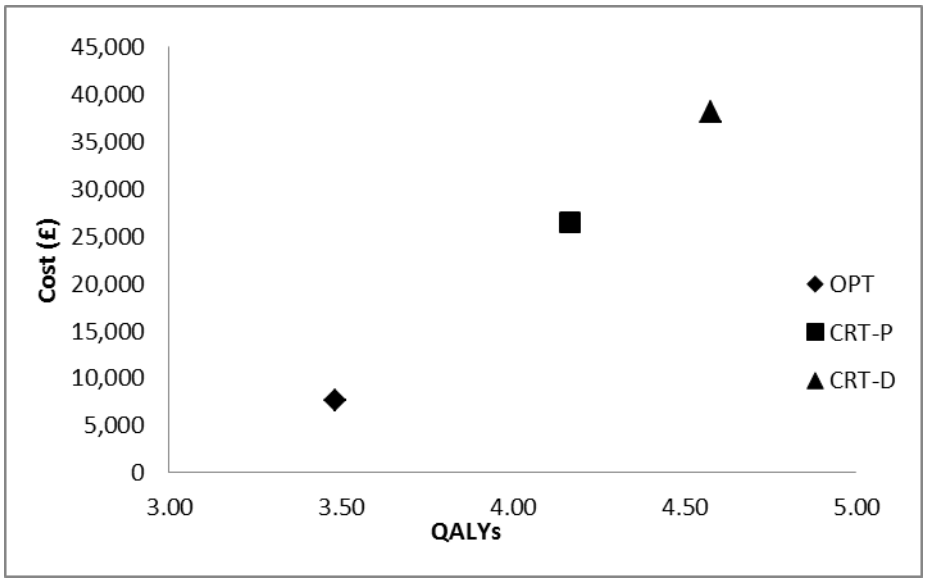
For our base case analysis, a 70 year-old mixed-gender cohort of patients with heart failure was modelled receiving the relevant treatment strategies. Table 123 below presents the estimated discounted costs, life years, and QALYs accrued for patients managed with OPT, CRT-P + OPT, or CRT-D + OPT as well 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 threrapy, 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 colleagues[20] 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/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(λ),γ	-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)			

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(λ),γ	-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(λ), 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(λ), 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

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 colleagues[43] and those used in the current model.

Table 130. Device lifetime estimates

Device	**Fox et al.[43]** Mean, years	**SHTAC** 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 colleagues[43] (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 bythe 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 (£27,893per 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 haveICERs 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

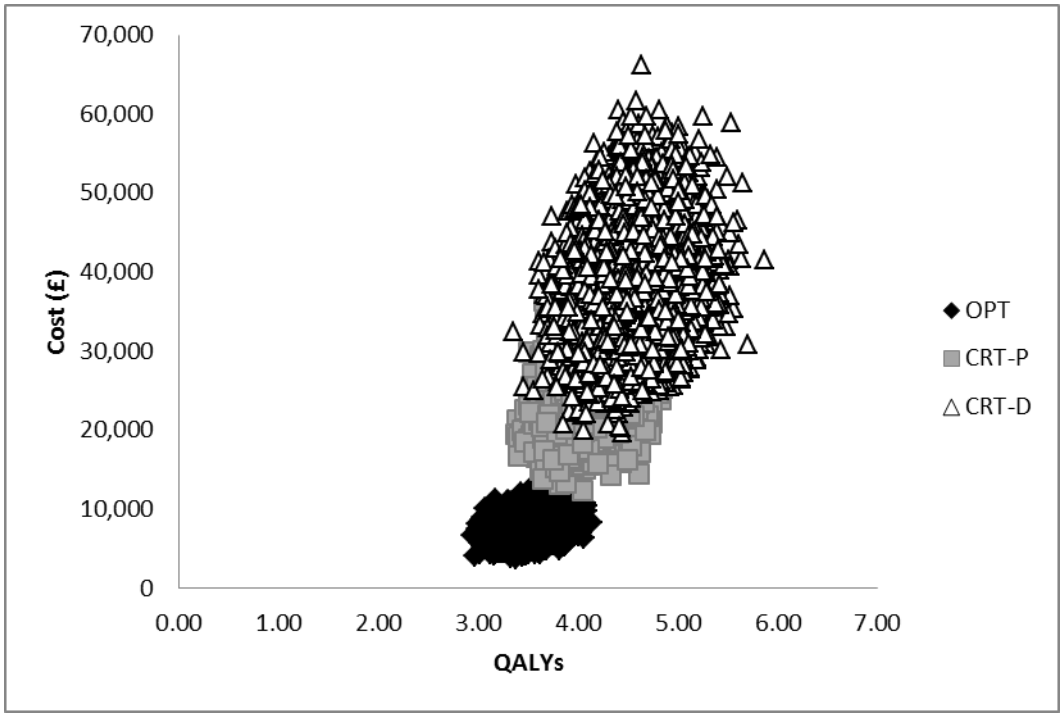
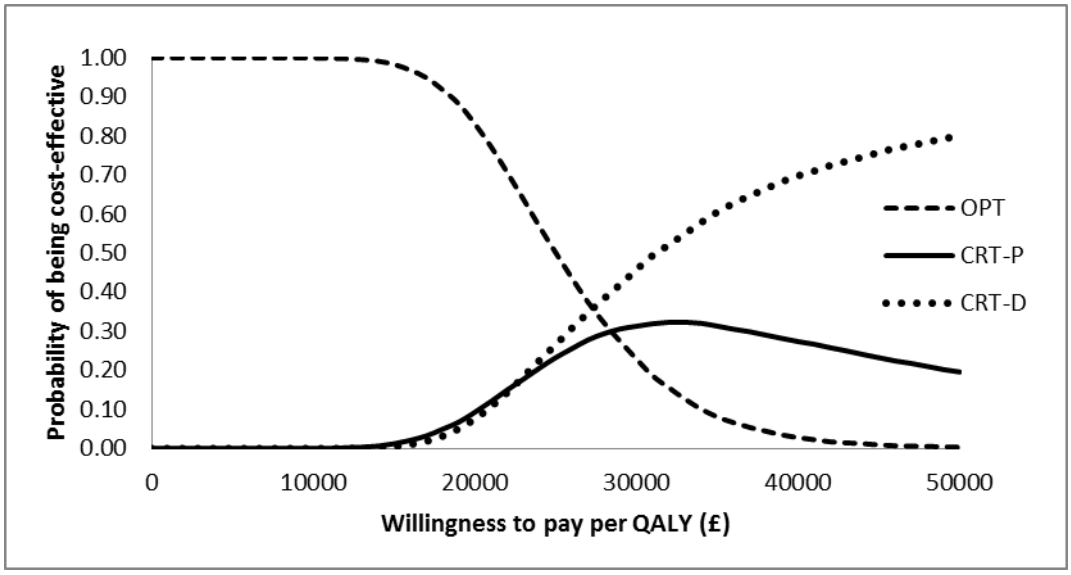


Figure 39 below shows the variation in the probability of the three treatment strategies being cost effective as the WTP increases from £0 to £50,000 per QALY gained. At a WTP of £20,000 per QALY gained, the probability of OPT alone (with subsequent upgrades) being cost-effective is 83%, 9% for CRT-P + 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

RAFT[141] 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) haa similar an 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 slightlyfewer 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

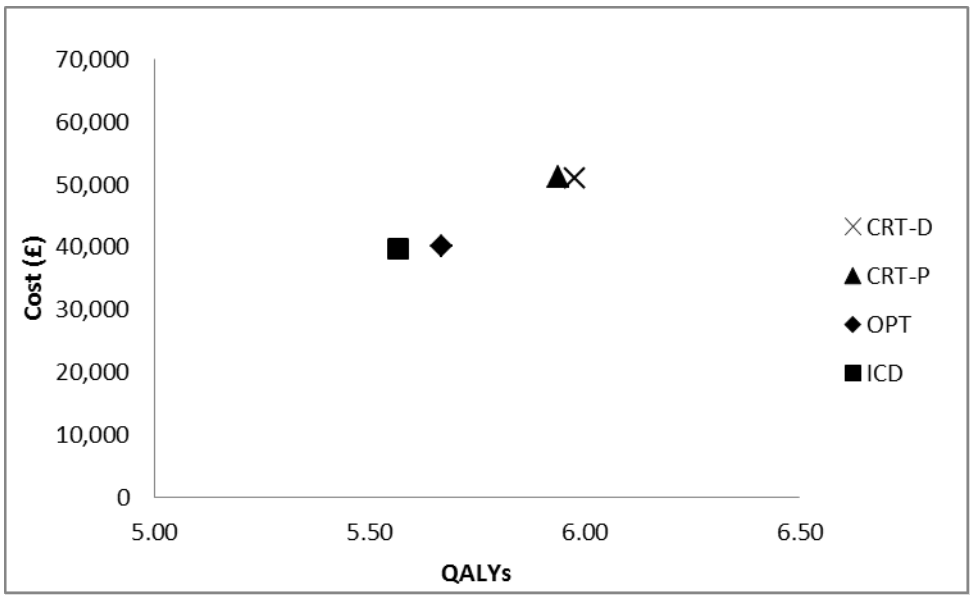
Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs next best option [a]	ICER (£/QALY gained) vs ICD + OPT
ICD + OPT	39,719	7.45	5.57	-	-

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-CRT[132] and the respective HR for ICD for the whole population of MADIT-CRT[132] (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
[a] Treatments 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/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 paramaters 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 af 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 + OTP 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(λ),γ	-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(λ),γ	-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 defibrilator (CRT-P and OPT alone) yield a greater reduction (about £10,000 less) than those with a defibrilator 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(λ),γ	-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)			

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 defibrilator 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 hospitalisaiton 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(λ),γ	-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(λ),γ	-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(λ),γ	-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 defibrilator 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(λ),γ	-15.465, 1.935 (~7y)	UL: -14.934, 2.006 (~4y)	ICD + OPT	ICD + OPT
Device lifetime (ICD), ln(λ),γ	-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 colleagues[43] (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 benefitial 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
[a] Treatments 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 colleagues[43] (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
[a] Treatments 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

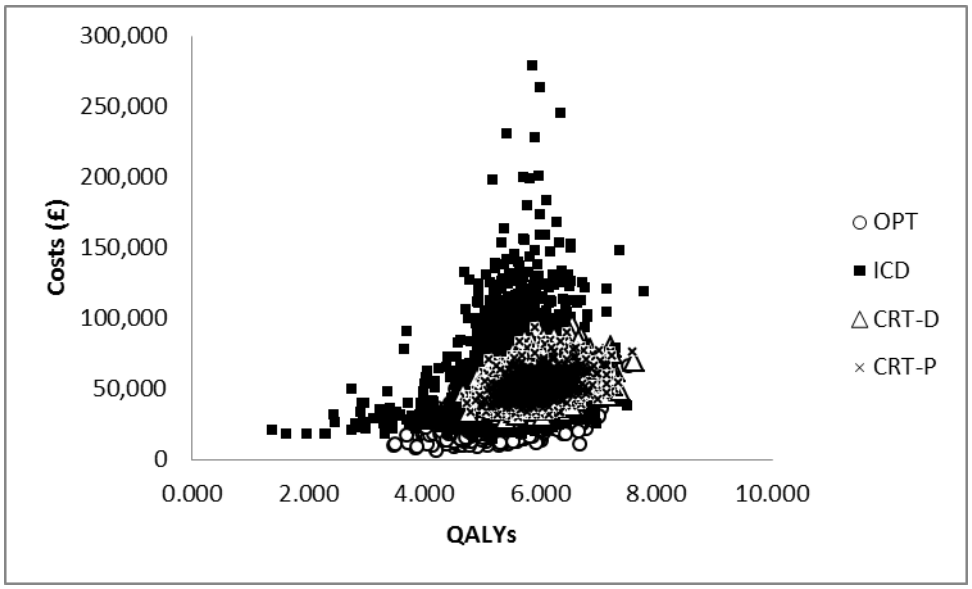
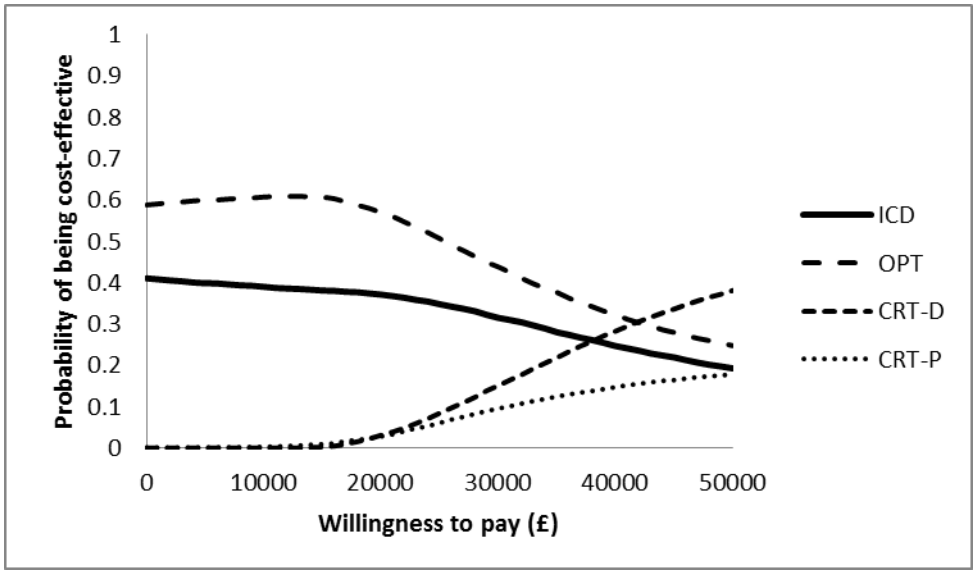


Figure 42 below shows the variation of the probability of being cost-effective for the three treatment strategies as the willingness to pay increases from £0 to £50,000 per QALY gained. At a willingness-to-pay of £20,000 per QALY gained, the probability of OPT alone being cost-effective is 57%, 37% for 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 influent 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-ischaemic 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 TAR[65] (CAT); the other two RCTs (AMIOVIRT, DEFINITE) were excluded from the previous TAR[65] 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 tachyarrhthmic, 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 expertise 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, NHYA 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 TAR[43] 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 (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.

