HEALTH TECHNOLOGY ASSESSMENT

VOLUME 18 ISSUE 56 AUGUST 2014
ISSN 1366-5278

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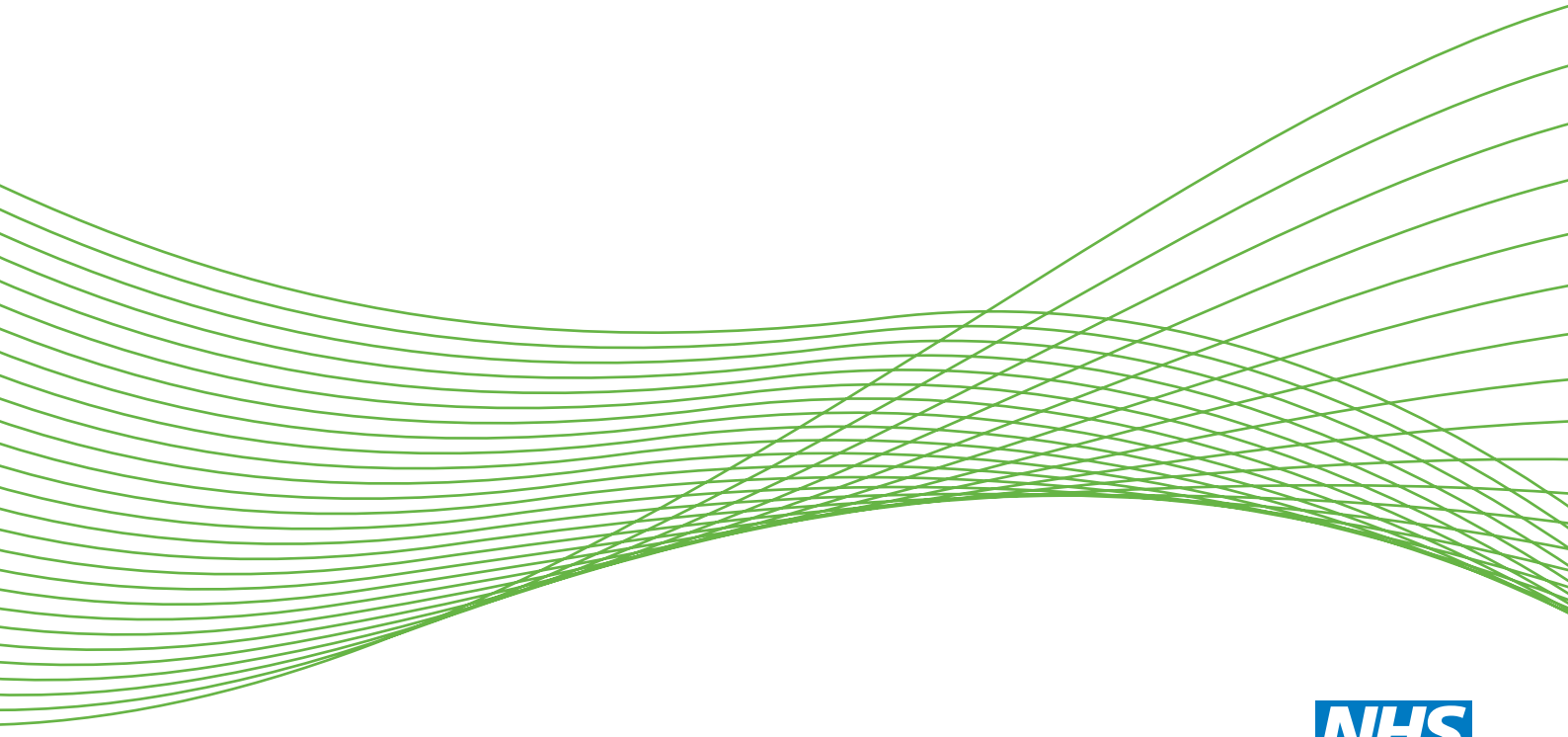

NHS
National Institute for Health Research

DOI 10.3310/hta18560

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Declared competing interests of authors: none

Published August 2014
DOI: 10.3310/hta18560

This report should be referenced as follows:

Colquitt JL, Mendes D, Clegg AJ, Harris P, Cooper K, Picot J, *et al*. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. *Health Technol Assess* 2014;**18**(56).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 10/109/01. The protocol was agreed in February 2011. The assessment report began editorial review in February 2013 and was accepted for publication in July 2013. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

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

Jill L Colquitt,* Diana Mendes, Andrew J Clegg, Petra Harris, Keith Cooper, Joanna Picot and Jackie Bryant

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Background: This assessment updates and expands on two previous technology assessments that evaluated implantable cardioverter defibrillators (ICDs) for arrhythmias and cardiac resynchronisation therapy (CRT) for heart failure (HF).

Objectives: To assess the clinical effectiveness and cost-effectiveness of ICDs in addition to optimal pharmacological therapy (OPT) for people at increased risk of sudden cardiac death (SCD) as a result of ventricular arrhythmias despite receiving OPT; to assess CRT with or without a defibrillator (CRT-D or CRT-P) in addition to OPT for people with HF as a result of left ventricular systolic dysfunction (LVSD) and cardiac dyssynchrony despite receiving OPT; and to assess CRT-D in addition to OPT for people with both conditions.

Data sources: Electronic resources including MEDLINE, EMBASE and The Cochrane Library were searched from inception to November 2012. Additional studies were sought from reference lists, clinical experts and manufacturers' submissions to the National Institute for Health and Care Excellence.

Review methods: Inclusion criteria were applied by two reviewers independently. Data extraction and quality assessment were undertaken by one reviewer and checked by a second. Data were synthesised through narrative review and meta-analyses. For the three populations above, randomised controlled trials (RCTs) comparing (1) ICD with standard therapy, (2) CRT-P or CRT-D with each other or with OPT and (3) CRT-D with OPT, CRT-P or ICD were eligible. Outcomes included mortality, adverse events and quality of life. A previously developed Markov model was adapted to estimate the cost-effectiveness of OPT, ICDs, CRT-P and CRT-D in the three populations by simulating disease progression calculated at 4-weekly cycles over a lifetime horizon.

Results: A total of 4556 references were identified, of which 26 RCTs were included in the review: 13 compared ICD with medical therapy, four compared CRT-P/CRT-D with OPT and nine compared CRT-D with ICD. ICDs reduced all-cause mortality in people at increased risk of SCD, defined in trials as those with previous ventricular arrhythmias/cardiac arrest, myocardial infarction (MI) > 3 weeks previously, non-ischaemic cardiomyopathy (depending on data included) or ischaemic/non-ischaemic HF and left ventricular ejection fraction ≤ 35%. There was no benefit in people scheduled for coronary artery bypass graft. A reduction in SCD but not all-cause mortality was found in people with recent MI. Incremental cost-effectiveness ratios (ICERs) ranged from £14,231 per quality-adjusted life-year (QALY) to £29,756 per QALY for the scenarios modelled. CRT-P and CRT-D reduced mortality and HF hospitalisations, and

improved other outcomes, in people with HF as a result of LVSD and cardiac dyssynchrony when compared with OPT. The rate of SCD was lower with CRT-D than with CRT-P but other outcomes were similar. CRT-P and CRT-D compared with OPT produced ICERs of £27,584 per QALY and £27,899 per QALY respectively. The ICER for CRT-D compared with CRT-P was £28,420 per QALY. In people with both conditions, CRT-D reduced the risk of all-cause mortality and HF hospitalisation, and improved other outcomes, compared with ICDs. Complications were more common with CRT-D. Initial management with OPT alone was most cost-effective (ICER £2824 per QALY compared with ICD) when health-related quality of life was kept constant over time. Costs and QALYs for CRT-D and CRT-P were similar. The ICER for CRT-D compared with ICD was £27,195 per QALY and that for CRT-D compared with OPT was £35,193 per QALY.

Limitations: Limitations of the model include the structural assumptions made about disease progression and treatment provision, the extrapolation of trial survival estimates over time and the assumptions made around parameter values when evidence was not available for specific patient groups.

Conclusions: In people at risk of SCD as a result of ventricular arrhythmias and in those with HF as a result of LVSD and cardiac dyssynchrony, the interventions modelled produced ICERs of < £30,000 per QALY gained. In people with both conditions, the ICER for CRT-D compared with ICD, but not CRT-D compared with OPT, was < £30,000 per QALY, and the costs and QALYs for CRT-D and CRT-P were similar. A RCT comparing CRT-D and CRT-P in people with HF as a result of LVSD and cardiac dyssynchrony is required, for both those with and those without an ICD indication. A RCT is also needed into the benefits of ICD in non-ischaemic cardiomyopathy in the absence of dyssynchrony.

Study registration: This study is registered as PROSPERO number CRD42012002062.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

CONTAK-CD Randomised controlled trial of the CONTAK-CD device.

QRS interval An electrocardiogram trace pattern (comprising three electrocardiogram 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 an electrocardiogram.

List of abbreviations

AAD	antiarrhythmic drug
ABHI	Association of British Healthcare Industries
ACE	angiotensin-converting enzyme
AIC	Akaike information criterion
AMIOVIRT	Amiodarone Versus Implantable Cardioverter-Defibrillator Randomized Trial
ARB	angiotensin receptor blocker
AVID	Antiarrhythmics Versus Implantable Defibrillators
BIC	Bayesian information criterion
BNF	*British National Formulary*
CABG Patch	Coronary Artery Bypass Graft Patch
CARE-HF	CArdiac REsynchronization in Heart Failure
CASH	Cardiac Arrest Study Hamburg
CAT	Cardiomyopathy Trial
CCAD	Central Cardiac Audit Database
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CIDS	Canadian Implantable Defibrillator Study
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Patients with Left Ventricular Systolic Dysfunction
CONTAK-CD	randomised controlled trial of the CONTAK-CD device
COPD	chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemination
CRT	cardiac resynchronisation therapy
CRT-D	cardiac resynchronisation therapy – defibrillator
CRT-P	cardiac resynchronisation therapy – pacer
CVD	cardiovascular death
DASI	Duke Activity Status Index
DEBUTE	Defibrillator versus Beta-Blockers for Unexplained Death in Thailand
DEFINITE	Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation
df	degree of freedom
DIC	deviance information criteria
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
ECG	electrocardiogram
ECHOES	Echocardiographic Heart of England Screening Study
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EQ-5D	European Quality of Life-5 Dimensions
FDA	US Food and Drug Administration
GPRD	General Practice Research Database
HF	heart failure
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HRS	Heart Rhythm Society
HTA	Health Technology Assessment
HUI3	Health Utilities Index 3

ICD	implantable cardioverter defibrillator
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
IQR	interquartile range
IRIS	Immediate Risk Stratification Improves Survival
ITT	intention to treat
LBBB	left bundle branch block
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
MAVERIC	Midlands Trial of Empirical Amiodarone versus Electrophysiology-Guided Interventions and Implantable Cardioverter-Defibrillators
MCS	mental component summary
MD	mean difference
MHI	Mental Health Inventory
MHI-5	Mental Health Inventory 5
MI	myocardial infarction
MIRACLE	Multicenter InSync Randomized Clinical Evaluation
MIRACLE ICD	Multicenter InSync ICD Randomized Clinical Evaluation
MLWHFQ	Minnesota Living with Heart Failure Questionnaire
MS	manufacturers' submission
MUSTIC	Multisite Stimulation in Cardiomyopathies
MUSTT	Multicenter Unsustained Tachycardia Trial
NBRM	negative binomial regression model
NHP	Nottingham Health Profile
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	network meta-analysis
NSVT	non-sustained ventricular tachycardia
NYHA	New York Heart Association
OPT	optimal pharmacological therapy
PCS	physical component summary
PES	programmed electrical stimulation
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL	quality of life
QWBS	Quality of Well-Being Scale
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure Trial
RCT	randomised controlled trial
RESPOND	Resynchronization in Patients with Heart Failure and a Normal QRS Duration
RethinQ	Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS
REVERSE	REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction
RHYTHM ICD	Resynchronization for the HemodYnamic Treatment for Heart failure Management Implantable Cardioverter Defibrillator
RR	risk ratio
RRR	risk ratio reduction

SCD	sudden cardiac death	SNP	serum natriuretic peptide
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial	STAI	State–Trait Anxiety Inventory
SD	standard deviation	SUDS	sudden unexplained death syndrome
SE	standard error	TA	technology appraisal
SEM	standard error of the mean	TAR	technology assessment report
SF-12	Short Form questionnaire-12 items	VECTOR	Ventricular Resynchronization Therapy Randomized Trial
SF-36	Short Form questionnaire-36 items	VF	ventricular fibrillation
SHTAC	Southampton Health Technology Assessments Centre	VO_2	oxygen consumption
S-ICD	subcutaneous implantable cardiac defibrillator	VT	ventricular tachycardia
		WTP	willingness to pay

Note

This monograph is based on the technology assessment report produced for the National Institute for Health and Care Excellence (NICE). The full report contained a considerable number of data that were deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'commercial-in-confidence information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Scientific summary

Background

Management of people at increased risk of sudden cardiac death (SCD) as a result of ventricular arrhythmias and of people with heart failure (HF) due to left ventricular systolic dysfunction (LVSD) and cardiac dyssynchrony has continued to evolve. Implantable cardioverter defibrillators (ICDs), which can restore normal heart rhythm using pacing, cardioversion or defibrillation, and cardiac resynchronisation therapy (CRT), which resynchronises the contraction of the heart using biventricular pacing [CRT-pacer (CRT-P)] or combines the functionality of CRT-P and an ICD (known as CRT-defibrillator CRT-D), are used to manage these conditions. Given the considerable overlap in the conditions experienced by the different patient groups, some uncertainty remains as to which device(s) provide the most effective option(s) for their treatment.