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 $\geq$ 120ms 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 ≥150ms. It also had an effect for people with a QRS ≥120 to <150ms 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 ≥150ms 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 appraisal[64]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 collegues 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 utilies 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 submited 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 colleagues[224] 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-Majed[225] 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 colleagues[226] 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 colleagues[227] 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 CDT-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 the absence of dyssynchrony.

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10 APPENDICES

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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

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Appendix 1: Comparison of inclusion criteria in previous and present TARs

	ICD TAR [1]	**CRT TAR [2]**	**Present TAR**
Population	Adults at high risk of SCD due to arrhythmia: (a) 'Secondary prevention' (i) Cardiac arrest due to either VT or VF. (ii) Spontaneous sustained VT causing syncope or significant haemodynamic compromise. (iii) Sustained VT without syncope/cardiac arrest, and who have an associated reduction in EF (<35%) but are no worse than NYHA class III. (b) 'Primary prevention' (i) A history of previous MI and – 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. (ii) A history of previous MI and depressed heart function (EF ≤0.30). (iii) Non-ischaemic (dilated) cardiomyopathy with arrhythmia at high risk of SCD and depressed heart function (EF ≤0.30).	People with heart failure (any NYHA class) due to LVSD with evidence of cardiac dyssynchrony (QRS >120 ms) and LVSD (LVEF ≤ 35%)	People at increased risk of sudden cardiac death as a results 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 above.
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 colleagues[6] (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	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)	

	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)	
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Searched 11/01/2012	As per medline	77

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 venticula*") 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)	

	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)	
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	# 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	783

	# 19 77,723 (TS=("randomised controlled trial" or "randomized controlled trial")) AND Language=(English # 20 2,213 (TS=(random NEAR allocat*)) AND Language=(English) # 21 252,439 (TS=(random* NEAR trial*)) AND Language=(English) # 22 253,954 #21 OR #20 OR #19 # 23 1,080 #22 AND #18 Refined by: Document Type=(ARTICLE OR PROCEEDINGS PAPER OR MEETING ABSTRACT) # 24 790 #22 AND #18 (6 chapters in books taken out 784)	
Biosis All years searched Searched 17/01/2012 Keywords: BIOSIS CLINICAL EFFECTIVENESS KW	Strategy as per Web of Science above.	63
Cochrane Issue 1 of 12 Jan 2012 All years searched Searched 18/01/2012	#1 MeSH descriptor Defibrillators, Implantable, this term only 708 edit delete #2 (implant* NEAR (defibrilat* or defibrillat*)) 939 edit delete #3 (ICDs or "S-ICD" or S-ICDs) 230 edit delete #4 subcutaneous NEAR ICD* 2 edit delete #5 implant* NEAR ICD* 455 edit delete #6 (CRT or "CRT-D" or "CRT-P") 744 edit delete #7 ("dualchamber*" AND ICD*) 15 edit delete #8 ("dual chamber*" AND ICD*) 46 edit delete #9 "singlechamber" AND ICD* 8 edit delete #10 "single chamber" AND ICD* 25 edit delete #11 resynch* NEAR therapy 290 edit delete #12 ((heart or cardiac or myocardial or coronary) NEAR (resynch* or depolari* or repolari*)) 468 edit delete #13 (atriobiventricular NEAR pacing) 3 edit delete #14 (atriobiventricular NEAR stimulat*) 0 edit delete #15 BVP 17 edit delete #16 biventricular NEAR pac* 137 edit delete #17 biventricular NEAR stimulat* 18 edit delete #18 (cardiover* or "cardio-ver*" or cardioconver* or "cardio-conver*" or "cardio conver*") 1241 edit delete #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	Total 1577 (CENTRAL 1465 CDSR 37 DARE 75)

	#18) 2517 edit #20 MeSH descriptor Arrhythmias, Cardiac explode all trees 5728 edit delete #21 MeSH descriptor Cardiomyopathy, Dilated explode all trees 410 edit delete #22 ventricula* remodel* 655 edit delete #23 MeSH descriptor Bundle-Branch Block explode all trees 82 edit delete #24 MeSH descriptor Heart Failure explode all trees 4620 edit delete #25 "congestive heart failure" 3269 edit delete #26 MeSH descriptor Death, Sudden, Cardiac explode all trees 444 edit delete #27 MeSH descriptor Heart Arrest, this term only 533 edit delete #28 (ventricul* NEAR (tachycardia* or fibril* or arrhythmia*)) 2774 edit delete #29 ((heart or cardiac or myocardial or coronary) NEAR (failur* or arrest* or sudden)) 12656 edit delete #30 ((cardiac or ventricular or intraventricular) NEAR asynchron*) 28 edit delete #31 ((cardiac or ventricular or intraventricular) NEAR dyssynchron*) 66 edit delete #32 tachyarrhythmia* 576 edit delete #33 ("unexpected death" or "sudden death") 837 edit delete #34 (cardiomyopathy or cardiomyopathies) 1494 edit delete #35 "heart infarction" 1098 edit delete #36 "heart attack*" 418 edit delete #37 "long QT syndrome" 156 edit delete #38 (syncope NEAR (heart or cardiac or cardio* or myocardial)) 120 edit delete #39 (atrial NEAR (fibril* or flutter*)) 3572 edit delete #40 ("sudden cardiac death" or "sudden arrhythmic death") 436 edit delete #41 abnormal* NEAR "heart rhythm*" 14 edit delete #42 (unstable NEAR ("heart rhythm*")) 1 edit delete #43 "left ventricular systolic dysfunction" 231 edit delete #44 ((reduced or reduction or impair*) NEAR ("left ventricular ejection fraction")) 142 edit delete #45 (LVEF NEAR (reduced or reduction or impair*)) 96 edit delete #46 LVSD 36 edit delete #47 ((heart or cardiac or myocardial) NEAR dysfunction*) 1209 edit delete #48 MeSH descriptor Cardiomyopathies explode all trees 1181 edit delete #49 "brugada syndrome" 21 edit delete #50 "arrhythmogenic right ventricular dysplasia" 10 edit delete #51 ARVD 12 edit delete #52 (surg* NEAR ("congenital heart disease")) 79 edit delete #53 ((familial or genetic or inherited) NEAR "heart disease") 28 edit delete #54 ("heart failure" or "cardiac failure" or "ventricular failure") 9933 edit delete	

	#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**	
CRD DARE AND HTA Searched 18/12/2012	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	CRD HTA 89 CRD DARE 76

	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	

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

Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S *et al*. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). *Journal of the American College of Cardiology* 2011;**57(24)**:2416-23.

Reason for exclusion: Study design

Barsheshet A, Moss AJ, McNitt S, Jons C, Glikson M, Klein HU *et al*. Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator. *Heart Rhythm* 2011;**8(2)**:212-8.

Reason for exclusion: Study design

Beshai JF,.Truong Q. Resynchronization therapy in patients with narrow QRS (RethinQ). *ACC Cardiosource Review Journal* 2008;**17(1)**:44.

Reason for exclusion: Study design

Beshai JF,.Daubert J-C. RethinQ (The Resynchronization Therapy in Normal QRS Study). *Clinical Cardiology* 2008;**31(2)**:89-90.

Reason for exclusion: Abstract (insufficient details)

Beshai JF. Resynchronization therapy in patients with narrow QRS (RethinQ). *ACC Cardiosource Review Journal* 2007;**16(12)**:30.

Reason for exclusion: Abstract (insufficient details)

Birnie, D. H., et al. "Importance of qrs duration and morphology in determining response to cardiac resynchronization therapy: Results from the resynchronization-defibrillation for ambulatory heart failure trial (RAFT)." *Heart rhythm* 2012; **Conference**: 5-S296.

Reason for exclusion: Outcomes

Boerrigter G, Costello-Boerrigter LC, Abraham WT, Sutton MG, Heublein DM, Kruger KM *et al*. Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *Journal of Cardiac Failure* 2008; **14(7)**:539-46.

Reason for exclusion: Study design

Brachmann J, Freigang K, Saggau W. Coronary artery bypass graft patch trial. *Pacing & Clinical Electrophysiology* 1993;**16(3:Pt 2)**:t-5.

Reason for exclusion: Comparator and outcomes

Breithardt G. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy): Cardiac resynchronization therapy towards early management of heart failure. *European Heart Journal* 2009;**30(21)**: 2551-3.
Reason for exclusion: Outcomes and study design

Brenyo A, Link MS, Barsheshet A, Moss AJ, Zareba W, Wang PJ *et al*. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *Journal of the American College of Cardiology* 2011;**58(16)**:1682-9.
Reason for exclusion: Outcomes

Brodine WN, Tung RT, Lee JK, Hockstad ES, Moss AJ, Zareba W *et al*. Effects of beta-blockers on implantable cardioverter defibrillator therapy and survival in the patients with ischemic cardiomyopathy (from the Multicenter Automatic Defibrillator Implantation Trial-II). *American Journal of Cardiology* 2005;**96(5)**:691-5.
Reason for exclusion: Comparator and study design

Brodsky MA, McAnulty J, Zipes DP, Baessler C, Hallstrom AP, Investigators AVID. A history of heart failure predicts arrhythmia treatment efficacy: data from the Antiarrythmics versus Implantable Defibrillators (AVID) study. *American Heart Journal* 2006; **152(4)**:724-30.
Reason for exclusion: Study design

Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators.[Erratum appears in N Engl J Med 2000 Apr 27;342(17):1300]. *New England Journal of Medicine* 1999; **341(25)**:1882-90.
Reason for exclusion: Intervention and comparator (while the study is excluded, some details of the study are discussed in the report)

Campbell P, Bourgoun M, Shah A, Foster E, Brown MW, Moss AJ *et al*. Effect of baseline right ventricular function on outcomes after CRT: An analysis of the MADIT-CRT population. *Journal of the American College of Cardiology* 2011;**Conference**:14.
Reason for exclusion: Outcomes

Campbell P, Takeuchi M, Bourgoun M, McNitt S, Goldenberg I, Zareba W *et al*. Relationship between change in ventricular size and function and BNP in patients undergoing CRT therapy: MADIT-CRT. *Journal of Cardiac Failure* 2011; **Conference**:8.

Reason for exclusion: Abstract (insufficient details)

Cappato R, Boczor S, Kuck KH, Investigators CASH. Response to programmed ventricular stimulation and clinical outcome in cardiac arrest survivors receiving randomised assignment to implantable cardioverter defibrillator or antiarrhythmic drug therapy. *European Heart Journal* 2004;**25(8)**:642-9.
Reason for exclusion: Study design

Cawley PJ,.Al-Khatib SM. Amiodarone versus implantable cardioverter defibrillator for asymptomatic nonsustained ventricular tachycardia in nonischemic dilated cardiomyopathy. *American Heart Journal* 2004;**147(5)**:790-1.
Reason for exclusion: Intervention, comparator, outcomes and study design

Chung ES, Menon SG, Weiss R, Schloss EJ, Chow T, Kereiakes DJ *et al*. Feasibility of biventricular pacing in patients with recent myocardial infarction: impact on ventricular remodeling. *Congestive Heart Failure* 2007;**13(1)**:9-15.
Reason for exclusion: Population

Chung ES, Mazur W, Menon SG, Schloss EJ, Chow T, Kereiakes DJ. Peri-infarct pacing with CRT in the early postinfarct phase to attenuate long-term remodeling. *Journal of Cardiovascular Translational Research* 2009;**2(1)**:126-9.
Reason for exclusion: Outcomes

Chung ES, Dan D, Solomon SD, Bank AJ, Pastore J, Iyer A *et al*. Effect of peri-infarct pacing early after myocardial infarction: results of the prevention of myocardial enlargement and dilatation post myocardial infarction study. *Circulation: Heart Failure* 2010;**3(6)**:650-8.
Reason for exclusion: Population

Cleland JGF. New results from the CARE-HF programme. *ESC Congress Reports* 2005;13.
Reason for exclusion: Abstract (insufficient details)

Cleland JG, Ghosh J, Freemantle N. Can cardiac-resynchronization therapy reduce mortality in patients suffering from advanced chronic heart failure? *Nature Clinical Practice Cardiovascular Medicine* 2004;**1(1)**:10-1.
Reason for exclusion: Outcome and study design

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Reason for exclusion: Population and intervention

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Reason for exclusion: Comparator and study design

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Reason for exclusion: Outcomes
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Reason for exclusion: Comparator

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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 Kingdome 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 Medtronik, 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 trial[9] 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 trial[10] 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 trial[10] 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-HF[9] 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). COMPANION[10] 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

COMPANION[10] 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 COMPANION [10] 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] Cardiac Non-cardiac	388/617(63) 301/617 (49) 222/617 (36)	199/308 (65) 164/308 (53) 84/308 (27)		0.02 <0.01
		CRT-D, n/N (%)	**OPT, n/N (%)**		
	All admissions, CRT-D 15.7, OPT 11.9[c] Cardiac Non-cardiac	372/595 (63) 284/595 (48) 207/595 (35)	199/308 (65) 164/308 (53) 84/308 (27)		0.03 <0.01

[a] Mean. [b] COMPANION[12] 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 - Cardiac - Non-cardiac	 8.6 (7.2) 5.5 (7.2) 3.8 (8.8)	 11.0 (6.9) 8.1 (6.8) 2.8 (7.1)		
	No. of admissions per patient year for cardiac procedure	0.09	0.24		<0.01

[a] COMPANION[12] 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 study[13] 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 study[15] (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

[a] Numerator 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
Strickberger *et al.*, 2003[16] Wijetunga and Strickberger, 2003[17] AMIOVIRT *Study design*: RCT USA *Number of centres*: 10 *Funding*: unrestricted research grant from the Guidant Corporation	*Intervention*: ICD + OPT (ICD were inserted using conventional non-thoracotomy techniques) *Comparator*: Amiodarone + OPT (dose: 800 mg/day for first week, 400 mg/day for one year and then 300 mg/day) *Other interventions used*: 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.	*Indication for treatment*: Non-ischemic dilated cardiomyopathy (NIDCM) and asymptomatic non-sustained ventricular tachycardia (NSVT) *Number of randomised participants*: n = 103 ICD, n=51 OPT, n=52 *Inclusion criteria*: 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. *Exclusion criteria*: Syncope; Pregnancy; A contraindication to amiodarone or defibrillator therapy or concomitant therapy with a Class I antiarrhythmic drug	*Primary outcomes:* total mortality *Secondary outcomes:* Sudden cardiac death (SCD), non-SCD, non-cardiac death, syncope, arrhythmia-free survival, QoL and costs *Method of assessing outcomes:* 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. QoL: both completed by patients at the time of randomisation and during follow-up visits. • 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) 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) 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

		or NIDCM diagnosed within 6 months.[17]	treatment (until 30-6-2001). ICD: defibrillator follow-up was performed every 4 months, including evaluation of stored electrograms, and sensing and pacing functions. *Definitions:* • Arrhythmia-free survival: freedom from death, syncope, appropriate ICD therapy, and sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). *Length of follow-up:* 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 *Recruitment*: August 1996 - September 2000

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 1and 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
Spironolactone, %	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]

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 ±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 RCTs[4]

	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
AVID investigators, 1997,[18] AVID Investigators 1999,[19] Hallstrom 1995[20] & Schron et al. 2002[21] AVID (Antiarrhythmics Versus Implantable Defibrillators) *Study design*: RCT Country or countries: USA, Canada & New Mexico[18] *Number of centres*: 56 (52 USA, 3 Canada, 1 New Mexico).[18] *Funding*: National Heart, Lung, and Blood Institute, Bethesda, Md. Contract N01-HC-25117.	*Intervention*: ICDs. Investigators chose any 'state-of-the-art' ICD meeting pre-specified criteria. *Comparator*: Best contemporary antiarrhythmic drugs (AADs) 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). *Other interventions used*: aspirin, beta-blockers, and ACE inhibitors when clinically appropriate.	*Indication for treatment*: resuscitated from near-fatal ventricular fibrillation; or symptomatic sustained ventricular tachycardia with hemodynamic compromise. *Number of randomised participants*: 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. QoL substudy[21]: n=800. ICD n=416, AAD n=384 *Inclusion criteria*: 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 *Exclusion criteria*: contra-indication to amiodarone or ICD	*Primary outcome:* Overall mortality *Secondary outcomes:* cost and quality of life *Other:* ICD shock, sustained arrhythmia, syncope *Method of assessing outcomes:* Patients evaluated every 3 months and at the time of events. Cause of death reviewed by Events Committee. QoL substudy[21] - baseline (before randomisation), 3, 6 and 12 months after randomisation. - 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. - the 46 item patient concerns checklist (disease-specific) score range 0-46, higher sores indicate

		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]	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). Defibrillator shocks categorized as appropriate or inappropriate on the basis of clinical presentation, RR intervals, and electrograms. *Length of follow-up:* Mean 18.2 months (SD 12.2)[18] For QoL sub-study follow-up was 1 year.[21] *Recruitment*: June 1st 1993, to April 7th 1997.

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 - NYHA class I or II - NYHA class III	 45 48 7	 40 48 12	 [a]
Angina at enrolment, % - no angina - Canadian Cardiovascular Society (CCS) class I or II - CCS class III	 64 34 2	 65 33 2	
LVEF, mean (SD) - Median time from index event to measurement, days	0.32 (0.13) 3	0.31 (0.13) 3	
Findings on base-line electrocardiogram[b] - heart rate beats/min, mean (SD) - PR interval msec, mean (SD) - QRS complex msec, mean (SD)	 77 (18) 178 (37) 116 (26)	 78 (17) 183 (37) 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, %			
- atrial fibrillation or flutter	21	26	[a]
- 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)	**numbers not reported**[e]				
	Index VF	**Index VT**			<0.001 for VT vs VF
- at 3 months	15	36			
- at 1 year	39	68			
- at 2 years	53	81			
- at 3 years	69	85			
% 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	

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.)

- A Kaplan-Meier plot of overall survival is presented. The survival figures represent a decrease in death rates (±95% CI) of 39±20%, 27±21%, and 31±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 - at 2 years		 3 5		
Death due to pulmonary toxicity, n		1		
Thyroid replacement medication, % - at 1 year - at 2 years	 1 1	 10 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)				

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.

- 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	

Comments:

- Hazard ratios and 95% CIs estimated from a figure in the paper using Enguage 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 (± 95% CIs) attributable to the ICD were 37±22% at 1 year, 24±22% at 2 years, and 29±33% at 3 years. Estimates adjusted for the use of beta-blockers were unchanged from the unadjusted values (data not reported in paper).

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 substudy[21]	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 substudy[21]			
Outcomes	**ICD, n=416**	**AAD, n=384**	**p value**
SF-36 PCS score, mean (SD) - baseline - 12 months	 37.4 (10.9) 40 (10.5)	 36.5 (11.2) 38 (17)	 = 0.3
SF-36 MCS score, mean (SD) - baseline - 12 months	 45.9 (11.8) 49 (16.5)	 47.5 (11.5) 48 (17)	 =0.006
Patient concerns checklist baseline - follow-up	15.9 (8.6) nr	16.2 (8.9) nr	=0.06 =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 - SF-36 MCS score - Patient concerns	 -2.25 (-3.32, -1.18) p<0.001 -2.32 (-3.76, -0.88) p=0.002 1.84 (0.91, 2.76) p<0.001	 -1.64 (-2.89, -0.41) p=0.009 -0.51 (-1.97, 0.94) p=0.5 0.91 (0.07, 1.75) p=0.03	
Impact of ICD shocks on quality of life [i] - SF-36 PCS score - SF-36 MCS score - Patient concerns	 -1.45 (-2.74, -0.18) p=0.03 -1.82 (-3.56, -0.08) p=0.04 2.15 (1.07, 3.23) p<0.001		
ICD shocks - experienced ≥1 shock during 1st year of follow up, n/N (%) experienced 1 or 2 shocks experienced ≥3 shocks - proportion of shocks considered appropriate	ICD, n=373[i] 144/373 (39%) 71/144 (49%) 73/144 (51%) 94%		

Comments: Values in italics obtained from Figure in paper using Enguage 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.

- The occurrence of ≥1 versus no shocks was independently associated with significant reductions in metal 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

- *Allocation to treatment groups*: Stratified by clinical site and index arrhythmia[20] 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 costs[20] 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 substudy[21] both appropriate and inappropriate shocks were included in the analysis. Because follow-up QoL values cannot be reliable 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 or heart failure, and beta-blocker use to assess the independent relationship of variables with QoL. All analyses were ITT and $p\leq0.05$ 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 substudy[21]: 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 substudy[21]: 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 substudy[21] 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 RCTs[4]

	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
Bigger *et al.*, 1997[25-28]; Namerow *et al*., 1999[29] Spotnitz *et al.*, 1998[30] CABG Patch (Coronary Artery Bypass Graft Patch trial) *Study design*: RCT United States and Germany *Number of centres*: 37 (35 in USA, 2 in Germany) *Funding*: NHLBI grants HL-48120 and HL-48159, and a grant from Guidant/CPI, St. Paul, Minn.	*Intervention*: 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. *Comparator*: control group, OPT (subject to caveats described below). No defibrillator therapy[25] and no specific therapy for ventricular arrhythmias.[31] *Other interventions used*: ICD group: The protocol prohibited the use of antiarrhythmic drugs for asymptomatic ventricular	*Indication for treatment*: Patients scheduled for CABG surgery and at risk for sudden death (LVEF < 0.36 and abnormalities on an ECG). Prophylactic. *Number of randomised participants*: n = 900 ICD, n= 446 Control, n= 454 *Inclusion criteria*: Scheduled for CABG surgery, <80 years old, LVEF <0.36, marker of arrhythmia: abnormalities on an ECG (duration filtered QRS complex ≥ 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). *Exclusion criteria*: history of sustained ventricular tachycardia or fibrillation, diabetes	*Primary outcomes:* mortality *Secondary outcomes:* Not explicitly stated but quality of life and adverse events reported. *Method of assessing outcomes:* Follow-up visits every 3 months QoL study[29]: 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

	arrhythmias and specified that patients without contraindications should be treated with aspirin. 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.	mellitus with poor blood glucose control or recurrent infections, pervious or concomitant aortic-or mitral-vale 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.	perception that heath status has become worse) 3) Items on employment status, and body image (two two-item scales: satisfaction with appearance and satisfaction with scar). Higher scores = greater satisfaction. *Length of follow-up:* Mean of 32 months *Recruitment*: 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]

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.

- 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%, χ^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)	χ^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

Comments: [c] Total number of deaths and number of cardiac deaths reported differs slightly between the main trial publication[25] and that specifically reporting mechanism of death.[27] Results from the latter paper are reported above (main trial publication[25] 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.

- 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**

- 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**[e]
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 - other reasons	8 3		

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 heath 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.

- 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 - infection - ICD reached end of service period and not replaced - patient request	40 19 5 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 though 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'Briend-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 substudy[29]: 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 substudy[29]: 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 paper[25] 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 study[29] 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 RCTs[4]

	Judgement[j]	**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
Kuck *et al.*, 2000[32] CASH (Cardiac Arrest Study Hamburg) *Study design*: RCT Germany *Number of centres*: multicentre but number of centres not reported. *Funding*: supported by a grant from CPI/Guidant Corporation and ASTRA GmbH.	*Intervention*: ICD Cardiac Pacemakers, Inc. devices were used (Ventak AID, Ventak AICD, Ventak P, Ventak PRx, Ventak Mini) From recruitment start to June 1991 participants received an epicardial device (n=55). From July 1991 participants received an endocardial device (n=44). 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. *Comparator*: Antiarrhythmic drugs (AAD) either amiodarone or metoprolol (propafenone arm originally included but eliminated). Amiodarone oral loading dose of 1000mg/day for 7 days, followed by maintenance dose of 200 to 600mg/day.	*Indication for treatment*: 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) *Number of randomised participants*: n =349, but this dropped to 288 after termination of the propafenone arm. ICD, n= 99 Amiodarone, n= 92 metoprolol, n= 97 Some evidence for error in participant numbers &/or missing data. Details in methodological comments.	*Primary outcomes:* All-cause mortality *Secondary outcomes:* Sudden death Recurrence of cardiac arrest at 2-year follow-up *Method of assessing outcomes:* Evaluations at 2, 4, 6, 12, 18, and 24 months then every 12 months thereafter. Sudden death defined as death within 1 hour after the onset of symptoms or an unwitnessed death. Cardiac arrest defined as sudden circulatory collapse requiring resuscitation. *Length of follow-up:* Minimum of 2 years, study terminated March 1998. Mean 57 (SD 34) months.

	Metoprolol initiated at 12.5 to 25 mg/day and increased within 7 to 14 days to a maximum of 200mg/day if tolerated. Details reported for propafenone (study arm terminated early due to interim analysis) in other publications[33-35] – excluded comparator). *Other interventions used*: concurrent therapies at discharge reported (see below) but doses not provided.	*Inclusion criteria*: not reported. Rate was the only criterion selected for detection of a sustained ventricular arrhythmia. *Exclusion criteria*: cardiac arrest occurred within 72 hours of an acute myocardial infarction, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect.	*Recruitment:* March 1987 to March 1992 (propafenone arm terminated early) or to 1996 (remaining study arms)

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**

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)		
		43.5% (33.2 to 54.2)	45.4% (35.2 to 55.8)	0.845[b]
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)		
		29.5% (19.4 to 40.8)	35.1% (25.2 to 48.8)	0.467[b]
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	

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.