Objectives

To assess the clinical effectiveness and cost-effectiveness of:

- ICDs in addition to optimal pharmacological therapy (OPT) for 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 people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT
- CRT-D in addition to OPT for people with both conditions.

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 to the National Institute for Health and Care Excellence (NICE) were searched. Experts in the field were asked to identify additional published and unpublished references.

Study selection

Titles and abstracts were screened for eligibility by two reviewers independently. Inclusion criteria were applied to the full text of retrieved papers by one reviewer and checked independently by a second reviewer. Inclusion criteria were as follows:

- people at increased risk of SCD as a result of ventricular arrhythmias despite receiving OPT (studies comparing ICD with OPT)
- people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT (studies comparing CRT-P or CRT-D with each other or with OPT)
- people with both conditions described above (studies comparing CRT-D with ICD, CRT-P or OPT)
- outcome measures: mortality, adverse effects of treatment, health-related quality of life (HRQoL), symptoms and complications related to tachyarrhythmias and/or HF, HF hospitalisations, change in New York Heart Association (NYHA) class and change in left ventricular ejection fraction (LVEF)
- only randomised controlled trials (RCTs) or 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 manufacturer's submission to NICE was reviewed.

Data synthesis

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

Economic model

The model previously developed for the technology assessment of CRT for HF 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 that they follow. The key events modelled were hospitalisation because of HF or arrhythmia, transplant, surgical failure, death, perioperative complications of the 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 to cost all relevant resources consumed in the care of patients in the three populations. The resources considered in the current model included medication, resources involved in device implantation, device-related complications and maintenance, hospitalisation because of HF 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

A total of 4556 references were identified, of which 26 RCTs were included in the review: 13 compared ICDs with medical therapy in people at risk of SCD as a result of ventricular arrhythmias; four compared CRT-P (and CRT-D in one RCT) with OPT in people at risk of HF because of LVSD and cardiac dyssynchrony; and nine compared CRT-D with ICD in people with both conditions.

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

Previous ventricular arrhythmia/cardiac arrest (secondary prevention)

Compared with antiarrhythmic drugs, ICDs reduced the risk of all-cause mortality [four RCTs; risk ratio (RR) 0.75, 95% confidence interval (CI) 0.61 to 0.93, $p = 0.01$]. One RCT found no significant differences in quality of life (QoL), whereas a second RCT found improvements with ICD but not in the control group. Prespecified subgroups did not differ significantly.

Recent myocardial infarction (within 6–41 days or ≤ 31 days)

Meta-analysis found no difference in all-cause mortality between the groups (two RCTs; RR 1.04, 95% CI 0.86 to 1.25, $p = 0.69$). QoL was not reported. No significant differences in all-cause mortality were found for 13 prespecified subgroups in one RCT.

Remote myocardial infarction (> 3 weeks or > 1 month previously)

Meta-analysis found a reduction in all-cause mortality with the use of ICDs (two RCTs; RR 0.57, 95% CI 0.33 to 0.97, $p = 0.04$). One RCT reporting hospitalisations found higher rates per 1000 months' follow-up among people receiving an ICD (11.3 vs. 9.4, $p = 0.09$), with higher HF hospitalisations (19.9% vs. 14.9%).

Differences in QoL measured using the Health Utilities Index 3 (HUI3) were not statistically significant between groups. All-cause mortality for 12 prespecified subgroups was similar.

Non-ischaemic or idiopathic dilated cardiomyopathy

Meta-analysis found no significant difference in all-cause mortality between the groups (three RCTs; RR 0.77, 95% CI 0.52 to 1.15, $p = 0.20$). Two trials reported no significant differences in QoL. One trial reported no statistically significant differences in six prespecified subgroup analyses for all-cause mortality. Meta-analysis of the three cardiomyopathy trials and the non-ischaemic congestive HF subgroup of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) found a statistically significant reduction in all-cause mortality with ICD therapy (RR 0.74, 95% CI 0.58 to 0.93, $p = 0.01$).

Scheduled for coronary artery bypass graft

One RCT found no difference in all-cause mortality between the groups (RR 1.08, 95% CI 0.85 to 1.38, $p = 0.53$).

Health-related quality of life was significantly better among people receiving OPT for some measures. There was no difference in all-cause mortality among 10 prespecified subgroups.

A broad population with mild to moderate ischaemic/non-ischaemic heart failure and a left ventricular ejection fraction of ≤ 35%

One three-arm trial compared ICDs, amiodarone and placebo. Compared with placebo, ICDs reduced the risk of all-cause mortality [hazard ratio (HR) 0.77, 97.5% CI 0.62 to 0.96, $p = 0.007$]. No significant difference was found in QoL. QoL was lower in people who had had an ICD shock within the previous month than in those who had not received a shock. There was no interaction of ICD therapy with the cause of congestive HF. Compared with placebo, ICDs reduced the risk of all-cause mortality in those in NYHA class II but not in NYHA class III.

Adverse events

Between 5% and 61% of people with an ICD experienced an adverse event, 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% and 55%. Lead-, electrode- or defibrillator generator-related problems affected 1.8–14% of people in five trials reporting this.

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony

Compared with OPT, CRT-P reduced the risk of all-cause mortality (four RCTs; RR 0.75, 95% CI 0.58 to 0.96, $p = 0.02$). An improvement in NYHA class (three RCTs; RR 1.68, 95% CI 1.52 to 1.86, $p < 0.00001$), LVEF (one RCT; $p < 0.001$), exercise capacity (three RCTs) and QoL [four RCTs; Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score mean difference (MD) –10.33, 95% CI –13.31 to –7.36, $p < 0.00001$] was also found with CRT-P. Prespecified subgroup analysis found that 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 for 16 subgroups.

One RCT found that CRT-D reduced the risk of all-cause mortality compared with OPT (HR 0.64, 95% CI 0.48 to 0.86, $p = 0.003$). Improvements in NYHA class (57% vs. 38%, $p < 0.001$), exercise capacity (6-minute walk distance 46 m vs. 1 m) and QoL (MLWHFQ score –26 vs. –12, $p < 0.001$) were also found with CRT-D at 6 months.

The rate of SCD was higher with CRT-P than with CRT-D (RR 2.72, 95% CI 1.58 to 4.68, $p = 0.0003$), but all-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, $p = 0.12$), HF hospitalisations (28% vs. 29%) and changes in NYHA class, exercise capacity and QoL were similar for CRT-P and CRT-D.

Adverse events

The rate of device-related deaths was between 0.2% and 0.8% for CRT-P (two trials) and 0.5% for CRT-D. The rate of moderate or severe adverse events related to the implantation procedure was 10% for CRT-P and 8% for CRT-D in one trial, with 13% and 9% of CRT-P and CRT-D implantations, respectively, unsuccessful. Moderate or severe adverse events from any cause were more common with CRT-D than with 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 ICDs, CRT-D reduced the risk of all-cause mortality (eight RCTs; RR 0.84, 95% CI 0.73 to 0.96, $p = 0.01$) and HF hospitalisation (three 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 (four RCTs; RR 0.90, 95% CI 0.71 to 1.14, $p = 0.38$). An improvement in mean NYHA class (two RCTs; MD –0.19, 95% CI –0.34 to –0.05, $p = 0.008$) but not in the proportion of people who improved by one or more NYHA classes (three RCTs; RR 1.81, 95% CI 0.91 to 3.60, $p = 0.09$) was found with CRT-D. Improvements in LVEF (eight RCTs; MD 2.15, 95% CI 0.45 to 3.86, $p = 0.01$), exercise capacity and QoL (six RCTs; MLWHFQ score MD –6.9, 95% CI –10.4 to –3.4, $p = 0.0001$) were found with CRT-D compared with ICDs. Prespecified subgroup analyses found that longer QRS duration, women, left bundle branch block and non-ischaemic cardiomyopathy were associated with greater benefit from CRT-D for certain outcomes. One large RCT found significantly higher device- or implantation-related complications (13.3% vs. 6.8%, $p < 0.001$) and device-related hospitalisation (20% vs. 12.2%, HR 1.68, 95% CI 1.32 to 2.13, $p < 0.001$) with CRT-D than with ICDs.

Cost-effectiveness

A total of 1410 references were identified of which 51 economic evaluations were included in the review of cost-effectiveness (34 reported on ICDs, 15 reported on CRT and two reported on both ICDs and CRT). ICDs were reported to be cost-effective in almost half of the ICD studies. One relevant UK study reported a mean incremental cost-effectiveness ratio (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.

Six HRQoL studies were found. Two included people with an ICD; one found that the mean European Quality of Life-5 Dimensions (EQ-5D) score did not change with time after implant and the other reported no difference between EQ-5D scores of primary and secondary prevention patients and that QoL for ICD patients was similar to that of the general population. Four cohort studies reported EQ-5D scores in HF and the overall results showed decreased EQ-5D scores compared with scores in the general population, particularly in NYHA classes III and IV.

One joint manufacturer's submission was received from the Association of British Healthcare Industries (ABHI). The general approach taken in the manufacturer's submission seems reasonable although it is not clear whether or not uncertainty is properly assessed. Subgroups specified by ABHI do not directly address those scoped by NICE. Overall, the results show that for most subgroups there is at least one device with an ICER of < £30,000 per QALY gained, and in some cases a different device might have an ICER of < £20,000 per QALY gained.

Independent economic evaluation

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

The addition of ICD to OPT for the secondary prevention of SCD has an ICER of £19,479 per QALY gained compared with OPT alone. The probability of it being cost-effective at a willingness to pay (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 per QALY), as the ICER increased with age and 52% of these patients are

expected to be aged > 65 years. Subgroup analyses for ICD + OPT compared with OPT alone produced ICERs of £14,231 per QALY for people with remote myocardial infarction (MI), £29,756 per QALY for a broad population with mild to moderate HF and £26,028 per QALY for non-ischaemic cardiomyopathy. The parameters with the greatest 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 left ventricular systolic dysfunction and cardiac dyssynchrony

The addition of CRT-P to OPT (in the initial stage of management of HF) resulted in 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 resulted in 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 for CRT-D + OPT (£28,420 per QALY gained). At a WTP of £20,000 per QALY gained, initial management with OPT alone followed by implantation of the clinically necessary device is the strategy with the highest probability of being cost-effective (83%). Above a WTP of £28,000 per QALY, the strategy with the highest probability of being cost-effective is CRT-D + OPT (38%). The incremental cost-effectiveness results for the comparisons seem to be sensitive mainly to device-related costs and to parameters that determine the incremental benefit of the devices for patients' survival, such as the RRs of SCD and HF death for CRT-P. The device lifetime of CRT-D also was particularly influential because of 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 most cost-effective strategy for people with both conditions at a WTP range of £20,000–30,000 per QALY is initial management with OPT alone (followed by device implantation and subsequent upgrades as necessary). Both strategies with the initial implantation of CRT devices have ICERs of > £30,000 per QALY compared with OPT alone (CRT-D £35,193 per QALY; CRT-P £41,414 per QALY). Costs and QALYs for CRT-D and CRT-P are similar, as the effectiveness of CRT-P was assumed to be the same as for CRT-D. CRT-D + OPT has an ICER of £27,195 per QALY compared with ICD + OPT. At a WTP of £30,000 per QALY, OPT alone, ICD + OPT, CRT-D + OPT and CRT-P + OPT have a 44%, 31%, 15% and 10% probability of being cost-effective respectively. CRT-D + OPT becomes the intervention with the highest probability of being cost-effective above a WTP of £42,000 per QALY. Assuming the same HF progression as used in the model for people with HF and no ICD indication gives an ICER of £27,396 per QALY for CRT-D compared with OPT. The cost-effectiveness results for the comparison of CRT-D + OPT with ICD + OPT were fairly robust to the variation of input parameters. The most influential parameters were the RR of all-cause mortality for ICDs and the lifetime of the 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 independent model was adapted from the model structure used in the previous appraisal of CRT for HF [NICE technology appraisal (TA)120], providing a consistent approach and enabling comparability.

Despite following recognised guidance on developing economic models, the evaluation has some limitations. These include the use of structural assumptions about the risks and timing of reimplantation of devices and treatment options following occurrence of a major event from previous models; the extrapolation of trial survival estimates over time; and assumptions around parameter values when evidence was not available for specific patient groups, particularly for CRT-P in people with both

conditions. When limitations have arisen in the evaluation, these have been identified in the report. Assumptions made or data identified from alternative sources have been checked by seeking clinical advice and the effects of parameters thought to be influential to the results have been assessed through sensitivity analyses.

In general, the independent models were relatively robust to changes in the assumptions and data parameter values. Those parameters with the greatest impact on the cost-effectiveness results were the time horizon, the HR for all-cause mortality associated with the devices, and the lifetime of the devices.