- Survival curves presented for
  - 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 - Hyperthyroidism, - Drug discontinuation required		 0 3 (3.3%) 9 (9.8%)	 nr 10 (10.3%)	
- Perioperative deaths, or for drug arms deaths within the same time frame.	5 (5.1%) 3 (5.4%) epicardial ICD, 2 (4.5%)	2 (1.1%) 2	 0	p=0.029

RESULTS				
Outcomes	**ICD, n=99**	**Amiodarone, n=92**	**Metoprolol, n=97**	**p value**
	endocardial ICD			
Other complications - Infection - Haematoma or seroma - Pericardial effusion - Pleural effusion - Pneumothorax - Dislodgement or migration of system leads - Device dysfunction Overall complication rate	 3 (explantation required for 2) 6 1 3 1 3 5 23.0% (including an explantation rate of 2.1%)			
Comments:				

Methodological comments

- *Allocation to treatment groups*: 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.
- *Blinding*: Not reported
- *Comparability of treatment groups*: 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.
- *Method of data analysis*: 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).
- *Sample size/power calculation*: 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.
- *Attrition/drop-out*: 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

- *Generalisability*: 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 RCTs[4]

	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 *et al.*, 2002[36] The German dilated cardiomyopathy study investigators 1992[37] CAT (Cardiomyopathy Trial) *Study design*: RCT	*Intervention*: ICD + OPT. Transvenous electrode systems (Endotak, Cardiac Pacemakers, Inc). Pulse generators Ventak P2, P3, PrX II, CPI. Defibrillation threshold of < 20J mandatory. VT zone with detection rate of 200 bpm programmed for all	*Indication for treatment*: recent onset idiopathic dilated cardiomyopathy (DCM) and impaired LVEF & without documented symptomatic VT. *Number of randomised participants*: n = 104 ICD, n= 50 Control, n= 54	*Primary outcomes:* all-cause mortality at 1 year *Secondary outcomes:* Heart transplantation, cardiac mortality (sudden and non-sudden cardiac death), sustained VT (adequate ICD therapy), symptomatic ventricular

(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.	*Inclusion criteria*: NYHA class II or III LVEF ≤ 30% LVEDD not reported QRS interval not reported Aged 18-70 years symptomatic DCM ≤ 9 months. *Exclusion criteria*: 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. *Method of assessing outcomes:* Visits every 3 months & encouraged to make additional visit if the first shock, cluster of shocks or syncope had occurred. Electrograms stored on devices. *Length of follow-up:* 2 years *Recruitment*: 1991 to 1997

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

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.

- 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		

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.

- 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 paper[37]
- 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 bardycardias 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 RCTs[4]

	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
Connolly *et al.*, 2000[38] Connolly *et al.*, 1993[39] Irvine *et al.*, 2002[40] Sheldon *et al.*, 2000[41] (no additional data extracted) Bokhari *et al.*, 2004[42] CIDS (Canadian Implantable Defibrillator Study) *Study design*: RCT Canada Australia US *Number of centres*: Canada: 19 Australia: 3 US: 2 *Funding*: Medical Research Council of Canada	*Intervention*: ICD Implant criteria met with 3 consecutive successful defibrillations at ≥10 J below maximum device output. Either thoracotomy or nonthoracotomy lead systems used. *Comparator*: Amiodarone ≥1200 mg/day for ≥ 1 week in hospital, ≥400 mg/day for ≥10 weeks, then ≥300 mg/day. Dose could be lowered to a minimum of 200 mg/day for intolerable side-effects. *Other interventions used*: Antiarrhythmic drugs could be used in both groups to control supra-ventricular or nonsustained ventricular tachycardias that were symptomatic or	*Indication for treatment*: Previous sustained ventricular arrhythmia *Number of randomised participants*: ICD randomised: 328 ICD received implant: n=310 Amiodarone, n=331 For QOL: 317 randomised and eligible 287 survived to 12 months 178 had data at 6 and 12 months *Inclusion criteria*: 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 ≤35%; or unmonitored syncope with subsequent	*Primary outcomes:* Death from any cause. *Secondary outcomes:* Arrhythmic death (based on clinical classification of cardiac deaths, Hinkle and Thaler (ref provided), QoL[40], side effects, arrhythmia recurrence. *Method of assessing outcomes:* 2 and 6 months after randomisation then every 6 months. All deaths adjudicated by an External Validation Committee not blinded to treatment. QoL:[40] Emotional functioning: Rand Corporations 38-item Mental Health Inventory HRQoL: Nottingham Health Profile Assessed in hospital

	might cause discharge of the ICD.	documentation of either spontaneous VT≥10 s or sustained (≥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. *Exclusion criteria*: Amiodarone or ICD not considered appropriate, excessive perioperative risk for ICD implantation, previous amiodarone therapy for ≥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. *Length of follow-up:* ICDs: mean 3.0 years Amiodarone: mean 2.9 years; *Recruitment*: 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).

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 - VT with syncope - Other VT - Unmonitored syncope	 45.1 15.9 23.8 15.2	 50.1 10.6 26.9 12.4	
Primary cardiac diagnosis, % - Ischaemic heart disease with myocardial infarction - Ischaemic heart disease without myocardial infarction - Dilated cardiomyopathy - Valvular heart disease - Other heart disease - No heart disease	 75.6 7.3 8.5 1.2 3.7 3.7	 73.1 9.1 10.6 3.0 2.4 1.8	
Congestive heart failure, % - NYHA Class 1 or 2 - NYHA Class 3 or 4 - None	 51.2 37.8 11.0	 49.5 39.9 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 - Inducible VT or VF	62.2 154/204 (75.7%)	62.8 147/208 (70.7%)	
Coronary angiography, % - Ever done - 3-Vessel disease	 75.6 19.0	 78.2 18.9	
Chest x-ray, % - Interstitial abnormality (document on previous standard chest x-ray report) - Other abnormality	 15.5 31.4	 17.6 34.6	
Current pharmacological therapy			
Cardiac history, % - Angina pectoris - Myocardial infarction - Coronary artery bypass grafting surgery	 51.2 77.1 31.4	 57.1 75.8 28.1	
Previous treatment			
Medical conditions, % - Liver disorder - Respiratory disease - Thyroid disease	 1.5 17.5 5.8	 2.7 17.8 3.9	
Comments: • 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) - in patients with nonthoracotomy lead system (n=277)	 1/33 (3.3%) 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, % Total mortality - 1 year - 2 years - 3 years Arrhythmic mortality - 1 year - 2 years - 3 years	 9.46% 14.75% 23.32% 4.37% 6.68% 9.77%	 11.18% 20.97% 27.03% 6.23% 9.74% 11.88%	ARR[b], RRR 1.72%, 15.4% 6.22%, 29.7% 3.71%, 13.7% 1.86%, 29.9% 3.06%, 31.4% 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 antiarrythmic 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	

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.

- 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 mobitity[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 neuropahy		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 centre[42]

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 centre[42]

RESULTS[42]			
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)[g]
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)		

- 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 (≤ 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≤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 completing 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 date 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 RCTs[4]

	Judgement[a]	**Support for Judgement**
Selection bias		
Random sequence generation	Unclear	'Central randomisation was stratified by clinical centre and LVEF (≤ 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
Nademanee *et al.*, 2003[43] DEBUT (Defibrillator versus B-Blockers for Unexplained Death in Thailand) *Study design*: RCT - pilot study - main study Country Thailand *Number of centres*: Not reported. *Funding*: Grant-in Aid from Cardiac Rhythm Management and Guidant Corporation, St Paul, Minn.	*Intervention*: ICD (Guidant Corporation, St Paul, Minn) *Comparator*: B-blockade (long-acting propranolol 40 mg/day up to 160 mg/day) *Other interventions used*: Other B-blocking agents or amiodarone permitted if intolerable side-effects developed from propranolol or if frequent shocks from recurrent VF developed.	*Indication for treatment*: Sudden Unexplained Death Syndrome (SUDS) survivors or probable survivors. *Number of randomised participants*: Pilot study n=20 ICD, n=10 B-Blocker n=10 Main study n = 66 ICD, n=37 B-Blocker, n=29 (155 screened, 88 not randomised, 1 randomised but refused ICD) *Inclusion criteria*: SUDS survivor defined as a healthy subject without structural heart disease who had survived unexpected VF or cardiac arrest after successful resuscitation. 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.	*Primary outcomes:* Death from all causes *Secondary outcomes:* Recurrent VT/VF or cardiac arrest. *Method of assessing outcomes:* First month, 3-month intervals. *Length of follow-up:* Maximum 3 years after randomisation. Median follow-up not reported. *Recruitment*: Pilot study January 1995 to April 1997 Main study May 1997 to December 2000 (trial terminated by Data Safety Monitoring Board).

		Exclusion criteria: 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 (≥300bpm), 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 (≥300bpm), 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 RCTs[4]

	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 *et al.*, 2004[44] Ellenbogen et al. 2006[45] Passman et al. 2007[46] Kadish et al. 2000[47] Schaechter et al.	*Intervention*: 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	*Indication for treatment*: nonischaemic cardiomyopathy & moderate-to-severe left ventricular dysfunction. *Number of randomised participants*: n = 458 ICD + OPT, n= 229	*Primary outcomes:* death from any cause *Secondary outcomes:* sudden death from arrhythmia Quality of life[46]

2003[48] DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) *Study design*: RCT USA & Israel *Number of centres*: 48 (44 USA, 4 Israel) *Funding*: St Jude Medical	at rate of 180bpm *Comparator*: OPT 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. *Other interventions used*: none reported.	OPT, n= 229 *Inclusion criteria*: 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 21-80[45] *Exclusion criteria*: 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.	(QoL) *Method of assessing outcomes:* 3 month intervals 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. ICD shocks assessed at each follow-up or when indicated by symptoms[46] 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] *Length of follow-up:* 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. *Recruitment*: July 1998 to June 2002

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.

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.

- 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.

- 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:

- Six pre-specified subgroup analyses (age, sex, LVEF, QRS interval, NHYA 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 ≥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

- *Allocation to treatment groups*: Randomisation stratified by centre and to the use or non-use of amiodarone for supraventricular arrhythmias.
- *Blinding*: 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 RCTs[4]

	Judgement[e]	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	

[e] 'Low risk', 'high risk' or 'unclear risk' of bias

DINAMIT

Reference and design	Intervention and Comparator	Participants	Outcome measures
Hohnloser *et al*. 2004,[49] 2000[50] DINAMIT (Defibrillator In Acute Myocardial Infarction Trial) *Study design*: RCT 12 countries worldwide *Number of centres*: 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)	*Intervention*: 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).	*Indication for treatment*: recent MI (6-40 days), reduced LVEF and impaired cardiac autonomic function *Number of randomised participants*: n = 674 ICD, n= 332 OPT, n=342 *Inclusion criteria*: • 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. *Exclusion criteria*:	*Primary outcomes:* death from any cause. *Secondary outcomes:* death due to cardiac arrhythmia *Method of assessing outcomes:* 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

Funding: Supported by a grant from St. Jude Medical, Sunnyvale, California.	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. *Comparator*: OPT (best conventional medical therapy). *Other interventions used*: 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).	• 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	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). 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. *Length of follow-up:* mean follow-up 30 months (SD 13), maximum 4 years from randomisation. *Recruitment*: April 1998 – June 2002

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. • 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. • 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: • 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 RCTs[4]

	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 *et al.*, 2009[51], Steinbeck 2004[52] IRIS (Immediate Risk Stratification Improves Survival) *Study design*: RCT Austria, Czech Republic, Germany, Hungary, Poland, Russia, Slovak Republic *Number of centres*: 92 *Funding*: grants from Medtronic Bakken Research Center, AstraZeneca,	*Intervention*: 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. *Comparator*: OPT (not further described) *Other interventions used*: not stated	*Indication for treatment*: Recent MI (≤ 31days) and predefined markers of elevated risk. *Number of randomised participants*: n = 898 ICD, n= 445 OPT, n= 453 *Inclusion criteria*: Predefined markers of elevated risk, at least one of: - heart rate ≥ 90 bpm on first available ECG (within 48 hrs of MI) and LVEF ≤ 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). *Exclusion criteria*: ventricular arrhythmia before the index MI or more than 48 hours after the event and required treatment. NYHA class IV,	*Primary outcomes:* overall mortality *Secondary outcomes:* 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 *Method of assessing outcomes:* 3 and 6 months after randomisation & then 6-months intervals. *Length of follow-up:* average 37 months (range 0-106) *Recruitment*: 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

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) - criterion 2 only (NSVT) - criteria 1 and 2	 299 (67.2) 99 (22.2) 47 (10.6)	 303 (66.9) 109 (24.1) 41 (9.1)	
LVEF %, mean (SD) - criterion 1 only - criterion 2 only - criteria 1 and 2	34.6 (9.3) 32.2 (6.3) 45.9 (10.8) 29.6 (7.0)	34.5 (9.4) 31.9 (6.7) 44.8 (11.0) 31.4 (6.7)	
Heart rate	not reported	not reported	
Electrophysiology findings	not reported	not reported	
Medical therapy on admission n/N (%) - antiplatelet agents - beta-blockers - ACE inhibitors	 438/443 (98.9) 394/442 (89.1) 361/443 (81.5)	 442/452 (97.8) 388/453 (85.7) 373/453 (82.3)	
ST-elevation myocardial infarction (STEMI), n (%)	341 (76.6)	348 (76.8)	
Reperfusion in STEMI, n/N (%) - none - percutaneous transluminal coronary angiography (PTCA) - thrombolytic therapy, with or without PTCA	 43/340 (12.6) 243/340 (71.5) 54/340 (15.9)	 48/348 (13.8) 253/348 (72.7) 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:

- 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 - up to 30 days after implantation - during follow up	65/415 (15.7%) patients 76 complications 19 (4.6%) patients 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.

ICDs removed in 15, and 39 in OPT group were given ICDs. • *Other*: 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.
General comments • *Generalisability*: people within 31 days of an MI • *Outcome measures*: appear appropriate • *Inter-centre variability*: not reported on • *Conflict of interests*: 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 RCTs[4]

	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**
Moss *et al.*, 1996;[53] MADIT executive Committee 1991;[54] MADIT (Multicenter Automatic Defibrillator Implantation Trial) *Study design*:	*Intervention*: ICD + medical therapy 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. Late in the trial, a	*Indication for treatment*: Previous myocardial infarction and left ventricular dysfunction. . *Number of randomised participants*: n = 196 ICD, n=95 (transthoracic stratum n=45; transvenous stratum n=50) OPT, n=101(transthoracic stratum n=53; transvenous stratum n=48) • Total transthoracic stratum: n=98 • Total transvenous stratum: n=98	*Primary outcomes:* death from all causes *Secondary outcomes:* none specified. Other outcomes reported: prevalence of medications; adverse events; impact of 11 pre-selected baseline characteristics and medication type on

RCT USA and Europe *Number of centres*: 32 (USA: 30, Europe: 2) *Funding*: research grant from CPI/Guidant Corporation, St. Paul, Minn (also donated ICDs)[54].	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). *Comparator*: conventional medical therapy Attending physician elected medical therapy and use of FDA approved antiarrhythmic medications in both groups. *Other interventions used*: none reported	Crossover: n=16 • ICD, n=5 (no ICD fitted) • Deactivated ICD, n=2 • OPT, n=11 (ICD fitted) Loss to follow up: ICD, n=1; OPT, n= 2 *Inclusion criteria*: 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). *Exclusion criteria*: 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.	observed hazard ratio for overall mortality. *Method of assessing outcomes:* 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. 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. *Length of follow-up:* < 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). *Recruitment*: 27/12/1990

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 RCTs[4]

	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 *et al.*, 2002;[55] 1999;[56] Greenberg *et al*., 2004;[57] Noyles *et al*., 2007[58] MADIT II (Multicenter Automatic Defibrillator Implantation Trial)	*Intervention*: ICD + Conventional Medial Therapy Transvenous defibrillator systems (Guidant, St. Paul, Minn) and standard defibrillator implant techniques were used. ICD	*Indication for treatment*: High risk cardiac patients with prior MI and advanced left ventricular dysfunction *Number of randomised participants*: n=1232 ICD, n=742 OPT, n=490 Crossovers: n=54 • ICD, n=32 (n=21 (2.8%)	*Primary outcomes:* All-cause mortality *Secondary outcomes:* adverse events; HRQoL, economic outcomes, incidence of SCD, incidence of cardiac death due to progressive LV failure. *Method of assessing outcomes:* patients followed

Study design: RCT USA and Europe *Number of centres*: 76 (USA: 71, Europe: 5) *Funding*: research grant from Guidant, St. Paul, Minn to the University of Rochester School of Medicine and Dentistry	programming and prescribing medications were at the discretion of the patients' physicians. *Comparator*: Conventional Medical Therapy (OPT) The appropriate use of beta-blockers, angiotensin-converting–enzyme inhibitors and lipid-lowering drugs was strongly encouraged in both study groups. *Other interventions used*: none reported	no ICD fitted; n=11 (1.5%) ICD removed (9 heart transplants) • Deactivated ICD, n=12 (usually due to terminal illness) • OPT, n 22 (4.5%) ICD fitted Loss to follow up: ICD, n=2; OPT, n= 1 had a status unknown *Inclusion criteria*: • 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) *Exclusion criteria*: • indication approved by the FDA for ICD (and patients who met the MADIT 1 criteria for ICD[56]) • NYHA class IV at enrolment • undergone coronary	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) *Cause of death definitions[57]: SCD (modified Hinkle-Thaler system)*: 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. SCD sub-classified into those with and without symptoms of severe LV dysfunction NYHA ≥III HF. *Non-SCD:* patients who died of progressive cardiac failure or patients who did not meet the time criteria for sudden death. *Progressive cardiac failure:* 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). *SCD (clinical classification):* 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. *Multiple cause category:* presence of several medical problems in which CHD

		revascularisation within last 3months • 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). *Length of follow-up:* average 20 months (range 6 days to 53 months; HUI3: up to 36 months[58]) *Recruitment*: 11-07-1997 to 20-11-2001.

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 subgroup[57]	**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
Comments: [d] adjusted for stopping rules; • 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)	

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.

[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).

- 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

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)

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 SCD[57]	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 mediations 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 analyse 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 events[57] 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 scores[58] 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 RCTs[4]

	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 *et al.*, 2005[59] Packer *et al.*, 2009[60] Michell *et al.* 2008[61] Mark *et al.* 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

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) *Study design*: RCT US (99%[62]), Canada, & New Zealand[61] *Number of centres*: 148[61] *Funding*: Grants from NHLBI, NIH, and by Medtronic, Wyeth-Ayerst Laboratories, and Knoll Pharmaceuticals.	sustained VT or VF). Detection rate of ≥187 bpm. Antitachycardia pacing therapies not permitted. *Group 2*: 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. *Group 3:* placebo, administered in the same way as amiodarone. *Other interventions used*: All participants received optimal HF medical therapy[60]. 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]	*Number of randomised participants*: n = 2521 ICD, n= 829 Amiodarone, n= 845 Placebo, n= 847 *Inclusion criteria*: NYHA class II or III chronic, stable CHF due to ischaemic or non-ischaemic causes. LVEF ≤ 35% ≥ 18 years Ischaemic CHF defined as LV systolic dysfunction associated with ≥ 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. *Exclusion criteria*: None stated	36-item Short Form (SF-36) Mental Health Inventory 5 (MHI-5) *Secondary outcomes:* 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. *Method of assessing outcomes:* Every 3 months with alternating clinic visits and telephone calls. Data downloaded from ICD memory regularly at visits. 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] QoL[62] - 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

			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. 'Bed days' defined as number of days in bed all or most of the day in the last 42 days. 'Disability days' defined as number of days (excluding bed days) patient cut down usual activities for health reasons. MLHFQ scored 0-105, higher score indicates worse function, clinically significant difference approximately 5 points. Health status utility 0 (dead) to 1 (excellent) assessed with time trade off technique. Global health rated on a scale of 0 (dead) -100 (excellent health) and 5-point difference (one quarter of 1 SD) approximating clinical significance. *Length of follow-up:* to October 31 2003. Median follow-up for surviving patients 45.5 months (range 24 - 72.6 months). *Recruitment*: Sept 1997 to July 2001

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 study[62] (ICD n=816; Amiodarone n=830; Placebo n=833) but have not been extracted.
- Baseline characteristics are reported by race[61] 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: • 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.

- 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 analyses[59-61]				
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] - cardiac				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.

- 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 study[62]	**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 study[62]

Outcomes	ICD, n= 816		p value
SF-36 score, mean change	Received shock[e] 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

Comments: [e]: 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 study[62]: 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 study[62]: 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 study[62]: 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. • *Other:* 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 • *Generalisability*: 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. • *Outcome measures*: Appear appropriate. • *Inter-centre variability*: For QoL study specific training was provided at each site to ensure standardisation of data collection.[62] No other details provided. • *Conflict of interests*: 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 RCTs[4]

	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
Cleland *et al.*, 2005;[9] 2001;[63] 2006;[64] 2007;[65] 2009;[66] Gras *et al.*, 2007;[67] Gervais *et al.*, 2009;[68] Ghio *et al.*, 2009[69] CARE-HF (Cardiac Resynchronization - Heart Failure) *Study design*: RCT Country or countries: European countries including UK, France, Germany, Switzerland, Italy[9] *Number of centres*: 82[9] *Funding*: Supported by a grant from Medtronic	*Intervention*:[9] CRT-P + Medical therapy. CRT (Medtronic InSync or InSync III device) providing atrial-based, biventricular stimulation + standard pharmacological therapy. Standard RV and Attain (Medtronic) LV leads. Backup atrial pacing set at 60 bpm, interventricular delay set at zero, atrioventricular delay echocardio-graphically optimised. *Comparator*:[9] Medical therapy (standard pharmacological therapy only) *Other interventions used*: None reported. Standard medications adjusted if needed at follow up visits.	*Indication for treatment*:[9] NYHA III or IV due to LVSD and cardiac dyssynchrony receiving standard pharmacological therapy *Number of randomised participants*:[9] n = 813 CRT-P + medical therapy, n= 409 Medical therapy alone, n= 404 *Inclusion criteria*:[9] NYHA class III or IV despite standard pharmacological therapy, LVEF ≤35%, LVEDD ≥30mm (indexed to height), QRS interval ≥120ms. 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. Age ≥18 years, heart failure for ≥ 6 weeks *Exclusion criteria*:[9] Major cardiovascular event in previous six weeks, conventional indications for a	*Primary outcomes:*[9] Composite of death from any cause or an unplanned hospitalisation for major cardiovascular event (only first hospitalisation counted). For extension phase: death from any cause[64] *Secondary outcomes:*[9] Death from any cause, composite of death from any cause and unplanned hospitalisation for HF 90 day NYHA class 90 day QoL For extension phase: mode of death.[64] *Method of assessing outcomes:*[9] Assessment at baseline, 1, 3, 6, 9, 12 & 18 months. Then at 6 month intervals. For QoL[66] baseline, 3 months, then disease specific instrument only at 18 months & study end. 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

		pacemaker or an ICD, heart failure requiring continuous intravenous therapy, atrial arrhythmias.	considered worse than death) *Length of follow-up:*[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] *Recruitment*: January 2001 to March 2003[9]

Participant characteristics[9]	**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:

- 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 - non-cardiovascular - not classifiable	167/202 (83) 34/202 (17) 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					
Outcomes[9]	**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 analysis[65] 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 analyses[68] 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 paper[69] 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 RESULTS[66]

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 RESULTS[66]			
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 publication[9] and those reported in this paper.[66] The reasons for these minor differences are not clear.

Adverse effects of treatment[9]	**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:

- 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 paper[9] 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)
Spironolactone, 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 QoL[66], and echocardiographic outcomes[69]) 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 outcomes[69] 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 interested 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 RCTs[4]

	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]	*Intervention*: OPT and either CRT-P Guidant model 1241 Contak TR or CRT-D Guidant model 1823 Contak CD	*Indication for treatment*: Advanced chronic heart failure and intraventricular conduction delays *Number of randomised*	*Primary outcomes:* All-cause mortality and all cause hospitalisation (composite end point) *Secondary outcomes:* Cardiac morbidity

Bristow et al., 2000[72] COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) *Study design*: RCT USA *Number of centres*: 128 *Funding*: Guidant corporation, St Paul, Minn.	*Comparator*: 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. *Other interventions used*: None reported	*participants*: n = 1520 CRT-P, n=617 CRT-D, n=595 OPT, n=308 *Inclusion criteria*: NYHA class III, IV; QRS ≥120 ms; PR interval > 150 ms; LVEF ≤35%; OPT; LVEDD ≥ 60 mm; ≥18 years; sinus rhythm. *Exclusion criteria*:[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.	All-cause mortality Cardiac hospitalisation Six minute walk NYHA class before and after treatment Adverse events Health related QoL – Minnesota Living with Heart Failure questionnaire *Method of assessing outcomes:* 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. Clinical evaluations at baseline, 1 week, 1 month, then 3 monthly[72] *Length of follow-up, median:* 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 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 *Recruitment*: Jan 2000-Dec 2002

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 - diastolic	 110 68	 112 68	 112 64	
Ischemic cardiomyopathy, %	54	55	59	
Pharmacological therapy, % - Beta-blocker - Spironolactone - ACE inhibitor - ACE inhibitor or angiotensin blocker - Loop diuretic	 68 53 70 89 94	 68 55 69 90 97	 66 55 69 89 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 - 12 month rate	 414 56%	 390 56%	 216 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 - 12month all-cause mortality rate	 131/617 (21.2%) 15%	 105/595 (17.6%) 12%	 77/308 (25.0%) 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 - 12 month event rate	 338 45%	 312 44%	 188 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 - 12 month event rate	 237 31%	 212 29%	 145 45%	 0.66 (0.53,0.87), 0.002; 0.60 (0.49, 0.75), <0.001
• [a]Kaplan-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%)	
- pacer / 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%)		

- 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.
- [d]States 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 - 6 months	 (n=422) 33 (99) (n=373) 40 (96)	 (n=420) 44 (109) (n=378) 46 (98)	 (n=170) 9 (84) (n=142) 1 (93)	 p<0.001; p<0.001 p<0.001; p<0.001
Increase in quality of life [e], %, mean change (SD) - 3 months - 6 months	 (n=510) -24 (27) (n=460) -25 (26)	 (n=514) -24 (28) (n=478) -26 (28)	 (n=243) -9 (21) (n=207) -12 (23)	 p<0.001; p<0.001 p<0.001; p<0.001
Proportion of patients with improvement in NYHA class symptoms, % - 3 months - 6 months	 (n=551) 58 (n=489) 61	 (n=543) 55 (n=497) 57	 (n=242) 24 (n=199) 38	 p<0.001; p<0.001 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:

- [e]21 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: [f] 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 RCTs[4]

	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 *et al.*, 2002[11] St John Sutton *et al.*, 2003 [73] Abraham 2000[74] FDA report[75] MIRACLE (Multicenter InSync Randomised Clinical Evaluation) *Study design*: RCT USA & Canada *Number of centres*: 45 *Funding*: Medtronic, Inc,	*Intervention*: Optimal medical therapy, CRT-P VDD 30. InSync model 8040, Medtronic Inc. 3 pacing leads. *Comparator*: Optimal medical therapy CRT-P OFF: VDI 30 (ventrical paced, A&V sensed, no response to sensing) InSync model 8040, Medtronic Inc. *Other interventions used*:	*Indication for treatment*: Moderate to severe heart failure and a prolonged QRS interval *Number of randomised participants*: n = 453 CRT-P, n= 228 OPT, n= 225 *Inclusion criteria*:[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. *Exclusion criteria*:[11;74] Pacemaker or ICD; indication for or contra-indication to cardiac pacing; cardiac or cerebral ischemic	*Primary outcomes:* NYHA class QoL 6 minute walk distance *Secondary outcomes:* All-cause mortality Heart failure hospitalisations Exercise capacity – peak 0_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 *Method of assessing*

Minneapolis, Minn	Medication for heart failure for both groups kept constant	event ≤ 3-months; AF ≤ 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 ≤ 3 months; life expectancy < 6 months.	*outcomes:* Questionnaires at baseline, 1, 3 & 6 months. Clinical Events Review committee adjudicated adverse events / endpoints.[74] *Length of follow-up:* 6 months *Recruitment*: Nov 1998 - Dec 2000

Participant characteristics (pre-randomisation and ≤ 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 intropic 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 RCTs[4]

	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
Cazeau *et al.*, 2001[76] MUSTIC (Multisite Stimulation in Cardiomyo-pathies) *Study design*: Randomised cross-over study Europe (France, Germany, Italy, Sweden, Switzerland, UK) *Number of centres*: 15 *Funding*: ELA Recherche, Medtronic and	*Intervention*: CRT-P ON Atriventricular (active) pacing Chorum 7336 MSP, ELA Medical, France; InSync 8040, Medtronic, USA *Comparator*: CRT-P OFF Ventricular (inhibited (inactive) pacing at a basic rate of 40 bpm. *Other interventions used*: No modification to medication other than adjustment of dose of diuretic permitted.	*Indication for treatment*: Severe heart failure and major intraventricular delay but without standard indications for a pacemaker. *Number of enrolled participants*: n=67 *Number of randomised participants*: n = 58 Group 1 (CRT-ON, CRT-P OFF), n= 29 Group 2 (CRT-P OFF, CRT-P ON), n=29 *Inclusion criteria*: 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.	*Primary outcomes:* Distance walked in 6 minutes *Secondary outcomes:* QoL Peak oxygen uptake, Hospital admissions due to decompensated heart failure, Patient's preference Death *Method of assessing outcomes:* 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.