Conclusions

Implantable cardiac defibrillators reduced all-cause mortality in people at increased risk of SCD, defined in trials as those with previous ventricular arrhythmias/cardiac arrest, remote MI, non-ischaemic cardiomyopathy (depending on data included) or ischaemic/non-ischaemic HF and LVEF $\leq 35\%$, but not in people scheduled for coronary artery bypass grafting or with recent MI. The addition of ICD to OPT was cost-effective at a WTP threshold of £30,000 for the scenarios modelled, and in some cases at a WTP threshold of £20,000, in patients at risk of SCD. CRT-P and CRT-D reduced all-cause mortality and HF hospitalisations and improved other outcomes in people with HF as a result of LVSD and cardiac dyssynchrony when compared with OPT. The rate of SCD was lower with CRT-D than with CRT-P, but other outcomes, including all-cause mortality, were similar. Both CRT-P and CRT-D had an ICER of $<$ £30,000 per QALY gained compared with OPT, as did the comparison between CRT-D and CRT-P in people with HF as a result of LVSD and cardiac dyssynchrony. In people with both conditions, CRT-D reduced the risk of all-cause mortality and HF hospitalisation, and improved other outcomes, compared with ICD. The ICER for the comparison of CRT-D + OPT with ICD + OPT but not with initial management with OPT alone was $<$ £30,000 per QALY (unless no difference in all-cause mortality was assumed). The costs and QALYs for CRT-D and CRT-P were similar.

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

Study registration

This study is registered as PROSPERO number CRD42012002062.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

This technology assessment has been undertaken on the request of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme to inform the National Institute for Health and Care Excellence (NICE) appraisal *Implantable Cardioverter Defibrillators for the Treatment of Arrhythmias and Cardiac Resynchronisation Therapy for the Treatment of Heart Failure (Review of TA95 and TA120)*.[1]

Description of the 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 HF 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 from LVSD are at risk of SCD from ventricular arrhythmia.

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 unco-ordinated and erratic contraction of the heart muscle of the ventricles. Patients with cardiomyopathies (diseases of heart muscle) account for a further 10–15% of cases 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]

Deaths in England and Wales from CHD in 2010 numbered 140,301 (*Table 1*). It is thought that approximately 50% of all CHD-related deaths are SCDs.[6] 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)[8,9] Commonly, VT develops initially followed by degeneration to VF, which then leads to the development of asystole.[10] According to guidelines of the American College of Cardiology, the American Heart Association and the European Society of Cardiology for the management of patients with ventricular arrhythmias and the prevention of SCD,[7] 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.[11–14]

People known to be at risk of SCD include those who have experienced a previous event that they survived, such as life-threatening arrhythmia (accounting for 5–10% of SCDs), haemodynamic abnormalities including HF (7–15% of SCDs) and acute coronary syndromes such as myocardial infarction (MI) and angina pectoris ($\leq$ 20% of SCDs).[6] However, in $\geq$ 30% of SCDs, CHD had not been previously diagnosed in the patient, and in one-third of SCDs the patients were known to have cardiac disease but were considered to be at low risk for SCD.[6]

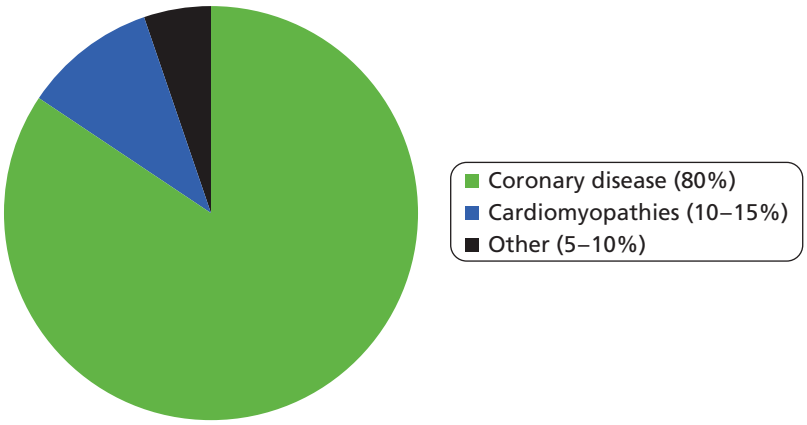

FIGURE 1 Proportions of SCD by different aetiologies.[3]

TABLE 1 Deaths in England and Wales from CHD and SCD in 2010

Cause of death	Total	Men	Women
[a]CHD[4]	140,301	81,405	58,896
SCD[b]	70,151	40,703	29,448
VF[c]	52,613–56,121	30,527–32,562	22,086–23,558

a Deaths from CHD defined as *International Classification of Diseases* codes I20–I25 inclusive.[5]
b Estimated as 50% of deaths from CHD.[6]
c Estimated as 75–80% of SCDs.[7]

A recent systematic review of 67 studies worldwide[15] estimated that the average survival rate for adults following an out-of-hospital cardiac arrest was 7%. Depending on the clinical scenario, a small proportion of people who do survive a first life-threatening cardiac episode may remain at 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 preventative strategies are implemented, recent studies have reported 5-year survival ranging from 69% to 100%,[16,17] although these may overestimate survival. It is important to recognise the multiple causes of the electrical process of VF, as not all patients with VF will be amenable to implantable cardiac defibrillator (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 on 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, the presence of inflammatory markers (e.g. C-reactive protein), hypertension, left ventricular hypertrophy, intraventricular conduction abnormalities [e.g. left bundle branch block (LBBB)], obesity, diabetes and lifestyle factors (e.g. smoking, excessive alcohol consumption, lack of physical activity, social and economic stressors).[7] Currently no optimal strategy for risk stratification exists.[18]

Heart failure

Heart failure 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 aged > 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 one-third of cases in the two UK studies.[20,21] The NICE scope for this appraisal[1] focuses 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 of 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 this study for those with HF and LVSD was 27.4%.[23] The severity of HF graded according to the New York Heart Association (NYHA) classification system 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 that they interpret and assign these classes.[28]

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 the incidence of HF was higher in Wales (men 44.6 and women 24.9 per 100,000 person-years) than in England (men 37.5 and women 23.0 per 100,000 person-years). The incidence of HF increased with age, being highest in those aged > 75 years (e.g. in England, men 326.0 and women 256.2 per 100,000 person-years), and incidence rates are higher in men than in women at all ages. From these data and those for Scotland and Northern Ireland, it has been estimated that there are > 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, of the total number of 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 that there were approximately 80,000 cases of HF with LVSD in 2009.

TABLE 2 The NYHA HF classification system

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

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
- '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-Ps) (or biventricular pacers).

Implantable cardioverter defibrillators 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 the 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 the functionality of both a CRT-P and an ICD and these are referred to as CRT-defibrillators (CRT-Ds).

Cardiac resynchronisation therapy is aimed at a specific subset of the HF 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 devices are appropriate for patients with a high risk of SCD, whereas CRT-P devices are appropriate in patients with less serious cardiac arrhythmias. However, as noted earlier, heart disease is a complex and progressive condition and patients who are initially implanted with a CRT-P may subsequently develop heart disease and be at risk of SCD, and an upgrade from a CRT-P to a CRT-D or an 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 ml, weight around 70 g, thickness approximately 13 mm) – 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) that 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 using the transthoracic method, but current CRT and ICD devices are placed under the skin in the pectoral region with transvenous 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 a 1-night stay in hospital. For secondary prevention the length of stay will depend on any underlying health problems. The longevity of CRT and ICD devices is limited by their battery life, which is in the range of 4–7 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. When possible the connecting leads are left in situ and only the generator unit itself is replaced, although eventually one or more of the connecting leads may also require replacement.

Modern devices can be specifically programmed to deliver resynchronisation pacing independently to the atria and ventricles of the heart to maximise synchronisation. 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 (HRS) 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], three letters to describe the sensed chamber (A, V or D) and a further three letters to describe whether pacing is inhibited (I) or triggered (T) in response to the sensed beat or, if dual pacing and sensing are programmed, whether dual (D) inhibition and triggering (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 (FDA) 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. A RCT comparing S-ICD with transvenous ICD (ClinicalTrials.gov identifier NCT01296022)[34] is currently under way and is due to complete in March 2015 and a registry study of S-ICD (ClinicalTrials.gov identifier 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 left ventricular 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.[36] The left phrenic nerve (which sends signals between the brain and the diaphragm) may be stimulated by the left ventricular pacing lead, causing uncomfortable diaphragmatic twitch, which could prevent optimal left ventricular lead placement and can hinder left ventricular stimulation. Phrenic nerve stimulation occurs in around 20% of patients with bipolar leads.[37] A recent systematic review of implantation-related complications in 11 ICD and seven 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. The 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%. The reported overall rate of leads dislodged during and after 3095 successful implantations was 5.9%. 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 a 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. The 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. Because of 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 ICD and CRT devices might at least in part explain why the number of device-related infections has increased.[40]

Setting, cost and equipment

Cardiac resynchronisation therapy and ICD device implants are carried out in local hospital or cardiac centres and can take from 1 to 3 hours depending on the type of device. Implantation of biventricular or resynchronisation devices is more complicated and takes longer than implantation of 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 3–12 months, requiring support from senior cardiologists, cardiac nurses and technicians. According to the HRS/European Heart Rhythm Association (EHRA) Expert Consensus on the Monitoring of Cardiovascular Implantable Electronic Devices,[41] whereas neither direct nor remote monitoring follow-up visits should be longer than 12 months, 6-monthly follow-up for ICD and CRT-D devices is recommended. The increasing complexity of devices could impact on the time needed for follow-up visits.

The average cost of the devices, including leads, has been estimated at £9692 for the ICD device, £3411 for CRT-P and £12,293 for CRT-D (see *Chapter 5*, *Parameters common to all populations*, and see *Table 109* for further details). 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 left ventricular 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.

Management of the disease

Existing guidelines for SCD and HF include NICE guidance on ICDs for arrhythmias[42] and CRT for HF,[43] and a NICE clinical guideline on the management of chronic HF.[44] Guidelines on the use of CRT have also been published by the European Society of Cardiology,[45] the Heart Failure Society of America[46] and the American College of Cardiology Foundation and the American Heart Association.[47] A 10-year *National Service Framework for Coronary Heart Disease* was published by the UK Department of Health in 2000,[48] 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.[49]

Sudden cardiac death

Diagnosis of sudden cardiac death

As 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 electrocardiogram (ECG) can detect abnormalities in the heart's electrical activity and may reveal evidence of heart damage from CHD, or signs of a previous or current heart attack. Electrophysiological testing is sometimes used to identify the origins of an arrhythmia and programmed electrical stimulation (PES) of the heart may be used to stimulate the heart to induce the arrhythmia. An electrophysiological or PES study may be used before

implantation of an ICD to confirm the need for an ICD or for diagnostic work-up. Other tests that may be used to identify SCD risk include ultrasound echocardiography and cardiac magnetic resonance imaging (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 sudden cardiac death

Ventricular arrhythmias, particularly sustained VT and VF, are life-threatening events. For patients who meet specified treatment criteria, the NICE guidance issued in 2006 [technology appraisal (TA)95[42]] recommends that ICD (or CRT-D) therapy is recommended for primary prevention (prevention of a first life-threatening arrhythmic event) and secondary prevention (prevention of an additional life-threatening event in survivors of sudden cardiac events or patients with recurrent unstable rhythms) of SCD. 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 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 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[42] (which does not cover non-ischaemic dilated cardiomyopathy) are that ICDs may be used as primary prevention for patients who have a history of previous ($\leq$ 4 weeks) MI and *either* left ventricular dysfunction with a left ventricular ejection fraction (LVEF) $<$ 35% (no worse than NYHA class III) *and* non-sustained VT on Holter (24-hour ECG) monitoring *and* inducible VT on electrophysiological testing *or* left ventricular dysfunction with a LVEF of $<$ 30% (no worse than NYHA class III) and a QRS duration of $\geq$ 120 milliseconds; or who have a familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia, or have undergone surgical repair of congenital heart disease.

Implantable cardioverter defibrillators 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).[42]

Optimal pharmacological therapy for sudden cardiac death

Chronic prophylactic antiarrhythmic drug (AAD) therapy is aimed at suppressing the development of arrhythmias in patients at high risk of SCD. The class III drugs such as amiodarone are used for specific indications. 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.[50] 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 fivefold increased risk of pulmonary and thyroid toxicity respectively[50] Other drugs that may be included in the OPT of SCD are angiotensin-converting enzyme (ACE) inhibitors (recommended for all patients with LVSD to improve ventricular geometry and function), aldosterone receptor antagonists (for people resistant to other drug therapy) and beta-blockers (to reverse ventricular remodelling) among others.[51]

Heart failure

Diagnosis of heart failure

The NICE clinical guideline CG108, *Chronic Heart Failure: Management of Chronic Heart Failure in Adults in Primary and Secondary Care*,[44] provides a diagnostic pathway for HF, the key elements of which are shown in *Figure 2*. Serum natriuretic peptides (SNPs; protein substances secreted by the wall of the heart when it is stretched or under increased pressure) should be measured in people with suspected HF without MI, although the guideline cautions that levels of SNPs can be reduced by certain conditions (e.g. obesity) or treatments (e.g. diuretics, 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 ECG and other tests (e.g. chest radiography, blood tests, urinalysis, spirometry) may be required to evaluate other possible diagnoses. Transthoracic Doppler two-dimensional 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 two-dimensional echocardiography) can be considered.