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%.	*Exclusion criteria*: 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. *Length of follow-up:* Participants received intervention and comparator for 3 months each in random order. *Recruitment*: March 1998-March 1999

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
• 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.

- 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	

- 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. Stares than 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 RCTs[4]

	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
Higgins *et al.*, 2003[77], Lozano *et al.*, 2000[78], FDA report[79], Saxon *et al.*, 1999[80] CONTAK-CD *Study design*: Crossover RCT in phase I. Parallel RCT in phase II USA (see General Comments - Inter-centre variability) *Number of centres*: 47 *Funding*: Guidant Corporation, St. Paul, Minnesota.	*Intervention*: CRT-D + optimised pharmacological therapy (OPT) *Comparator*: ICD +OPT Devices were either Model 1822 Ventak CHF Automatic Implantable Cardioverter Defibrillator or Model 1283 Contak CD device (Guidant Corporation, St. Paul, Minnesota). 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. Details of lead positioning are reported but have not been data extracted. 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. *Other interventions used*: none stated.	*Indication for treatment*: Patients with symptomatic heart failure, intraventricular conduction delay, and malignant ventricular tachyarrhythmias (VT/VF) requiring therapy from an ICD. *Number of randomised participants*: n=490. CRT-D, n=245 CRT, n=245 *Inclusion criteria*: 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] *Exclusion criteria*: 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	*Primary outcome:* 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 (VO_2) but this was changed when the study design was changed) *Secondary outcomes:* VO_2, QoL, six minute walk distance, biventricular antitachycardia pacing efficacy, defibrillation therapy safety.[80] *Method of assessing outcomes:* VO_2 assessed by cardiopulmonary exercise test[80] QoL used the Minnesota Living with Heart Failure Questionnaire A Heart Failure Events Committee (HFEC) adjudicated all deaths and hospitalisations. Operative mortality defined as death from any cause within 30 days of the implant procedure

		cardioversion/defibrillation leads other than those specified in the protocol; involved in other cardiovascular clinical investigations of active therapy or treatment.[80]	*Length of follow-up:* maximum of six months (but some patients, presumed to be all those in phase I, only 3 months). *Recruitment*: February 1998 to December 2000

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 - non-specific - right bundle-branch block	 54 32 14	 55 33 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 study[78] 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 study[78] 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%)		

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.

- Adverse events reported in the Summary of Safety and effectiveness[79] 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 mortality[79], 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 2003[77] and the Summary of Safety and Effectiveness for the device used[79] state that the centres were based in the USA. However, an earlier paper reporting on phase 1 of the study[78] 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 paper[77], the Summary of Safety and Effectiveness[79] 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 RCTs[4]

	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.

[f] 'Low risk', 'high risk' or 'unclear risk' of bias

MADIT-CRT

Reference and design	Intervention and Comparator	Participants	Outcome measures
Moss *et al.*, 2009 ;[81] 2005 ;[82] Solomon *et al.* 2010 ;[83] Goldenberg *et al.* 2011 ;[84;85] Arshad *et al.* 2011[86] MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) *Study design*: RCT *Number of centres*: Text states 110, 88 in USA, 2 in Canada, 20 in Europe.	*Intervention*: CRT-ICD Programmed mode was DDD with lower rate of 40 bpm and hysteresis off. *Comparator*: 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. Commercially available transvenous devices (Boston Scientific) were	*Indication for treatment*: mild cardiac symptoms, reduced ejection fraction and wide QRS complex. All met the guideline indication for ICD therapy. *Number of participants*: n = 1820 (1271 in US, 22 in Canada, 527 in Europe) CRT-ICD, n= 1089 ICD only, n= 731 *Inclusion criteria*: NYHA class: I or II; LVEF: ≤30%; QRS interval: ≥130 msec; people ≥ 21 years of age with ischaemic	*Primary outcomes:*death or nonfatal heart-failure events (whichever came first) *Secondary outcomes:* *Method of assessing outcomes:* Baseline 12-lead electrocardiogram and echocardiogram. Baseline physical examination and 6-minute walk test (6MWT). Two dimensional echocardiography assessed changes in left

(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. *Funding*: 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.	used. *Other interventions used*: Optimal pharmacologic therapy for heart failure.[82]	cardiomyopathy (NYHA class I or II) or nonischaemic cardiomyopathy (NYHA class II only); sinus rhythm; ejection fraction ≤30% and prolonged intraventricular conduction with QRS duration of ≥130 msec; met guideline indication for ICD therapy. *Exclusion criteria*: 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.	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). 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. 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. *Length of follow-up:* to trial termination. The trial was stopped on June 22, 2009. Average follow up was 2.4 years *Recruitment dates*: December 22 2004 to April 23 2008

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 - Black - Other	 979/1083 (90.4%) 87/1083 (8.0%) 17/1083 (1.6%)	 657/724 (90.7%) 56/724 (7.7%) 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 ≥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 ≥ 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± 60	251± 65	
Left ventricular end-systolic volume	175±48	179±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 ≥30	385/1072 (35.9)	263/723 (36.4)	
- coronary-bypass surgery	317/1088 (29.1)	208/730 (28.5)	

Comments:

- 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 reported[83] 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 - Left ventricular end-diastolic volume average change[b] from baseline to 1 year, ml -Left ventricular end-systolic volume average change[b] from baseline to 1 year, ml	 0.11 (n=746) -52 (n=746) -57 (n=746)	 0.03 (n=620) -15 (n=620) -18 (n=620)	 <0.001 <0.001 <0.001
Exercise capacity outcomes	Not reported	Not reported	

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.

- 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 analysis[87] 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 - infection - pocket haematoma requiring evacuation	 1.7 1.1 3.3	 0.8 0.7 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 1st 30 days	44 patients (4.0%)		
Frequency of serious device-related adverse events during long-term follow-up after the 1st 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 ≥ 65 years	 142/852 230/968	 [c] 0.80 [c] 0.60
Sex male female	 294/1367 78/453	 0.76 (0.59 to 0.97) 0.37 (0.22 to 0.61), 0.01 for interaction
NYHA class Ischaemic I Ischaemic II Nonischaemic II	 53/265 186/734 133/821	 [c] 0.76 [c] 0.62 [c] 0.60
QRS duration <150ms ≥150ms	 147/645 225/1175	 1.06 (0.74 to 1.52) 0.48 (0.37 to 0.64), 0.001 for interaction
LVEF ≤25% >25%	 101/646 271/1174	 [c] 0.70 [c] 0.60
LVEDV ≤240ml > 240ml	 184/828 184/969	 [c] 0.70 [c] 0.62
LVESV ≤170ml > 170ml	 190/835 178/962	 [c] 0.66 [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.

- 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 gender[86]	**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:

- 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 study[83] 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 (Δ=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 RCTs[4]

	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 *et al.*, 2006[88] *Study design*: RCT Italy *Number of centres*: 1 *Funding*: not	*Intervention*: CRT-D *Comparator*: 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	*Indication for treatment*: CHF (with low ejection fraction and prolonged QRS interval) secondary to ischaemic dilated cardiomyopathy *Number of randomised participants*: n = 31 CRT-D, n=16 ICD, n=15	*Not stated if primary or secondary outcome:* spectral indexes based on power spectral analysis and changes in spectral indices (not data extracted). Also reported: mortality and

reported	rest (setting essential to allow power spectral analysis of HRV) 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) *Other interventions used*: none reported	Also reported data for healthy, non-randomised control group, n=12. Data not extracted. *Inclusion criteria*: LVEF ≤ 35; QRS interval >120 msec and sinus rhythm. *Exclusion criteria*: 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.	change in NYHA class *Method of assessing outcomes:* 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. *Length of follow-up:* 1 year *Recruitment*: not reported

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	
Biskoprolol, 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/m2) , 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. • 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. • 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

- *Allocation to treatment groups*: patients were randomly assigned in a 1:1 ratio to ICD or CRT-D
- *Blinding*: spectral recording assessment blinded (outcomes not extracted), but no other blinding reported.
- *Comparability of treatment groups*: 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).
- *Method of data analysis*: 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

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. • *Sample size/power calculation*: none reported. • *Attrition/drop-out*: none, all patients completed the study.
General comments • *Generalisability*: sample size too small to generalise, but results would be limited to patients with post-ischaemic dilated cardiomyopathy, excluding primary dilated cardiomyopathy patients. • *Outcome measures*: extracted outcome measures appear appropriate. • *Inter-centre variability*: not applicable, one centre only. • *Conflict of interests*: not reported.

Criteria for assessment of risk of bias in RCTs[4]

	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**
Pinter *et al.*, 2009[15] *Study design*: RCT Canada *Number of centres*: 7	*All patients:* 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	*Indication for treatment*: 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. *Number of randomised participants*: n = 72	*Primary outcomes:* Left ventricular end-systolic volume (LVESV) change from baseline to 6 months. *Secondary outcomes:* Change in: QoL Stroke volume Cardiac volume

Funding: Guidant Inc, Minneapolis, MN	ventricular pacing lead (Guidant Inc). *Intervention*: 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. *Comparator*: ICD (CRT OFF) Dual chamber non-tracking pacing mode (DDI) 40 beats/min backup biventricular pacing. *Other interventions used*: Not reported, but inclusion criteria state ≥ 2 weeks treatment with maximal tolerated doses of ACE inhibitors or beta-blockers unless adverse effects or contraindicated.	CRT-D, n=36 ICD, n=36 *Inclusion criteria*: Heart failure: unequivocal symptoms of dyspnoea or fatigue on climbing ≤2 flights of stairs or 6-min walk distance ≤ 450 m; LVEF ≤ 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. *Exclusion criteria*: 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.	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. *Method of assessing outcomes:* 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. *Length of follow-up:* 6 months *Recruitment*: not reported

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, µmol/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

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).

- 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			

Methodological comments

- *Allocation to treatment groups*: 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.
- *Blinding*: Patients blinded to treatment allocation. All post implant study evaluations were performed by personnel blinded to treatment allocation.
- *Comparability of treatment groups*: no significant differences, although there were more patients with significant mitral regurgitation in the CRT ON group, p=0.09.
- *Method of data analysis*: 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.
- *Sample size/power calculation*: 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.
- *Attrition/drop-out*: 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).

General comments

- *Generalisability*: 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.
- *Outcome measures*: 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.
- *Inter-centre variability*: Not reported.
- *Conflict of interests*: 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 RCTs[4]

	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
Tang *et al.*, 2010;[13] 2009[89] RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) *Study design*: RCT Canada, Europe, Turkey and Australia *Number of centres*: 34 (Canada 24, Europe & Turkey 8, Australia 2) *Funding*: University-industry peer-	*Intervention*: ICD-CRT (commercially available transvenous leads and devices, Medtronic). Standard implantation technique. Programming standardised to maximise ventricular pacing *Comparator*: ICD Programming standardised to minimise ventricular pacing. *Other interventions used*: OPT for both groups beta-	*Indication for treatment*: 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. *Number of randomised participants*: n =1798 ICD-CRT, n=894 ICD, n=904 *Inclusion criteria*: 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	*Primary outcomes:* composite outcome of death from any cause or heart failure leading to hospitalisation *Secondary outcomes:* 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). *Method of assessing outcomes:* hospitalisation for heart failure was defined as admission to a health care facility lasting >24hrs with symptoms of

reviewed grant from the Canadian Institutes of Health Research. Medtronic of Canada (industry partner) provided funding and CRT components.	blocker, an angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker, spironolactone, aspirin and statins when appropriate; provide uniform arrhythmia detection and therapy.	test) or planned atrioventricular-junction ablation after device implantation) and planned ICD implantation for indicated primary or secondary prevention of sudden cardiac death; Optimal heart failure pharmacological therapy.[89] *Exclusion criteria*: 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.	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). 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. 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. *Length of follow-up:* minimum of 18mths mean 40 months (SD 20); mean follow-up for surviving patients 44 months (SD 18) *Recruitment*: January 2003 through February 2009

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
Spironolactone	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

Comments: 12 patients underwent cardiac transplantation before reaching the primary outcome (ICD–CRT n=7; ICD n=5).

- 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; QRSA duration intrinsic QRS <150msc 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/1.73m^2): <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.