Management of heart failure

A patient presenting with the typical signs and symptoms of HF should receive specialist assessment including echocardiography.[44] If HF is diagnosed the goals of treatment are to reduce mortality and improve the health outcome of the patient. In clinical practice, pharmacological agents are routinely used as the first-line therapy in managing HF[44] (details of OPT for HF are given in *Optimal pharmacological therapy for heart failure*).

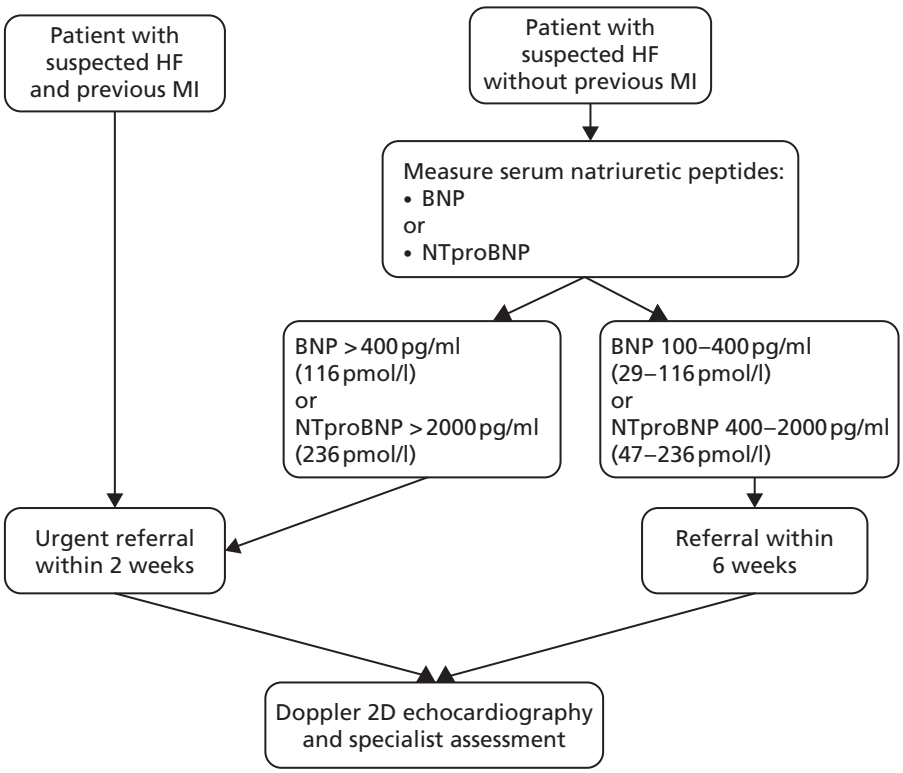

FIGURE 2 Key elements in the NICE HF guideline diagnostic pathway.[52] BNP, B-type natriuretic peptide; NTproBNP, N-terminal pro-B-type natriuretic peptide.

In addition to drug therapy, according to the NICE clinical guideline,[44] 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. Similarly, the European Society of Cardiology recommends that individuals with HF should be enrolled in a multidisciplinary care management programme.[53]

Implantable devices for heart failure

As the severity of HF symptoms increases, a patient's symptoms may no longer be controlled by OPT or lifestyle changes. There are multiple syndromes associated with HF that could predispose patients to the need for further intervention. In patients with HF, 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 HF[52] indicates that, when symptoms are not controlled by OPT, treatment with CRT-P or CRT-D can be considered for patients meeting specific criteria.

Current NICE guidance issued in 2007 (TA120[43]) recommends CRT-P as a treatment option for individuals with HF who fulfil all of 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 $\geq$ 150 milliseconds estimated by standard ECG or with a QRS duration of 120–149 milliseconds estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography; have a LVEF of $\leq$ 35%; are receiving OPT. CRT-D may be considered for individuals who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD device (see *Implantable devices for sudden cardiac death*).

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 HF. 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 may be indicated.[54]

Optimal pharmacological therapy for heart failure

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 the use of 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 comorbid hypertension and angina).

The NICE 2010 clinical guideline[44] suggests that medical drug therapy for HF has two aims – first, to improve morbidity (by reducing symptoms, improving exercise tolerance, reducing hospital admissions and improving QoL) and, second, to improve 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.

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 (also known as an angiotensin receptor blocker or 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)].[44]

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.[44]

Current service provision

Current service provision is difficult to ascertain as the most recent audits of the use of CRT devices and ICDs in England and Wales[55,56] suggest that 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.[57]

The National Heart Failure Audit April 2010–March 2011[58] 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*,[55] which compared the rates of implantation of bradycardia pacemakers, ICDs and CRT devices during 2000–10 in comparison with national targets (a recent update of the audit[56] provides additional data for January–December 2011 but is an interim version pending final publication). 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 and other networks 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[55] but other estimates that assume adherence to published guidelines suggest that the annual implant rate for ICDs should be higher, between 105 and 504 per million patients.[57] The wide regional variation in implant rates appears to suggest underuse in those regions with low implant rates.[57] The audit[55] 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[57] found that implant rates were higher in areas where the local hospital was a regional cardiac centre compared with 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.[57] The discrepancy observed within the study of cardiac networks 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.[57] A related study in the same cardiac network retrospectively investigated the management of ICD-implanted patients who developed HF.[59] Such patients may potentially benefit by being upgraded from an ICD to a CRT device. However, only a low proportion of these patients were 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.[59]

TABLE 3 Device implant rates in England during 2010 compared with national targets[55]

Device type	Average[a] (range) no. of implants per million patients, adjusted for age and sex	National target (no. 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[55] reported data on the types of physiological pacing that were employed and also some data on the presenting symptoms and ECG patterns in patients with implants. As there is substantial overlap in the indications for resynchronisation and defibrillation devices,[59] the choice of clinicians between ICD, CRT-D and CRT-P devices may in some cases have been arbitrary,[55] and the audit did not discriminate between all of the possible pacing and defibrillation modes that can be programmed in modern implantable devices. Overall, in England during 2010, an ICD was the device type employed most frequently for syncope/cardiac arrest with VT/VF; CRT-D devices were the most frequent type implanted for HF with VT/VF; and CRT-P devices were the most frequent type employed in patients who had HF without VT/VF. Both CRT-D and ICD devices, but rarely CRT-P devices, were used for prophylaxis (*Table 4*). All device types were implanted more often in men than in women (80.1% of ICD, 83.4% of CRT-D and 68.4% of CRT-P devices were implanted in men). In 2011, a much higher proportion of CRT-D devices were implanted for primary prevention than for secondary prevention (78.3% vs. 21.7% respectively), although the proportions of ICDs implanted for primary and secondary prevention were similar (48.3% and 51.4% respectively).[55]

The demand for device implants will increase because of a growing ageing population. In addition, there are increasing demands to expand the use of CRT devices, that is, to include individuals with NYHA class I–II symptoms, an ejection fraction of < 30% and a QRS interval 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[55] confirms that there has been a substantial increase in the number of CRT and ICD devices implanted in England and Wales during 2000–10. The interim update of the audit[56] 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 (see *Table 3*), there is considerable variation in the utilisation of implantable defibrillators across Europe,[55] and ICD/CRT-D implant rates are considerably higher in the USA than in Europe.[60] The UK has approximately 0.7 ICD implant centres per million population, which is lower than in France, Germany, Italy and the USA.[60] 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.[60] The recently collected data[55,60] suggest that systematic planning of ICD services is lacking in the UK, with underutilisation of CRT and ICD devices, although it is unclear if this impacts on the equality of service provision.

TABLE 4 Combinations of presenting symptoms and ECGs in resynchronisation and defibrillation device implant patients in England, 2010[55]

Presenting symptom and ECG	ICD (%)	CRT-D (%)	CRT-P (%)	Total (rounded) (%)
Syncope/cardiac arrest and VT/VF	79.3	20.4	0.2	100
HF and VT/VF	29.8	68.2	1.9	100
HF 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

Chapter 2 Definition of the decision problem

This chapter 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.[61] This assessment updates and expands on two previous technology assessment reports (TARs), *The Clinical and Cost-Effectiveness of Implantable Cardioverter Defibrillators: a Systematic Review*[62] (which itself was an update of a TAR published in 2000[63]) and *The Clinical Effectiveness and Cost-Effectiveness of Cardiac Resynchronisation (Biventricular Pacing) for Heart Failure: Systematic Review and Economic Model*.[64] The key differences between the present assessment and the previous assessments are outlined below and summarised in *Appendix 1*.

Decision problem

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

Three populations are defined by the NICE scope:[61]

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 ICD TAR.[62] For the present assessment this population is not restricted by NYHA classification and there is no specified cut-off for LVEF. The second group, people with HF as a result of LVSD and cardiac dyssynchrony, includes and expands on the population considered in the previous CRT TAR.[64] 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, was not considered in the previous TARs.[62,64] People with cardiomyopathy are not excluded from consideration in this assessment.

Although 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 there is considerable overlap between the groups: people with HF due to LVSD are at risk of SCD from ventricular arrhythmia.

The NICE scope[61] did not indicate whether any subgroups of patients were of interest. No subgroups were predefined in the earlier guidance (TA95[42]), but subgroup analyses were reported in some included studies by LVEF, QRS duration and history of HF requiring treatment. Subgroups that were thought to be of interest in TA120[43] and were therefore predefined were age, atrial fibrillation, NYHA class, degree of LVSD, degree of dyssynchrony and ischaemic and non-ischaemic HF. 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 LVEF, 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.

Overall aims and objectives of the 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 an increased risk of both SCD as a result of ventricular arrhythmias and HF as a result of LVSD and cardiac dyssynchrony despite OPT.

Chapter 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, which was sent to the advisory group 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.

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 HF. 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 HF. Searches to inform cost-effectiveness modelling were also conducted. Sources of information and search terms are provided in *Appendix 2*. 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, the Centre for Reviews and Dissemination (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; ClinicalTrials.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 (MS) to NICE were assessed for relevant studies that met the inclusion criteria, and the expert advisory group was contacted to identify additional published and unpublished evidence.

Inclusion and exclusion criteria

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

Population

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

Left ventricular systolic dysfunction was defined as a 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 a reduced LVEF, cardiac dyssynchrony and an indication for an ICD were considered as having both conditions.

TABLE 5 Summary of inclusion criteria

Population	People at increased risk of SCD as a result of ventricular arrhythmias despite OPT	People with HF as a result of LVSD 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)	ICDs; CRT-P; standard care (OPT alone)

Interventions

The interventions under consideration for each patient group are:

- for people at increased risk of SCD: ICDs in addition to OPT
- for people with HF: CRT-P or CRT-D in addition to OPT
- for people with both conditions: CRT-D in addition to OPT.

Comparators

The comparators under consideration for each patient group are:

- for people at increased risk of SCD: standard care (OPT without ICD)
- for people with HF: CRT-P or CRT-D were compared with each other; standard care (OPT without CRT)
- for people with both conditions: ICDs; CRT-P; standard care (OPT alone).

When screening studies for inclusion it became apparent that the pharmacological therapy in some of the older studies might 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 arm or the comparator arm was not optimal (i.e. was not current best practice based on clinical opinion) would be included in the systematic review.

Outcomes

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

- mortality (including progressive HF mortality, non-HF mortality, all-cause mortality and SCD)
- adverse effects of treatment
- HRQoL
- symptoms and complications related to tachyarrhythmias and/or HF
- HF hospitalisations
- change in NYHA class
- change in LVEF.

Study design

- For the systematic review of clinical effectiveness, only RCTs were eligible.
- Studies published as abstracts or conference presentations from 2010 onwards were included only 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 included only 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 QoL, primary studies or QoL data collected as part of a trial using the European Quality of Life-5 Dimensions (EQ-5D) (not visual analogue scale), and specified by NYHA class for people with HF, were included.
- Non-English-language studies were excluded.

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 earlier. 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 potentially 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 when necessary.

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

Critical appraisal

The risk of bias of the clinical effectiveness studies was assessed according to criteria devised by The Cochrane Collaboration.[65] 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 Jefferson,[66] the requirements of the NICE reference case[67] and the suggested guideline for good practice in decision-analytic modelling by Philips and colleagues[68] (see *Appendix 3*). Published studies carried out from the UK NHS and Personal Social Services (PSS) perspective were examined in more detail.

Method of data synthesis

Clinical effectiveness data were synthesised through a narrative review with tabulation of the results of included studies. When data were of sufficient quality and homogeneity, meta-analysis of the clinical effectiveness studies was performed to estimate the risk ratio (RR) and 95% confidence intervals (CIs) for relevant outcomes. The random-effects method was used. Meta-analysis was performed using Review Manager 5 (RevMan; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity was assessed using the chi-squared test and degrees of freedom (df), and the I^2 statistic. When standard deviations (SDs) were not presented in the published papers, these were calculated from the available statistics [CIs, standard errors (SEs) or *p*-values].[65] A minority of papers reported median values with 95% CIs; 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.

Chapter 4 Clinical effectiveness

Overall quantity of evidence identified

Searches identified a total of 4556 references after deduplication 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 that were retrieved but later excluded are listed in *Appendix 4* with reasons for exclusion. Papers were often excluded for more than one reason, with 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, summaries of which can be found in *Appendix 5*.

Twenty-six eligible RCTs were identified (*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 SCD as a result of ventricular arrhythmias (see *People at risk of sudden cardiac death as a result of ventricular arrhythmias*), four trials were considered to involve people with HF as a result of LVSD and cardiac dyssynchrony (see *People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony*) and nine RCTs were considered to involve people with both of these conditions (see *People with both conditions*). Further details on the quantity and quality of research for each of these populations are described in the following sections.

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

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 [the Multicenter Unsustained Tachycardia Trial (MUSTT)[146]] were included in the 2005 TAR,[62] as can be seen in *Table 7*. One further RCT [the Midlands Trial of Empirical Amiodarone versus Electrophysiology-Guided Interventions and Implantable Cardioverter-Defibrillators (MAVERIC)[147]] was noted in the 2005 TAR[62] as in progress at that time. The interventions in the MUSTT[146] and MAVERIC[147] trials did not meet the scope of the present review; however, as these were included in the previous TARs[62,63] they are discussed in *Subgroup analyses reported by included randomised controlled trials*. A list of other excluded studies can be seen in *Appendix 4*.

The RCTs used different criteria to identify groups at 'high risk' of SCD from ventricular arrhythmia. The Antiarrhythmics Versus Implantable Defibrillators (AVID),[71] Cardiac Arrest Study Hamburg (CASH),[81] Canadian Implantable Defibrillator Study (CIDS)[84] and Defibrillator versus Beta-Blockers for Unexplained Death in Thailand (DEBUT)[89] trials included people who had had a previous ventricular arrhythmia or who had been resuscitated from cardiac arrest. Four studies included people with either a recent MI [Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)[95] and the Immediate Risk Stratification Improves Survival (IRIS) trial[97]] or a MI > 3–4 weeks before study entry [Multicenter Automatic Defibrillator Implantation Trial I (MADIT I),[99] MADIT II[101]]. The Amiodarone Versus Implantable Cardioverter-Defibrillator Randomized Trial (AMIOVIRT),[69] Cardiomyopathy Trial (CAT)[82] and Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE)[90] trial included people with cardiomyopathy. The Coronary Artery Bypass Graft Patch (CABG Patch) trial[75] recruited patients scheduled for coronary artery bypass graft surgery and at high risk for sudden death, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[105] recruited a broad population of patients with mild to moderate HF. The results will be discussed according to the 'high-risk' group of the participants.

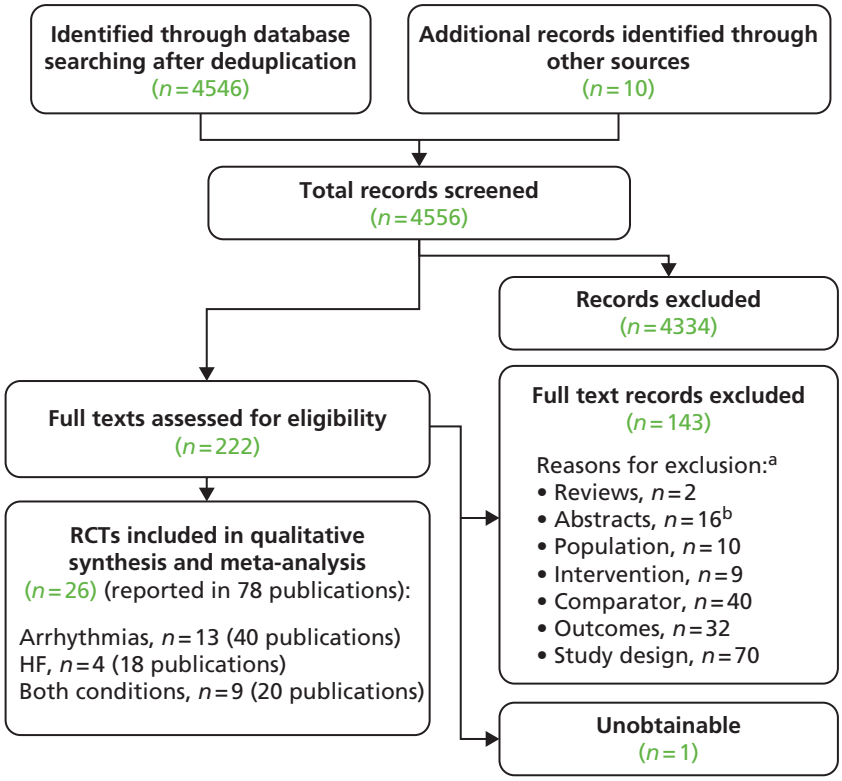

FIGURE 3 Flow chart of identification of studies. a, Studies could be excluded for more than one reason; b, 16 of the abstracts/conference presentations were published from 2010 onwards (see *Appendix 4*) and were excluded as there were insufficient details included to allow an appraisal of the methodology and an assessment of the results as per the protocol.

TABLE 6 List of RCTs included in the systematic review of clinical effectiveness

Study	Publication[a]
People at increased risk of SCD as a result of ventricular arrhythmias	
AMIOVIRT	**Strickberger *et al.* 2003,[69]** Wijetunga and Strickberger 2003[70]
AVID	**AVID investigators 1997[71]** and 1999,[72] Hallstrom 1995,[73] Schron *et al.* 2002[74]
CABG Patch	**Bigger 1997,[75]** CABG Patch Trial Investigators and Coordinators 1993,[76] Bigger *et al.* 1998[77] and 1999,[78] Spotnitz *et al.*1998,[79] Namerow *et al.* 1999[80]
CASH	**Kuck *et al.* 2000[81]**
CAT	**Bänsch *et al.* 2002,[82]** German Dilated Cardiomyopathy Study investigators 1992[83]
CIDS	**Connolly *et al.* 2000[84]** and 1993,[85] Sheldon *et al.* 2000,[86] Irvine *et al.* 2002,[87] Bokhari *et al.* 2004[88]
DEBUT	**Nademanee *et al.* 2003[89]**
DEFINITE	**Kadish *et al.* 2004[90]** and 2000,[91] Schaechter *et al.* 2003,[92] Ellenbogen *et al.* 2006,[93] Passman *et al.* 2007[94]
DINAMIT	**Hohnloser *et al.* 2004[95]** and 2000[96]
IRIS	**Steinbeck *et al.* 2009[97]** and 2004[98]
MADIT I	**Moss *et al.* 1996,[99]** MADIT Executive Committee 1991[100]
MADIT II	**Moss *et al.* 2002[101]** and 1999,[102] Greenberg *et al.* 2004,[103] Noyes *et al.* 2007[104]
SCD-HeFT	**Bardy *et al.* 2005,[105]** Mitchell *et al.* 2008,[106] Mark *et al.* 2008,[107] Packer *et al.* 2009[108]

TABLE 6 List of RCTs included in the systematic review of clinical effectiveness (*continued*)

Study	Publication[a]
People with HF as a result of LVSD and cardiac dyssynchrony	
CARE-HF	**Cleland *et al.* 2005,**[109] 2001,[110] 2006,[111] 2007[112] and 2009,[113] Gras *et al.* 2007,[36] Gervais *et al.* 2009,[114] Ghio *et al.* 2009[115]
COMPANION	**Bristow *et al.* 2004**[116] and 2000,[117] US Food and Drug Administration 2004,[118] Carson *et al.* 2005,[119] Anand *et al.* 2009[120]
MIRACLE	**Abraham *et al.* 2002**[121] and 2000,[122] US Food and Drug Administration 2001,[123] St John Sutton *et al.* 2003[124]
MUSTIC	**Cazeau *et al.* 2001**[125]
People with both conditions described above	
CONTAK-CD	**Higgins *et al.* 2003,**[126] Saxon *et al.* 1999,[127] Lozano *et al.* 2000,[128] US Food and Drug Administration 2002[129]
MADIT-CRT	**Moss *et al.* 2009**[130] and 2005,[131] Solomon *et al.* 2010,[132] Goldenberg *et al.* 2011,[133,134] Arshad *et al.* 2011[135]
MIRACLE ICD	**Young *et al.* 2003**[136]
MIRACLE ICD II	**Abraham *et al.* 2004**[137]
Piccirillo 2006	**Piccirillo *et al.* 2006**[138]
Pinter 2009	**Pinter *et al.* 2009**[139]
RAFT	**Tang *et al.* 2010**[140] and 2009[141]
RethinQ	**Beshai *et al.* 2007,**[142] Beshai and Grimm 2007[143]
RHYTHM ICD	**US Food and Drug Administration 2004**[144] and 2005[145]

AMIOVIRT, Amiodarone Versus Implantable Cardioverter-Defibrillator Randomized Trial; AVID, Antiarrhythmics Versus Implantable Defibrillators; CABG Patch, Coronary Artery Bypass Graft Patch; CARE-HF, CArdiac REsynchronization in Heart Failure; CASH, Cardiac Arrest Study Hamburg; CAT, Cardiomyopathy Trial; CIDS, Canadian Implantable Defibrillator Study; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Patients with Left Ventricular Systolic Dysfunction; CONTAK-CD, RCT of the CONTAK-CD device; DEBUT, Defibrillator versus Beta-Blockers for Unexplained Death in Thailand; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; IRIS, Immediate Risk Stratification Improves Survival; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD, Multicenter InSync ICD Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RethinQ, Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS; RHYTHM ICD, Resynchronization for the HemodYnamic Treatment for Heart failure Management Implantable Cardioverter Defibrillator; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.
a Bold text indicates primary or key publication.

TABLE 7 Comparison of included studies in the previous and present TARs: people at risk of SCD as a result of ventricular arrhythmia

Study	2005 TAR[62] (reason for exclusion)	Present TAR (participants)	Publication[a]
Secondary prevention			
AVID	Included	Included (cardiac arrest)	**AVID investigators 1997[71]** and 1999,[72] Hallstrom 1995,[73] Schron *et al.* 2002[74]
CASH	Included	Included (cardiac arrest)	**Kuck *et al.* 2000[81]**
CIDS	Included	Included (cardiac arrest)	**Connolly *et al.* 2000[84]** and 1993,[85] Sheldon *et al.* 2000,[86] Irvine *et al.* 2002,[87] Bokhari *et al.* 2004[88]
DEBUT	Excluded (participants)	Included (sudden unexpected death syndrome)	**Nademanee *et al.* 2003[89]**
Primary prevention			
DINAMIT	In progress	Included (early post MI)	**Hohnloser *et al.* 2004[95]** and 2000[96]
IRIS	New	Included (early post MI)	**Steinbeck *et al.* 2009[97]** and 2004[98]
MADIT I	Included	Included (remote from MI)	**Moss *et al.* 1996,[99]** MADIT Executive Committee 1991[100]
MADIT II	Included	Included (remote from MI)	**Moss *et al.* 2002[101]** and 1999,[102] Greenberg *et al.* 2004,[103] Noyes *et al.* 2007[104]
AMIOVIRT	Excluded (participants)	Included (cardiomyopathy)	**Strickberger *et al.* 2003,[69]** Wijetunga and Strickberger 2003[70]
CAT	Included	Included (cardiomyopathy)	**Bänsch *et al.* 2002,[82]** German Dilated Cardiomyopathy Study investigators 1992[83]
DEFINITE	Excluded (participants)	Included (cardiomyopathy)	**Kadish *et al.* 2004[90]** and 2000,[91] Schaechter *et al.* 2003,[92] Ellenbogen *et al.* 2006,[93] Passman *et al.* 2007[94]
CABG Patch	Included	Included (need for CABG)	**Bigger 1997,[75]** CABG Patch Trial Investigators and Coordinators 1993;[76] Bigger *et al.* 1998[77] and 1999,[78] Spotnitz *et al.*1998,[79] Namerow *et al.* 1999[80]
MUSTT	Included	Excluded because of intervention	**Buxton *et al.* 1999,[146]** Lee *et al.* 2002[148]
SCD-HeFT	In progress, in NICE TA95[42]	Included (HF)	**Bardy *et al.* 2005,[105]** Mitchell *et al.* 2008,[106] Mark *et al.* 2008,[107] Packer *et al.* 2009[108]

AMIOVIRT, Amiodarone Versus Implantable Cardioverter-Defibrillator Randomized Trial; AVID, Antiarrhythmics Versus Implantable Defibrillators; CABG Patch, Coronary Artery Bypass Graft Patch; CASH, Cardiac Arrest Study Hamburg; CAT, Cardiomyopathy Trial; CIDS, Canadian Implantable Defibrillator Study; DEBUT, Defibrillator versus Beta-Blockers for Unexplained Death in Thailand; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; IRIS, Immediate Risk Stratification Improves Survival; MADIT, Multicenter Automatic Defibrillator Implantation Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.
a Bold text indicates primary or key publication.

Characteristics of the included studies

Study characteristics are summarised in *Tables 8–10* and participant characteristics are summarised in *Tables 11–13*. Additional details can be found in *Appendix 7*.