- 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 2yrs[89]) 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 RCTs[4]

	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
Beshai *et al.*, 2007; [90] Beshai & Grimm, 2007[91] RethinQ (Cardiac Resynchroniza-tion Therapy in Patients with Heart Failure and Narrow QRS) *Study design*: RCT USA *Number of centres*: 34 *Funding*: Jude St Medical	*Intervention*: 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] *Comparator*: ICD + OPT (device as above). Detection and therapy of tachyarrhythmias turned on. [91] *Other interventions used*: 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).	*Indication for treatment*: standard indication for an ICD, narrow QRS interval and intraventricular mechanical dyssynchrony, ischemic or non-ischemic cardiomyopathy. *Number of randomised participants*: n = 172 CRT-D ON, n= 87 CRT-D OFF, n=85 *Inclusion criteria*: 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] *Exclusion criteria*: Standard indication for cardiac pacing or previous treatment with CRT; standard bradycardic indication for pacing; continuous atrial	*Primary outcomes:* proportion of patients with an increase of ≥1.0 ml/kg body weight/ minute in peak oxygen consumption during cardiopulmonary exercise testing [90] and survival from CRT-D system –related complications[91] *Secondary outcomes:* QoL and NYHA class *Method of assessing outcomes:* baseline evaluation 14 days after successful implantation, including cardiopulmonary exercise testing (max. exercise tolerance on treadmill/bicycle ergonometry 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,

	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]	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]	echocardiography for optimisation of atrioventricular and interventricular delay and 12-lead electrocardio-graphy. Evaluation repeated at 6 months. 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) Follow up: cardiopulmonary-exercise testing, NYHA class, 6-minute walking test, QoL and echocardiography. *Length of follow-up:* 6 months *Recruitment*: August 2005 to January 2007

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.

- 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 VO2	(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 RCTs[4]

	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**
Summary of Safety and Effectiveness 2004[87;92] RHYTHM-ICD (Resynchronization for Hemodynamic Treatment for Heart Failure Management) *Study design*: RCT Country not stated *Number of centres*: 50 *Funding*: not stated but presumed to be the device manufacturer, St. Jude medical, Sunnyvale, CA	*Intervention*: CRT-D St. Jude Medical® Epic™ HF model V-338 (maximum output 30 J) CRT-D with Aescula LV leads. *Comparator*: ICD *Other interventions used*: not stated	*Indication for treatment*: patients indicated for ICD therapy with NYHA Class III/IV heart failure and a prolonged QRS duration. *Number of randomised participants*: n = 205 enrolled, n=182 successful implants, baseline visit n=179. CRT-D, n= 119 ICD, n= 60 *Inclusion criteria*: 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. *Exclusion criteria*: Standard bradycardic indication for pacing; chronic atrial fibrillation (continuous AF lasting > I	*Primary outcomes:* 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 $V0_2$). *Secondary outcomes:* Improvement at 6-months in: NYHA class; QoL; six minute walk test. Aescula LV lead performance and lead pacing capture threshold. *Method of assessing outcomes:* 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

		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. *Length of follow-up:* Average 12.1 (3.4) months, range 0.3 to 20.3 patient months. Outcomes reported at 6 months. *Recruitment*: July 2002 to October 2003

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		

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.

- 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), 31events	
- 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.

- 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 VO_2 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-up[87]) 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/6month 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 RCTs[4]

	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 ≤ 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 ≤ 40% or those who may not have (LVEF) ≤ 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 2007 [2] and others.

- *Are the MS conclusions are 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 MIRCALE 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	
8. Are the statistical procedures adequately described and executed?	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. 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. **All-cause mortality** 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, Akaiko 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.

	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?	Results are presented through a series of tabulations and illustrations, specifically: **All-cause mortality** 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. **All-cause hospitalisation** 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. **HRQoL** 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.
14. Is there a narrative commentary on the results?	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). 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).
15. Does the discussion of the results	The discussion of results for the 3 outcomes does reflect the results presented and provides warnings about the

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.

SHTAC peer review of the economic evaluation within the ABHI joint submission

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	[redacted]	[redacted]
CRTP*QRS>=120	[redacted]	[redacted]
CRTP*LBBB	[redacted]	[redacted]
CRTP*GENDER=M	[redacted]	[redacted]
CRTP*AGE>=60	[redacted]	[redacted]
CRTD*QRS>=120	[redacted]	[redacted]
CRTD*LBBB	[redacted]	[redacted]
CRTD*GENDER=M	[redacted]	[redacted]
CRTD*AGE>=60	[redacted]	[redacted]

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.

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 [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.

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	βCoefficient	Std. error	Z score	e^β
NYHA = III	[redacted]	[redacted]	[redacted]	[redacted]
NYHA = IV	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	[redacted]	[redacted]	[redacted]	[redacted]
Gender= Male	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

* 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	[redacted]	[redacted]	[redacted]
ICD	[redacted]	[redacted]	[redacted]
CRT-P	[redacted]	[redacted]	[redacted]
CRT-D	[redacted]	[redacted]	[redacted]

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:

$$h(t) = \exp(-(\log(scale) - \boldsymbol{\beta} \cdot \boldsymbol{X}) \cdot shape) \cdot shape \cdot t^{shape}$$

$$S(t) = \exp\left(-\int_0^t h(t)dt\right)$$

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)	[redacted]	[redacted]	[redacted]
Male gender	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]
Ischaemic aetiology	[redacted]	[redacted]	[redacted]
QRS duration <120ms	[redacted]	[redacted]	[redacted]
LVEF>20% and <=25%	[redacted]	[redacted]	[redacted]
LVEF>25% and <=30%	[redacted]	[redacted]	[redacted]
LVEF>30%	[redacted]	[redacted]	[redacted]
log(scale)	[redacted]	[redacted]	[redacted]
log(shape)	[redacted]	[redacted]	[redacted]

(a) Hazard ratio = exp(β/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	[redacted]	[redacted]	[redacted]
QRS 120-149ms	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]
Ischaemic aetiology			
QRS <120ms	[redacted]	[redacted]	[redacted]
QRS 120-149ms	[redacted]	[redacted]	[redacted]
QRS ≥150ms	[redacted]	[redacted]	[redacted]

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 ≤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)

				C-E Sequence				ICERs			
NYHA Class	Etiology	QRS Duration	N	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 1st	2nd	3rd	4th	ICERs 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

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 REsychronization 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
Y – yes, N – no, ? - unclear	
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 dysynchrony (QRS direction >120 ms).
Intervention(s), Comparator(s)	CRT *versus* OPT[a] CRT-D[b] *versus* CRT OPT *versus* CRT *versus* 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
Y – yes, N – no, ? - unclear	
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 probablistic 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	HR 18-59	0.62	0.0459	0.54	0.72	Lognormal
multiplier	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				
		Mean	SE	LL	UL	Distribution
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 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	
	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				
		Mean	SE	LL	UL	Distribution
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	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						
	No HF	0.855	0.0048	0.845	0.864	Beta
per NYHA class	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

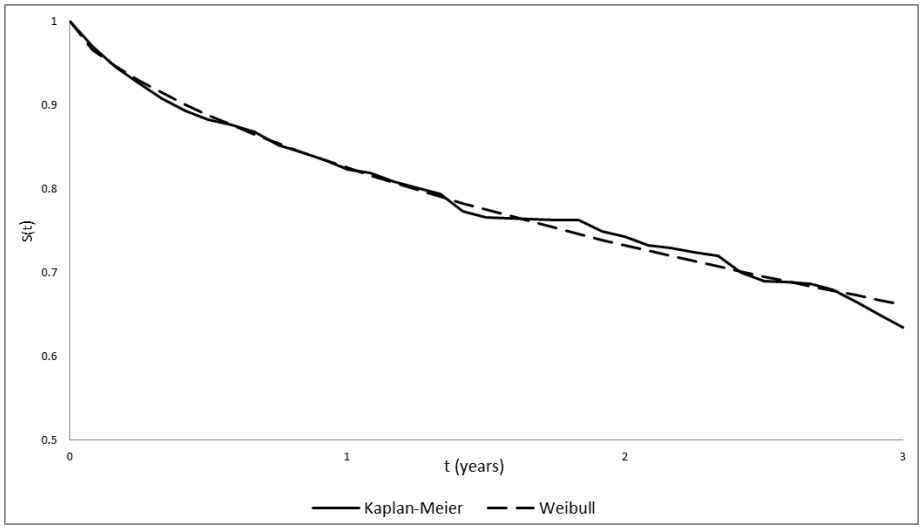
Parameter	**Mean (SE)**			
	AVID[18] (R^2 = 0.994)	MADIT II [55] (R^2 = 0.9903)	SCD-HeFT[99] (R^2 = 0.993)	SCD-HeFT[99;100] non-ischaemic CHF subgroup (R^2 = 0.985)
ln(λ)	-3.380 (0.026)	-4.628 (0.047)	-5.288 (0.039)	-4.821 (0.037)
γ	0.696 (0.009)	1.007 (0.017)	1.083 (0.011)	0.883 (0.011)

Weibull model: ln(-ln(S))= ln(λ)+γ ln(t); S(t) = exp(-λ.t^γ)

Secondary prevention

Figure 1 shows the Weibull approximation fitted to the Kaplan-Meier curve for overall survival of patients in the AVID trial[18] – 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.

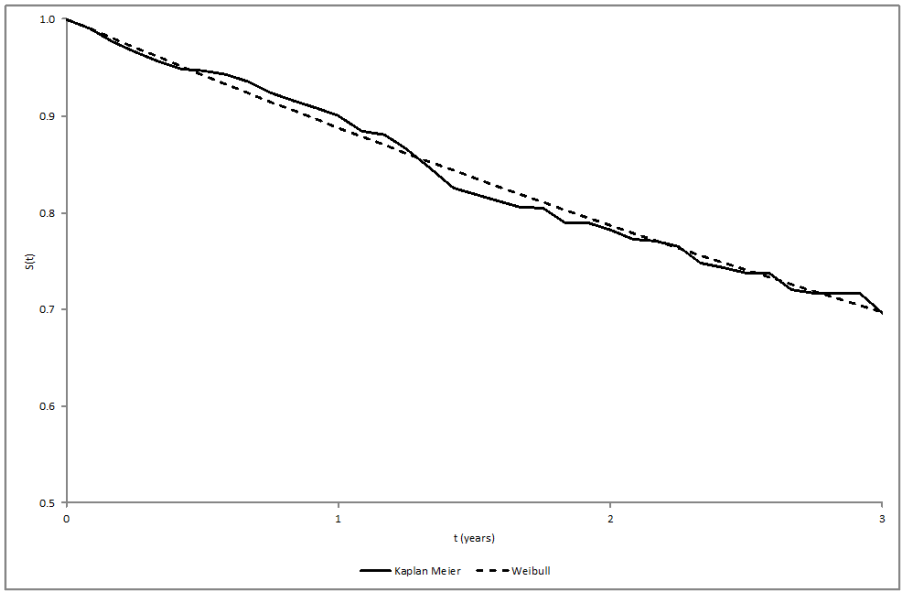
Figure 1. Kaplan-Meier survival estimates for all-cause mortality from the AVID trial[18]



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.

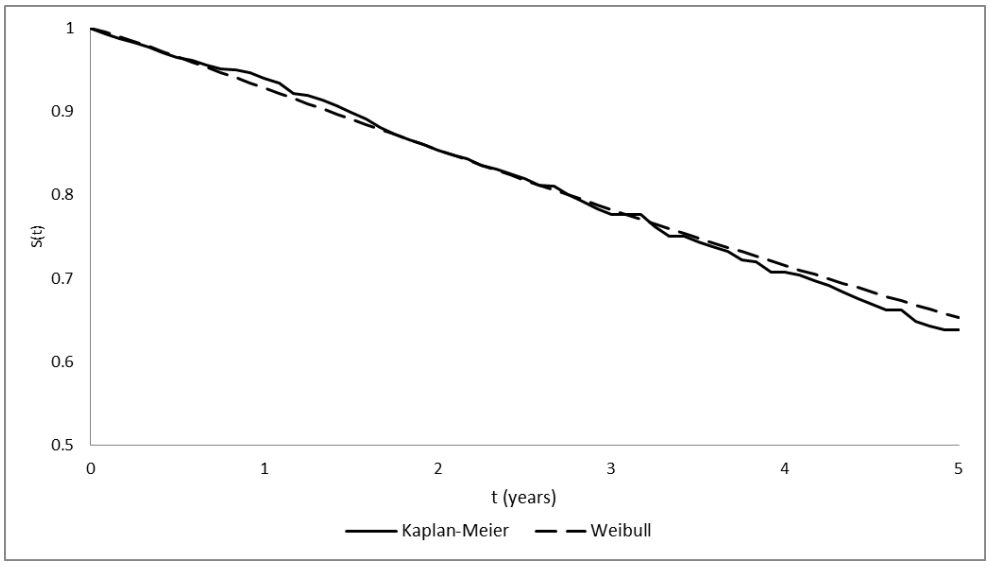
Figure 2. Kaplan-Meier survival estimates for all-cause mortality in patients with remote MI and reduced LVEF (MADIT II population) [55]



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 trial[99] 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-HeFT[99] 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]

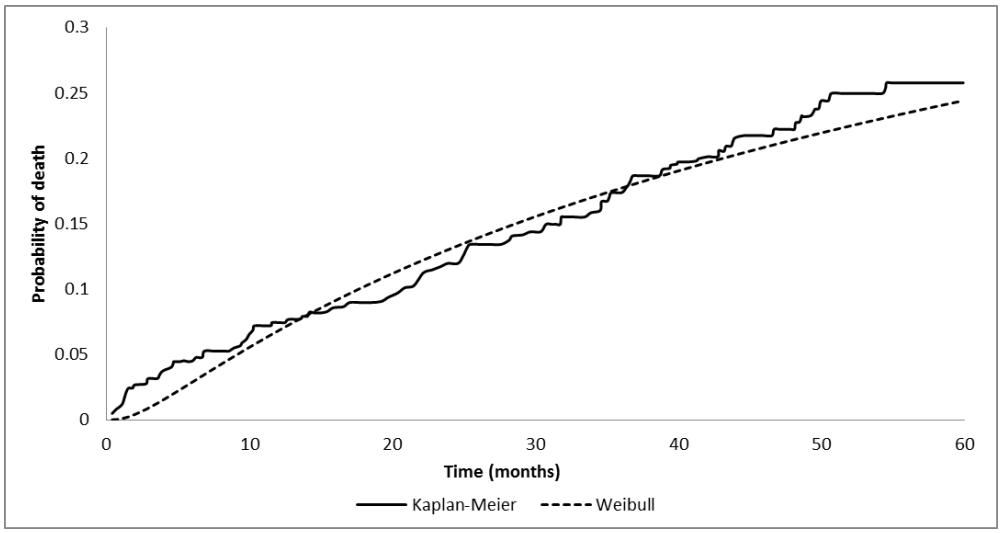


Table 2 reports a comparison of observed survival at given years reported for each trial against model predictions.