TABLE 8 Study characteristics: cardiac arrest survivors/ventricular arrhythmia – secondary prevention

Parameter	AVID[71]	CASH[81]	CIDS[84]	DEBUT[89]
Study design	RCT	RCT	RCT	RCT (pilot and main study)
Target population	Resuscitated from near-fatal VF; or symptomatic sustained VT with haemodynamic compromise	Resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmia	Previous sustained ventricular arrhythmia	SUDS survivors or probable survivors
Intervention	ICD + medical therapy	ICD + medical therapy	ICD + AAD for symptomatic VT	ICD + beta-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 beta-blockers if intolerable side effects
Country (no. of centres)	USA (53), Canada (3)	Germany (multicentre, number unclear)	Canada (19), Australia (3), USA (2)	Thailand (unclear)
Sample size (randomised)	1016	288	659	Pilot 20, main trial 66
Length of follow-up	Mean 18.2 (SD 12.2) months	Mean 57 (SD 34) months	Mean 3 years	Maximum 3 years
Key inclusion criteria	VF, VT with syncope or VT without syncope but with ejection fraction ≤ 0.40 and systolic blood pressure < 80 mmHg; chest pain or near syncope.[73] If patients underwent revascularisation their ejection fraction had to be ≤ 0.40	Not reported. Rate was the only criterion selected for detection of a sustained ventricular arrhythmia	Any of following in the absence of either recent acute MI (≤ 72 hours) 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 ≥ 150 bpm causing presyncope or angina in a patient with a LVEF ≤ 35%; or unmonitored syncope with subsequent documentation of either spontaneous VT ≥ 10 seconds or sustained (≥ 30 seconds) monomorphic VT induced by programmed ventricular stimulation	SUDS survivor: a healthy subject without structural heart disease who had survived unexpected VF or cardiac arrest after successful resuscitation 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 electrophysiological testing

bpm, beats per minute; RBBB, right bundle branch block; SUDS, sudden unexplained death syndrome.

TABLE 9 Study characteristics: post MI – primary prevention

Parameter	DINAMIT[95]	IRIS[97]	MADIT I[99]	MADIT II[101]
Target population	Recent MI (6–40 days); reduced LVEF and impaired cardiac autonomic function	Recent MI (≤ 31 days) and predefined markers of elevated risk	Previous MI and left ventricular dysfunction	High-risk cardiac patients with previous MI and advanced left ventricular dysfunction
Study design	RCT	RCT	RCT	RCT
Intervention	ICD + OPT	ICD + OPT	ICD + conventional medical therapy	ICD + conventional medical therapy
Comparator	OPT	OPT	Conventional medical therapy	Conventional medical therapy
Country (no. of centres)	Canada (25), Germany (21), France, (8), UK (4), Poland (4), Slovakia (2), Austria (2), Sweden (2), USA (2), the Czech Republic (1), Switzerland (1), Italy (1)	Austria, the Czech Republic, Germany, Hungary, Poland, the Russian Federation, Slovakia (total 92)	USA (30), Europe (2)	USA (71), Europe (5)
Sample size	674	898	196	1232
Length of follow-up	Mean 30 (SD 13) months	Average 37 (range 0 to 106) months	Average 27 (range < 1 to 60) months	Average 20 months (range 6 days to 53 months)
Key inclusion criteria	Recent MI (6–40 days previously); LVEF ≤ 0.35; SD of normal-to-normal RR intervals of ≤ 70 milliseconds or a mean R–R interval of ≤ 750 milliseconds (heart rate ≥ 80 bpm) over a 24-hour period as assessed by 24-hour Holter monitoring performed at least 3 days after the infarction	Predefined markers of elevated risk – at least one of heart rate ≥ 90 bpm on first available ECG (within 48 hours of MI) and LVEF ≤ 40% (on one of days 5–31 after the MI); non-sustained VT of three or more consecutive ventricular premature beats during Holter ECG monitoring, with a heart rate ≥ 150 bpm (on days 5–31)	NYHA class I, II or III; LVEF ≤ 0.35; Q-wave or enzyme-positive MI > 3 weeks before entry; a documented episode of asymptomatic, unsustained VT unrelated to an acute MI; no indications for CABG or coronary angioplasty within past 3 months; sustained VT or fibrillation reproducibly induced and not suppressed after the intravenous administration of procainamide (or equivalent)	LVEF ≤ 0.30 in last 3 months; MI > 1 month before study entry

bpm, beats per minute.

TABLE 10 Study characteristics: cardiomyopathy, CABG surgery and HF – primary prevention

	Cardiomyopathy			CABG surgery	HF
Parameter	AMIOVIRT[69]	CAT[82]	DEFINITE[90]	CABG Patch[75]	SCD-HeFT[105]
Target population	Non-ischaemic (DCM) and asymptomatic non-sustained VT	Recent-onset idiopathic DCM and impaired LVEF and without documented symptomatic VT	Non-ischaemic cardiomyopathy and moderate to severe left ventricular dysfunction	Patients scheduled for CABG surgery and at risk for sudden death (LVEF < 0.36 and abnormalities on ECG)	Broad population of patients with mild to moderate HF
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 ventricular arrhythmia	Amiodarone or placebo (two 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 2 (SD 1.3) years	2 years	Mean 29 (SD 14.4) months	Mean 32 months	Median 45.5 (range 24 to 72.6) months
Key inclusion criteria	Non-ischaemic DCM (left ventricular dysfunction in the absence of, or disproportionate to the severity of, CAD); LVEF ≤ 0.35; asymptomatic non-sustained VT; NYHA class I–III	NYHA class II or III; LVEF ≤ 30%; aged 18–70 years; symptomatic DCM ≤ 9 months	LVEF < 36%; presence of ambient arrhythmias; history of symptomatic HF; presence of non-ischaemic DCM	Scheduled for CABG surgery; LVEF < 0.36; marker of arrhythmia: abnormalities on ECG	NYHA class II or III; chronic, stable CHF from ischaemic or non-ischaemic causes; LVEF ≤ 35%; ischaemic CHF defined as LVSD associated with marked stenosis or a documented history of MI; non-ischaemic CHF defined as LVSD without marked stenosis

CAD, coronary artery disease; CHF, congestive heart failure; DCM, dilated cardiomyopathy.
a AADs discouraged but allowed for symptomatic atrial fibrillation or supraventricular arrhythmias.

TABLE 11 Key participant characteristics: cardiac arrest – secondary prevention

	AVID[71]		CASH[81]			CIDS[84]		DEBUT (pilot trial)[89]		DEBUT (main trial)[89]	
				AAD							
Parameter	ICD	AAD	ICD	Amiodarone	Metoprolol	ICD	AAD	ICD	Beta-blocker	ICD	Beta-blocker
Sample size, *n*	507	509	99	92	97	328	331	10	10	37	29
Age (years), 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]
Sex, % 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
Ischaemic 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 CHF, %	45	40	0	0	0	51.2	49.5	0	0	0	0
NYHA I, %	48	48	23	25	32	37.8	39.9	100	100	100	100
NYHA II, %			59	57	55			0	0	0	0
NYHA III, %	7	12	18	18	13	11.0	10.6	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 (milliseconds), 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 (milliseconds), mean (SD) or [SEM]	116 (26)	117 (26)	NR	NR	NR	NR	NR	98 [29]	92 [12]	99 [30]	95 [16]
BBB (unspecified), %	23	25	17	23	19	NR	NR	NR	NR	NR	NR

BBB, bundle branch block; bpm, beats per minute; CHF, congestive heart failure; NR, not reported; SEM, standard error of the mean.
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: MI

	DINAMIT[95]		IRIS[97]		MADIT I[99]		MADIT II[101]	
Parameter	ICD	OPT	ICD	OPT	ICD	OPT	ICD	OPT
Sample size, *n*	332	342	445	453	95	101	742	490
Age (years), 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 (milliseconds), mean (SD)	107 (24)	105 (23)	NR	NR	NR	NR	50% ≥ 120 milliseconds	51% ≥ 120 milliseconds
LBBB/RBBB, %	NR	NR	10.1/NR	6.4/NR	7/NR	8/NR	19/9	18/7

NR, not reported; NSVT, non-sustained ventricular tachycardia; RBBB, right bundle branch block.
a At discharge for 885 surviving patients.

TABLE 13 Participant characteristics: cardiomyopathy, CABG surgery and HF

	Cardiomyopathy						CABG surgery		HF		
	AMIOVIRT[69]		CAT[82]		DEFINITE[90]		CABG Patch[75]		SCD-HeFT[105]		
Parameter	ICD	Amiodarone	ICD	Control	ICD + OPT	OPT	ICD	Control	ICD	Amiodarone	Placebo
Sample size, *n*	51	52	50	54	229	229	446	454	829	845	847
Age (years), 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 [51.9–69.2][a]	60.4 [51.7–68.3][a]	59.7 [51.2–67.8][a]
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
Ischaemic heart disease, %[b]	4.9	11	NR	NR	NR	NR	NR	NR	NR	NR	NR
Duration of cardiomyopathy, mean (SD) or [median, range]	2.9 (4.0) years	3.5 (3.9) years	[3.0 months]	[2.5 months]	[2.39, 0.00–21.33 years[c]]	[3.27, 0.0–38.5 years[c]]					
NYHA class, %											
I	18	13	0	0	25.3	17.9	NR	NR	0		
II	64	63	66.7	64.1	54.2	60.7	71	74	70		
III	16	24	33.3	35.8	20.5	21.4			30		
IV	0	0	0	0	0	0	NR	NR	0		
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 [19.0–30.0][a]	25.0 [20.0–30.0][a]	25.0 [20.0–30.0][a]
QRS interval (milliseconds), mean (SD) or [range]	NR	NR	102 (29)	114 (29)	114.7 [78–196]	115.5 [79–192]	71%[d]	74%[d]	NR	NR	NR
LBBB/RBBB, %	16/42	8/53	24/2	37/0	19.7/3.5	19.7/3.1	10/NR	12/NR	NR	NR	NR

NR, not reported; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex; RBBB, right bundle branch block.
a Median plus interquartile range.
b One major epicardial coronary artery with ≥ 70% stenosis.
c Duration of HF, $p = 0.04$.
d Proportion of people with a QRS interval > 100 milliseconds.

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 an ICD)'. Concepts of OPT have changed over time and OPT varies depending on the population (e.g. previous VF, post MI, HF), 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 ICDs with AADs, including either amiodarone or a beta-blocker (sotalol) (AVID[71]), amiodarone or a beta-blocker (metoprolol) in separate groups (CASH[81]) or amiodarone (CIDS[84]), or with a beta-blocker (propranolol) (DEBUT[89]). Use of other medication was permitted in these trials. AVID[71] permitted the use of aspirin, beta-blockers and ACE inhibitors when clinically appropriate in both groups. CASH[81] reported concurrent therapies at discharge (see *Pharmacological therapy* for further details of pharmacological therapy received by participants in all included trials). CIDS[84] stated that AADs could be used in both groups to control supraventricular or non-sustained VTs that were symptomatic or might cause discharge of the ICD. DEBUT[89] permitted other beta-blocking agents or amiodarone if intolerable side effects developed from propranolol or if frequent shocks from recurrent VF occurred, but did not provide additional data.

Trials of people with recent (IRIS,[97] DINAMIT[95]) or remote (MADIT I,[99] MADIT II)[101] MI compared ICDs + OPT with OPT, although the pharmacological therapy in MADIT may not be considered optimal by current standards.

The trials of people with cardiomyopathy compared ICDs + OPT with amiodarone + OPT (AMIOVIRT[69]) or ICDs + OPT with OPT (CAT,[82] DEFINITE[90]).

The CABG Patch trial[75] included people scheduled for CABG surgery and compared ICDs + OPT with OPT (the trial protocol prohibited use of AADs for asymptomatic ventricular arrhythmias), although the pharmacological therapy may not be considered optimal by current standards. 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.

The SCD-HeFT trial[105] was a three-arm trial comparing ICDs, amiodarone and placebo in a broad population of patients with mild-to moderate HF. All participants received OPT.

Participants

Cardiac arrest The DEBUT trial[89] differed notably from the other three trials (AVID,[71] CASH[81] and CIDS[84]) of people resuscitated from cardiac arrest as participants in the DEBUT trial[89] were survivors or probable survivors (symptoms indicative of the clinical presentation) of sudden unexplained death syndrome (SUDS) with otherwise normal hearts. All participants in the DEBUT study[89] 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 the AVID,[71] CASH[81] and CIDS[84] trials had ischaemic heart disease (70–83%). A small proportion of those in the CASH[81] and CIDS[84] trials had dilated cardiomyopathy. Two-thirds of participants in the AVID trial[71] and around three-quarters of those in the CIDS trial[84] had a previous MI.

All participants in the CASH[81] and DEBUT[89] trials, 60% in the AVID trial[71] and 50% in the CIDS trial[84] had congestive heart failure (CHF). The majority (approximately 87%) of people in the CASH trial[81] had NYHA class I or class II HF, whereas about 40% of those in the CIDS trial[84] and half of those in the AVID trial[71]

fell into these categories. Only 10–11% of participants in the AVID[71] and CIDS[84] trials had moderate to severe HF (NYHA class III and IV), whereas 16% of people in the CASH trial[81] had NYHA class III HF and none had NYHA class IV HF. Mean LVEF was higher in the CASH trial[81] (46%) than in the AVID trial[71] (32%) or the CIDS trial[84] (34%), suggesting that there may have been a disproportionate representation of relatively healthy participants in the CASH trial.[81] The mean QT interval ranged from 387 milliseconds (DEBUT[89]) to 445 milliseconds (AVID).[71]

The participants in the DEBUT trial[89] were younger (mean age 40–48 years) than those in the other three trials (mean age 56–65 years) and all had NYHA class I HF. LVEF was higher in the DEBUT trial[89] (mean LVEF 66–69%) than in the AVID,[71] CASH[81] and CIDS[84] trials.

Myocardial infarction The MADIT I[99] and MADIT II[101] trials included people who had had a MI > 3 weeks or > 1 month previously. Participants in MADIT I[99] were also required to have a LVEF of ≤ 35%, whereas the MADIT II trial[101] required advanced left ventricular dysfunction (LVEF ≤ 30%). The DINAMIT[95] and IRIS[97] trials recruited participants with a recent MI (within 6–40 days and 5–31 days respectively). DINAMIT[95] required participants to have a LVEF of ≤ 35% and a SD of normal-to-normal R–R intervals of ≤ 70 milliseconds or a mean R–R interval of ≤ 750 milliseconds (heart rate ≥ 80 beats per minute) over 24 hours. The IRIS trial[97] included people with at least one of the following markers of risk: heart rate ≥ 90 beats per minute on the first available ECG and LVEF ≤ 40%; or non-sustained ventricular tachycardia (NSVT) of ≤ 3 consecutive ventricular premature beats during Holter ECG monitoring with a heart rate of ≥ 150 beats per minute.

The DINAMIT trial[95] had the greatest majority of participants in NYHA class II or III (around 88%); the corresponding percentages in the IRIS,[97] MADIT I[99] and MADIT II[101] trials were 27%, 63–67% and 60% respectively. The trials had either no or very few participants in NYHA class IV. Mean LVEF ranged from 23%[101] to 35%,[97] reflecting the different inclusion criteria of the studies.

The mean age of the participants in these trials was similar, ranging from 61.5 years in the DINAMIT trial[95] to 65 years in MADIT II.[101] The majority of participants (from 76% in DINAMIT[95] to 92% in MADIT I[99]) were men.

Cardiomyopathy The AMIOVIRT[69] and DEFINITE[90] trials recruited people with non-ischaemic dilated cardiomyopathy, NSVT and a LVEF of ≤ 35%. CAT[82] enrolled people with recent-onset (< 9 months) idiopathic dilated cardiomyopathy and a LVEF of ≤ 30%, but without documented symptomatic ventricular arrhythmias. Note that despite participants not having suffered ventricular arrhythmias, the low LVEF indicates a risk of ventricular arrhythmias and SCD and CAT[82] was therefore judged eligible for inclusion in this review. Also, NSVT 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. The AMIOVIRT[69] (13–18%) and DEFINITE[90] (18–25%) trials included more people in NYHA class I than the CAT trial,[82] as this was an exclusion criteria of CAT.[82] Despite the lower cut-off for LVEF for inclusion in CAT,[82] the mean LVEF at baseline was similar or slightly higher than in the other two trials (CAT[82] 24–25%, AMIOVIRT[69] 22–23%, DEFINITE[90] 21–22%). The mean QRS interval was similar between CAT[82] [ICD 102 (SD 29) milliseconds, OPT 114 (SD 29) milliseconds] and DEFINITE[90] [115 (range 78–196) milliseconds], although the measures of variance suggest that some participants had cardiac dyssynchrony.

Participants in CAT[82] had a median duration of symptoms of just 3 months, compared with around 3 years in AMIOVIRT[69] and DEFINITE.[90] The participants in CAT[82] were also slightly younger (mean age 52 years) than in AMIOVIRT[69] (mean age 59 years) or DEFINITE[90] (mean age 58 years). The majority of participants (approximately 71% in AMIOVIRT[69] and DEFINITE[90] and 80% in CAT[82]) were men.

Coronary artery bypass graft surgery Participants in CABG Patch[75] were scheduled for CABG surgery and at risk for SCD (LVEF < 36%) with abnormalities on ECG. People with a history of sustained VT or VF

were excluded. The majority of participants (71–74%) were in NYHA class II or III with a mean LVEF of 27%. Most participants (83%) had had a previous MI. Mean age was about 64 years and 82–87% of participants were men.

Mild to moderate heart failure SCD-HeFT[105] included a broad population of people with mild to moderate HF from ischaemic or non-ischaemic causes and a LVEF of $\leq 35\%$. Ischaemic CHF was defined as LVSD associated with a $\geq 75\%$ narrowing of at least one of three major coronary arteries (marked stenosis) or a documented history of MI. Non-ischaemic CHF was defined as LVSD 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 one-quarter of participants had NSVT. The median age was 60 years and most participants (77%) were men.

Pharmacological therapy

Tables 14 and *15* display medication at hospital discharge.

Cardiac arrest Two-thirds of participants in the AVID trial[71] were receiving ACE inhibitors. Only 6% of the ICD group received AADs at discharge. Beta-blockers were more common among the ICD group (42.3%) than among 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 the AVID trial[71] 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 the AVID trial[71] received diuretics, around 37% received nitrates and 12% (AAD arm) and 18% (ICD arm) received calcium channel blockers. Digitalis was received by 41% (AAD arm) and 47% (ICD arm) of participants ($p = 0.04$). The pharmacological therapy provided in the AVID trial[71] would have been considered optimal at the time that 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 the CASH trial[81] received ACE inhibitors at hospital discharge. The ICD and metoprolol groups did not receive any AADs, 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 the CASH trial[81] received warfarin, less than one-third received diuretics, around 30% received nitrates and 12% (metoprolol arm) to 26% (ICD arm) received calcium channel blockers. Digitalis was received by 15% (metoprolol arm) to 26% (ICD arm) of participants. The pharmacological therapy provided in the CASH trial[81] would have been considered optimal at the time that 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 that the trial was undertaken.

None of the participants in the CIDS trial[84] received ACE inhibitors at hospital discharge. Class I antiarrhythmics 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 the CIDS trial[84] 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 in the DEBUT trial;[89] however, use of beta-blockers was low in the ICD group (8/47 in main trial and pilot study combined).

Myocardial infarction Both groups in the DINAMIT trial[95] 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%. The IRIS trial[97] had a similarly high usage of ACE inhibitors (91%), antiplatelet agents (96%), beta-blockers (96%) and statins (92%).

TABLE 14 Medication at discharge: cardiac arrest and MI

	Cardiac arrest (secondary prevention)							Recent MI				Remote MI			
	AVID[71]		CASH[81]			CIDS[84]		DINAMIT[95]		IRIS[97]		MADIT I[99a]		MADIT II[101b]	
Medication	ICD	AAD	ICD	Amiodarone	Metoprolol	ICD	Amiodarone	ICD	OPT	ICD	OPT	ICD	OPT	ICD	OPT
Sample size, *n*	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 AAD	4.2	1.2													
Class I antiarrhythmic						5.5	2.4					12	10	3	2
Anticoagulants and antiplatelets (%)								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-blockers, %	42.3	16.5				33.5[c]	21.4[c]	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		

	Cardiac arrest (secondary prevention)							Recent MI				Remote MI			
	AVID[71]		CASH[81]			CIDS[84]		DINAMIT[95]		IRIS[97]		MADIT I[99a]		MADIT II[101b]	
Medication	ICD	AAD	ICD	Amiodarone	Metoprolol	ICD	Amiodarone	ICD	OPT	ICD	OPT	ICD	OPT	ICD	OPT
Calcium channel blockers, %	18.4	12.1	26.3	16.3	12.4									9	9
Diuretics, %	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 agents, %	7.6	8.8													
Digitalis, %	46.8	40.6	26.3	25.0	15.5							58	38	57	57
Digoxin, %						29.6	22.7								
Lipid-lowering agents, %	13.2	11.5						76.8	79.5						
Statins, %										91.6	91.5			67	64

PT, pharmacological therapy.
a Medication at 1 month. Data missing for two ICD patients and eight PT patients. No antiarrhythmic medication: ICD 56%, PT 8%.
b Medication at discharge not reported by MADIT II;[101] medication at 'last contact' displayed here – mean 18 months (ICD) and 17 months (OPT) from enrolment.
c Other than solatol.

TABLE 15 Medication at discharge: cardiomyopathy, CABG surgery and HF

	Cardiomyopathy						CABG surgery		HF		
	[a]AMIOVIRT[69]		CAT[82]		DEFINITE[90]		CABG Patch[75]		[b]SCD-HeFT[105]		
Medication	ICD	Amiodarone	ICD	OPT	ICD	OPT	ICD	OPT	ICD	Amiodarone	Placebo
Sample size, *n*	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
ARB, %					13.5	8.7			14	14	16
Amiodarone, %					3.9	6.6	3.7	3.2			
Class I antiarrhythmic, %							16.7	12.0			
Anticoagulants, %							15.3	14.7			
Antiplatelets, %							82.8	85.1			
Acetylsalicylic acid (aspirin)									58	55	56
Warfarin			24.0	35.2					32	37	33
Beta-blockers, %	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 blockers, %			16.0	7.4			10.5	7.0			
Diuretics, %	71	67	88.0	85.2	87.3	86.0	57.2	47.1			
Loop									82	82	82
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 agents, %							9.5	8.4			
Statins, %									38	40	38

a Concomitant drug therapy at last follow-up.
b At enrolment.

Antiarrhythmics (mainly amiodarone) were taken by a small proportion of participants (ICD arm 13.4% vs. OPT arm 17.4%, $p = 0.11$). Pharmacological therapy is considered optimal by current standards in both the DINAMIT trial[95] and the IRIS trial.[97]

The MADIT I trial[99] presents data on drug use at 1 month (see *Table 14*) and last contact (see *Appendix 7*). Usage of ACE inhibitors (ICD arm 60%, medical therapy arm 55%) and beta-blockers (beta-blockers or sotalol: ICD arm 27%, medical therapy arm 15%) was low in this trial at 1 month and beta-blocker use was not balanced between the groups. Three-quarters of the medical therapy group received amiodarone at 1 month compared with 2% of the ICD group, but use of class I antiarrythmics was similar (ICD arm 12% vs. medical therapy arm 10%). At 1 month, 56% of the ICD patients and 8% of the medical therapy patients had no antiarrhythmic medication. Approximately half of the participants were receiving diuretics. Digitalis use was high by current standards (ICD arm 58%, medical therapy arm 38%). The pharmacological therapy provided in the MADIT I trial[99] would not be considered optimal by current standards.

The MADIT II trial[101] did not report medication at discharge but presented medication at last contact, which was a mean of 18 months (ICD arm) and 17 months (OPT arm) from enrolment. About 70% of participants received ACE inhibitors, about 10–13% received amiodarone and 2–3% received class I AADs. 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. The pharmacological therapy provided in the MADIT II trial[101] would be considered optimal by current standards.

Cardiomyopathy The AMIOVIRT trial[69] reports that OPT was encouraged in both the ICD group and the amiodarone group. Therapy at discharge was not reported but concomitant drug therapy was presented (see *Table 15*), with no statistically significant differences between the groups. A high proportion (81–90%) of participants received ACE inhibitors and approximately half received beta-blockers. Over two-thirds received diuretics and/or digoxin and one-fifth received spironolactone. Beta-blocker use is slightly lower in this trial than in current standards, but the pharmacological therapy is close to optimal.

About 96% of participants took ACE inhibitors at baseline in CAT,[82] but beta-blocker use was low (4% of participants). Diuretics were taken by the majority of participants (85–88%), warfarin was received by 24–35% of participants, nitrates were taken by 26–32% of participants and calcium channel blockers were taken by 7–16% of participants. Observed differences between the groups were not statistically significant. Although acceptable at the time, the pharmacological therapy in this trial would not be considered optimal by current standards because of the low beta-blocker use.

Optimal pharmacological therapy was described for both groups in the DEFINITE trial.[90] A high proportion (about 86%) of participants received ACE inhibitors and a small proportion (8.7–13.5%) received ARBs. Beta-blockers were taken by 85%, diuretics by 87% and digoxin by 42%. A small proportion of each group received amiodarone (ICD arm 3.9%, OPT arm 6.6%) and nitrates (ICD arm 9.2%, OPT arm 13.1%). The pharmacological therapy in this trial would be considered optimal by current standards.

Coronary artery bypass graft surgery ACE inhibitors were taken by over half of the participants in the CABG Patch trial.[75] In total, 63.3% of the ICD group and 65.2% of the control group received no oral AADs. Class I antiarrythmics were taken by 16.7% (ICD arm) and 12.0% (OPT arm) of participants, amiodarone by 3.7% (ICD arm) and 3.2% (OPT arm) and beta-blockers (other than sotalol) by 17.9% (ICD arm) and 24% (OPT arm). There is an excess of AAD 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 this trial would have been considered optimal at the time that the trial was conducted but use is low by current standards.

Mild to moderate heart failure A high proportion (94–98%) of participants in SCD-HeFT[105] were taking ACE inhibitors or an ARB at enrolment. Beta-blockers were taken by 69% of participants, digoxin by about 70%, aspirin by about 56%, warfarin by about 35% and statins by about 40%. Most (82%) received loop diuretics and 20% received potassium-sparing diuretics and a minority received thiazide (7%). This trial also reported medication at last follow-up, for which there was a statistically significant ($p < 0.001$) difference in beta-blocker use between groups (ICD arm 82%, amiodarone arm 72%, placebo arm 79%) (see *Appendix 7*). The pharmacological therapy in this trial would be considered optimal by current standards.

Outcomes

All-cause mortality was the primary outcome in all 13 trials in people at risk of SCD from ventricular arrhythmias.[69,71,78,81,82,84,89,90,95,97,99,101,105] Secondary outcomes tended to focus on other measures of mortality or survival. Ten RCTs assessed total cardiac deaths,[69,72,78,82,84,95,97,99,103,108] 13 RCTs assessed sudden cardiac and arrhythmic deaths,[69,72,78,81,82,84,89,90,95,97,99,103,108] 11 RCTs assessed cardiac non-arrhythmic deaths,[69,72,78,82,84,90,95,97,99,103,108] 10 RCTs assessed other non-cardiac causes of death,[69,72,78,82,84,95,97,99,103,108] five RCTs assessed cumulative mortality[75,84,90,97,105] and four RCTs assessed survival.[69,71,81,82] Other secondary outcome measures included heart hospitalisations (two RCTs[71,101]), symptoms and complications related to arrhythmias (three RCTs[69,82,103]), QoL (seven RCTs[69,74,80,87,94,104,107]) and adverse events (13 RCTs[69,71,75,81,82,84,89,90,95,97,99,101,105]).