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: **(R^2 = 0.994)** **λ = 0.0340** **γ = 0.6962**				
Year	**Trial report[18]**		**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: (R^2 = 0.9903) λ = 0.0098 γ = 1.0068				
Year	**Trial report[55]**		**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) λ = 0.0051 γ = 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 report[55] to the Weibull approximation. [c] Survival probabilities for year not reported in SCD-HeFT trial publication[99] – 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 report[99] 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 suddent cardiac death and heart failure mortality

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: $\ln(-\ln(S)) = \ln(\lambda) + \gamma \ln(t)$; $S(t) = \exp(-\lambda.t^{\gamma})$

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-CRT[86]) and RAFT[13]) 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**
RAFT			
ICD-CRT arm ($R^2 = 0.9894$)			
$\ln(\lambda)$	-6.334	-6.202	-6.467
γ	1.243	1.20	1.27
MADIT –CRT			
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

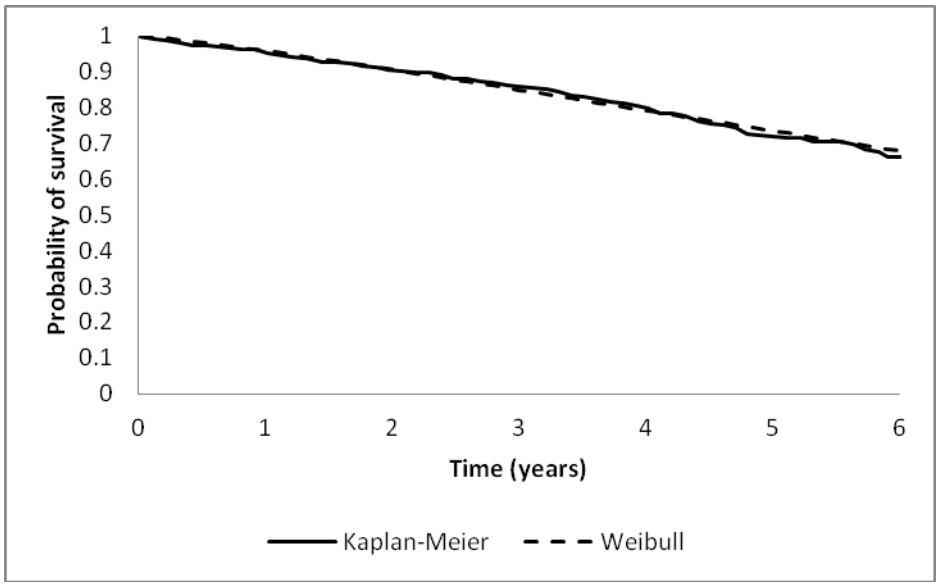


Table 5 reports a comparison of observed survival at times reported for the trial against model predictions.

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-CRT[13] 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 arm[86] to the Weibull approximation

Appendix 17 Validation of the independent economic model

Validation against the model developed by Fox and colleagues[2] for TA120

At an early stage of model development, the OPT arm of the model developed by Fox and colleagues[2] 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
Total	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 scope[101] 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 underestimates 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

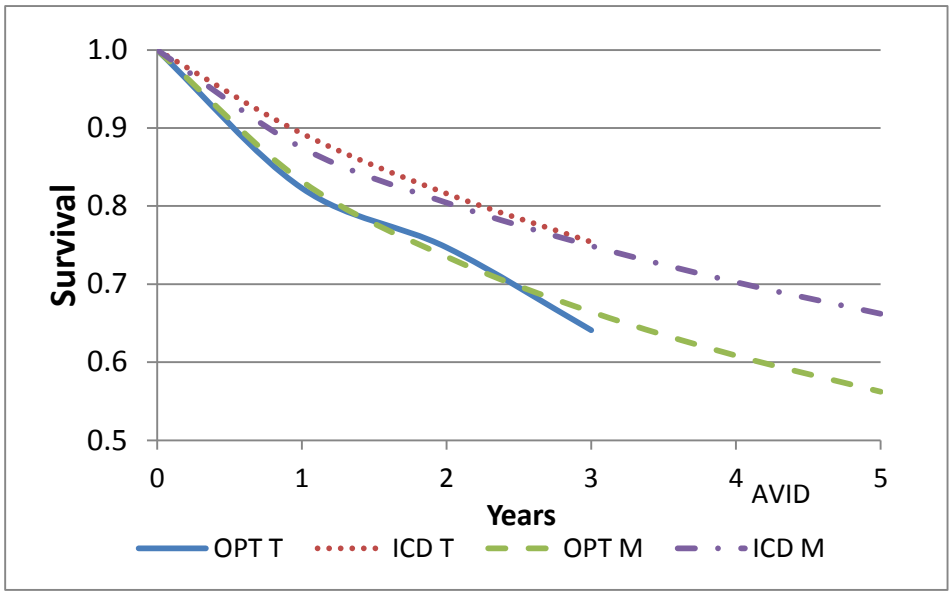


Figure 2 Overall survival curves for OPT and ICD compared to the MADIT II RCT data

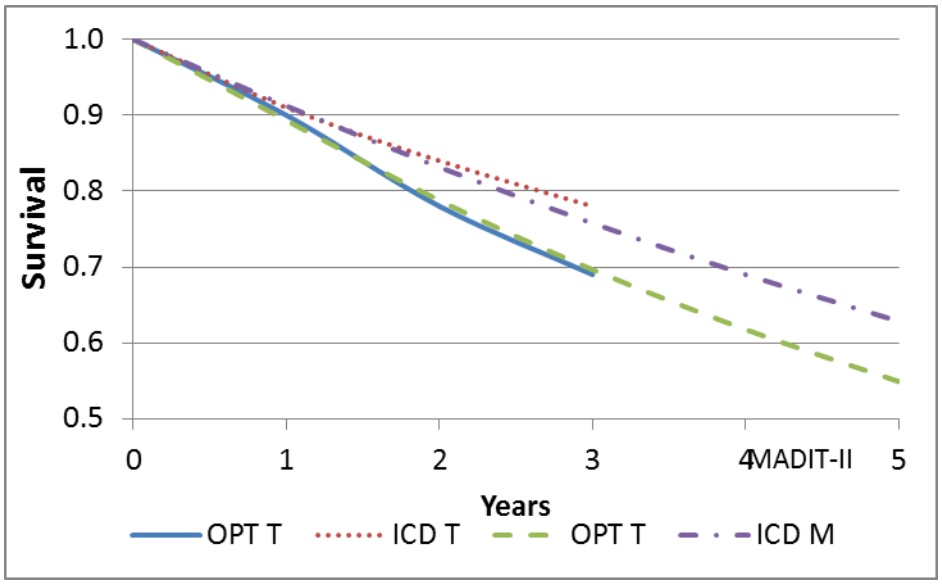
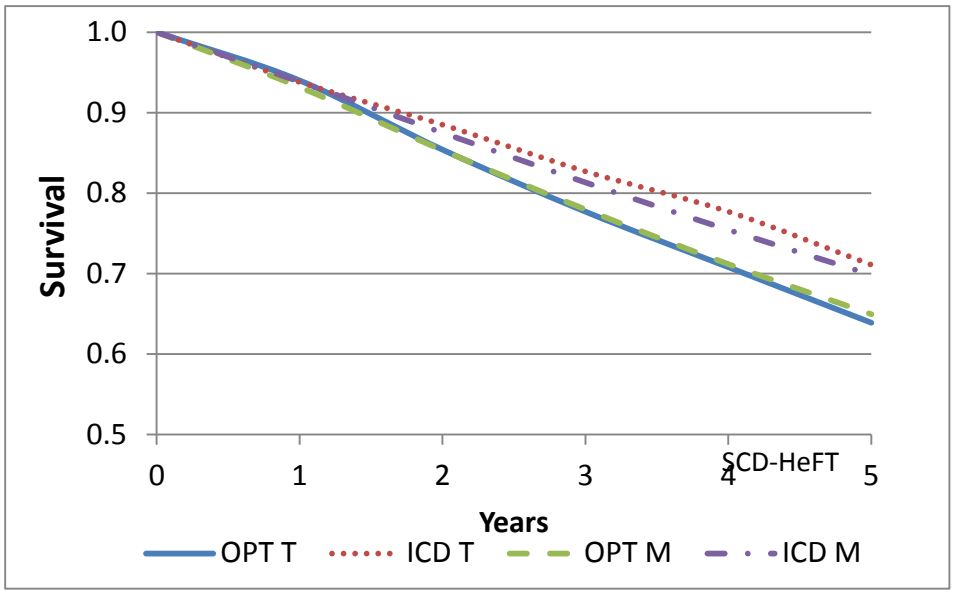


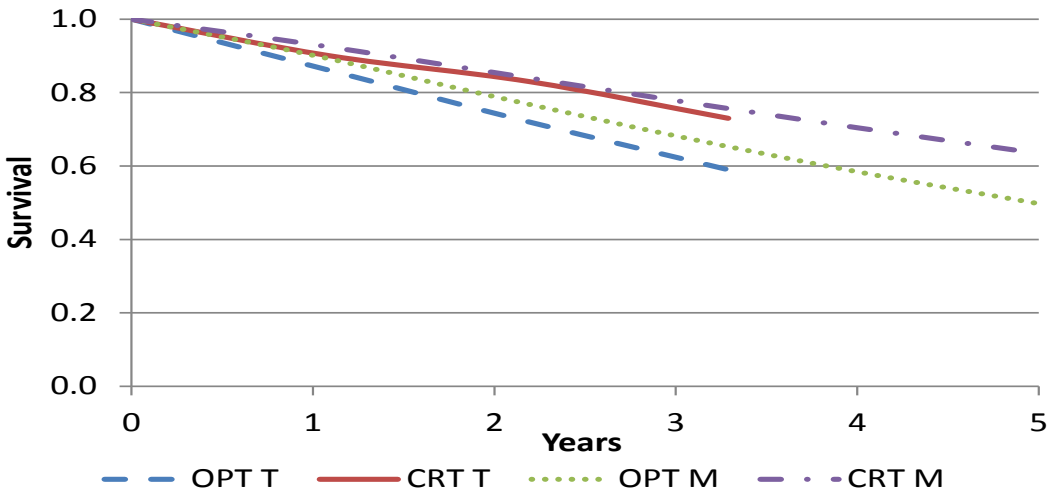
Figure 3 Overall survival curves for OPT and ICD compared to the SCD-HeFT RCT data



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 underestimates the benefit of CRT compared OPT, and therefore may be a conservative fit.

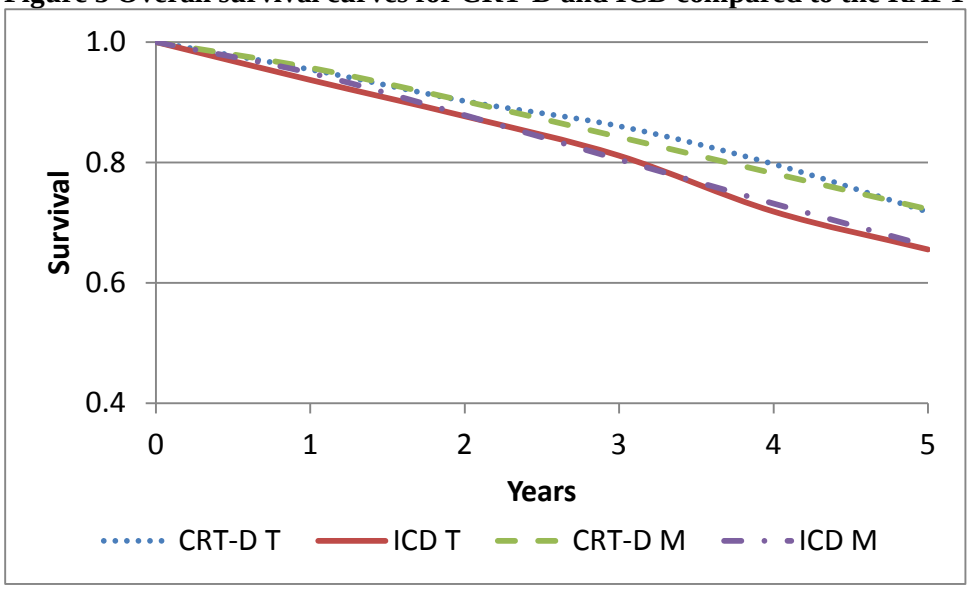
Figure Overall survival curves for CRT and OPT compared to the CARE-HF RCT data



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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