Setting

The AVID,[71] CASH[81] and CIDS[84] trials were multicentre studies, with the majority of the centres in the USA[71] or Canada[84] or in Germany.[81] The DEBUT study[89] was conducted in Thailand but the number of centres was not reported. The number of participants ranged from 66 (DEBUT main study[89]) to 1016 (AVID[71]). The DEBUT trial[89] also included a pilot study in which 20 participants were randomised. Length of follow-up ranged from a mean of 18.2 months (SD 12.2 months) in the AVID trial[71] to 57 months (SD 34 months) in the CASH trial.[81]

The DINAMIT,[95] IRIS,[97] MADIT I[99] and MADIT II[101] trials were multicentre studies. The majority of centres for the DINAMIT trial[95] were in Canada, Germany and Europe (four UK centres) and the IRIS trial[97] was conducted in Europe (not the UK) and the Russian Federation. The majority of centres for the MADIT I[99] and MADIT II[101] trials were in the USA. Sample size ranged from 196 (MADIT I[99]) to 1232 (MADIT II[101]). Mean follow-up ranged from 20 months in the MADIT II trial[101] to 37 months in the IRIS trial.[97]

The AMIOVIRT[69] and DEFINITE[90] trials were multicentre studies with the majority of centres in the USA, whereas CAT[82] was a multicentre study conducted in Germany. Sample size was relatively small in AMIOVIRT[69] and CAT[82] (103 and 104 participants randomised respectively), with CAT[82] designed as a pilot study. The DEFINITE trial[90] randomised 458 participants. The trials had similar lengths of follow-up: a mean of 2 years in the AMIOVIRT[69] and CAT[82] trials and a mean of 2.4 years in the DEFINITE trial.[90]

The CABG Patch trial[75] was a multicentre study conducted primarily in the USA, with 900 participants randomised. Mean follow-up was 32 months. SCD-HeFT[105] was also a multicentre study conducted mainly in the USA, with 2521 participants randomised. Median follow-up was 45.5 months.

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 7*. 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,[84] MADIT I,[99] IRIS,[97] DINAMIT,[95] CABG Patch[75]) did not report the randomisation method, although sufficient details were reported to establish that the allocation sequence was adequately concealed and they were judged to have a low risk of selection bias.

TABLE 16 Risk of bias

Domain	Judgement												
	AVID[71]	CASH[81]	CIDS[84]	DEBUT[89]	IRIS[97]	DINAMIT[95]	MADIT I[99]	MADIT II[101]	CAT[82]	AMIOVIRT[69]	DEFINITE[90]	CABG Patch[75]	SCD-HeFT[105]
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,[a] high[b]	Low	Low,[a] high[b]	Low	Low	Low	Low	Low,[a] high[b]	Low	Low,[a] high[b]	Low,[a] high[b]	Low,[a] high[b]	Low,[a] high[b]
Attrition bias													
Incomplete outcome data addressed	Low,[a] high[b]	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low,[a] high[b]	Low,[a] unclear[b]
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 Mortality.
b QoL.

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 because of 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 the AVID,[71] DEFINITE,[90] DINAMIT, [95] AMIOVIRT,[69] IRIS[97] and SCD-HeFT[105] trials. Outcome assessors were not blinded in the 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[69,71,75,84,90,101,105] were judged to have a high risk of detection bias for this outcome.

Risk of attrition bias (differences between groups in withdrawals from the study) was low in seven of the trials[69,81,90,95,97,99,101] and unclear in three trials.[82,84,89] In the AVID,[71] CABG Patch[75] and SCD-HeFT[105] trials, 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.[69,71,81,89,99,105] Five studies listed outcomes in a protocol or methods section that were not then reported.[82,84,90,95,97] Risk of selective reporting bias was unclear in two studies (MADIT II,[101] CABG Patch[75]).

Risk of other sources of bias was judged to be high in DINAMIT[95] as block randomisation in an unblinded trial can lead to prediction of allocation. The authors of the CASH study[81] 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;[69,71,75,82,89,99,101] however, simulation evidence suggests that inclusion of stopped-early trials in meta-analyses does not lead to substantial bias.[65]

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 participants appeared generally to be well balanced at baseline. However, some differences were evident. In the IRIS[97] trial the ICD group had a higher proportion than the OPT group of people with LBBB (10.1% vs. 6.4%, $p = 0.05$) and diabetes mellitus (37.2% vs. 30.2%, $p = 0.03$). The CAT[82] trial found a higher occurrence of bradycardias among the OPT group (18.8%) than among the ICD group (2.1%, $p = 0.015$). The DEFINITE[90] trial noted that the OPT group (3.27 years) had a significantly longer mean duration of HF than the ICD + OPT group (2.39 years) ($p = 0.04$).

Sample size

All 13 trials included a calculation of sample size or statistical power based on the primary outcome measure of all-cause mortality. The CIDS ($n = 659$),[84] DINAMIT ($n = 674$),[95] DEFINITE ($n = 458$),[90] CABG-Patch ($n = 900$)[75] and SCD-HeFT ($n = 2521$)[105] trials appeared to be adequately powered to detect a difference in all-cause mortality. In contrast, the CASH ($n = 288$),[81] DEBUT ($n = 66$),[89] MADIT II ($n = 1232$)[101] and CAT ($n = 104$)[82] trials were thought to be underpowered based on reported sample size calculations. Five trials were stopped early because they achieved an a priori stopping rule concerning crossing of efficacy boundaries [AVID ($n = 1016$),[71] MADIT I ($n = 196$),[99] MADIT II ($n = 1232$)[101]] or because interim analysis showed low event rates, which meant that further recruitment would not achieve adequate statistical power [AMIOVIRT ($n = 103$),[69] CAT ($n = 104$)[82]]. Because of lower than anticipated mortality in the IRIS trial,[97] an increase in sample size ($n = 900$) was recommended by the data and safety monitoring board.

Other issues

The CASH trial[81] was designed as a four-arm trial (ICD, amiodarone, metoprolol, propafenone); however, the propafenone arm was terminated early after the interim analysis had been carried out. The DEBUT trial[89] reports the results of a pilot study and the main trial, although both were small.

During the course of the MADIT I trial,[99] a change was made from transthoracic to transvenous leads. The authors of this trial note that this altered the type of patient referred for entry to the trial.

Funding

The AVID[71] and CIDS[84] trials received funding from the National Heart, Lung, and Blood Institute and the Medical Research Council of Canada respectively. All of the other RCTs[69,75,81,82,89,90,95,97,99,101,105] received some or all of their funding from the ICD manufacturers, which may represent a potential conflict of interests.

Assessment of effectiveness

All-cause mortality

All 13 trials comparing the use of ICDs with the use of AADs in people at increased risk of SCD from ventricular arrhythmias reported measures of all-cause mortality as their primary outcome measure.[69,71,75,81,82,84,89,90,95,97,99,101,105] Four trials[71,81,84,89] assessed the use of ICDs compared with the use of AADs in people at increased risk of SCD from previous ventricular arrhythmias. All four trials showed beneficial effects on crude mortality rates for those receiving an ICD, although only the AVID trial[71] (ICD arm 15.8%, AAD arm 24.0%, $p < 0.012$, follow-up 18.2 months) and the main DEBUT trial[89] (ICD arm 0%, AAD arm 13.8%, $p < 0.02$, follow-up 3 years) found statistically significant differences. A separate pilot study for the DEBUT trial[89] had previously shown no significant difference between the ICD arm and the AAD arm (ICD arm 0%, AAD arm 30.0%, $p = 0.07$, follow-up maximum 3 years). In the other two studies differences were either not statistically significant or not assessed. The CASH trial[81] reported an all-cause mortality rate of 36.4% for the ICD group compared with 44.4% for the AAD group (*p*-value not stated, follow-up 57 months). The CIDS trial[84] reported a crude mortality rate of 25.3% for the ICD group and 29.6% for the AAD group over the 3-year follow-up, equating to an annual crude mortality rate of 8.3% for the ICD group and 10.2% for the AAD group, a risk ratio reduction (RRR) of 19.7% (95% CI –7.7% to 40.0%, $p = 0.142$) (*Table 17*). A meta-analysis of the four studies (including the DEBUT pilot study[89]) using a random-effects model showed a statistically significant benefit for ICDs compared with AADs with a RR of 0.75 (95% CI 0.61 to 0.93, $p = 0.010$), with limited heterogeneity ($\chi^2 = 5.89$, df = 4, $I^2 = 32\%$) (*Figure 4*).

Of the nine trials[69,75,82,90,95,97,99,101,105,146] including people who had not suffered a life-threatening arrhythmia but who were at increased risk, three showed statistically significant benefits for all-cause mortality in the ICD + OPT group compared with the different comparators (see *Table 17*). In the MADIT I trial,[99] 15.8% of participants receiving an ICD + OPT died compared with 38.6% of participants receiving OPT (mean follow-up 27 months), equating to a hazard ratio (HR) of 0.46 (95% CI 0.26 to 0.82, $p = 0.009$) (see *Table 17*). The MADIT II trial[101] also found significant benefits, with 14.2% of those with an ICD + OPT dying compared with 19.8% of those who received OPT only (mean follow-up 20 months), a HR of 0.69 (95% CI 0.51 to 0.93, $p = 0.016$). Post-trial follow-up in the MADIT II study[101] found continued benefit of 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 intention-to-treat (ITT) analysis.[149] The SCD-HeFT trial,[105] which had a longer follow-up period (mean 45.5 months), reported that 22.0% of people who received an ICD + OPT died compared with 28.4% of those receiving amiodarone + OPT and 28.8% of those receiving placebo + OPT. HRs showed that the difference between the ICD + OPT group and the placebo + OPT group was statistically significant (HR 0.77, 97.5% CI 0.62 to 0.96, $p = 0.007$), whereas that between the amiodarone + OPT group and the placebo + OPT group was not statistically significant (HR 1.06, 97.5% CI 0.86 to 1.30, $p = 0.53$).[105] A meta-analysis of the two MADIT trials[99,101] using a random-effects model showed a statistically significant benefit for those receiving ICDs + OPT

TABLE 17 All-cause mortality

Study	Follow-up	ICD, *n*/*N* (%) [rate/year, %]	OPT, *n*/*N* (%) [rate/year, %]	Effect	95% CI, *p*-value
Cardiac arrest					
AVID[71]	Mean 18.2 (SD 12.2) months	80/507 (15.8, ± 95% CI 12.6 to 19)	AAD: 122/509 (24.0, ± 95% CI 20.3 to 27.7)		< 0.012
CASH[81]	57 (SD 34) months	36/99 (36.4, 95% CI 26.9 to 46.6)[a]	Amiodarone: 40/92 (43.5, 95% CI 33.2 to 54.2)[a]		
			Metoprolol: 44/97 (45.4, 95% CI 35.2 to 55.8)[a]		
			Both:[b] 84/189 (44.4, 95% CI 37.2 to 51.8)[a]		
CIDS[84c]	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[89] pilot study	Max. 3 years after randomisation	0/10 (0)	Propranolol: 3/10 (30.0)		0.07
DEBUT[89] main study	3 years	0/37 (0)	Propranolol: 4/29 (13.8)		0.02
Early post MI					
DINAMIT[95]	Average 30 (SD 13) months	62/332 (18.7) [7.5]	58/342 (17.0) [6.9]	HR 1.08	0.76 to 1.55, 0.66
IRIS[97]	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[99]	Average 27 months	15/95 (15.8)	39/101 (38.6)	HR 0.46	0.26 to 0.82, 0.009
MADIT II[101]	Average 20 months	105/742 (14.2)	97/490 (19.8)	HR 0.69	0.51 to 0.93, 0.016
Cardiomyopathy					
AMIOVIRT[69]	Mean 2.0 (SD 1.3) years	6/51 (11.8)	Amiodarone + OPT: 7/52 (13.5)		0.8
CAT[82]	1 year (primary end point)	4/50 (8.0)	2/54 (3.7)		0.3672
	Mean 5.5 (SD 2.2) years	13/50 (26.0)	17/54 (31.5)		
DEFINITE[90]	Mean 29.0 (SD 14.4) months	28/229 (12.2)	40/229 (17.5)	HR 0.65	0.40 to 1.06, 0.08

TABLE 17 All-cause mortality (*continued*)

Study	Follow-up	ICD, *n*/*N* (%) [rate/year, %]	OPT, *n*/*N* (%) [rate/year, %]	Effect	95% CI, *p*-value
Scheduled for CABG					
CABG Patch[78]	Mean 32 (SD 16) months	102/446 (22.9)	96/454 (21.1)		
HF					
SCD-HeFT[105]	Median for surviving patients 45.5 (range 24–72.6) months	182/829 (22.0)	Amiodarone + OPT:[b] 240/845 (28.4)		
			Placebo + OPT:[b] 244/847 (28.8)	HR 0.77[d]	0.62 to 0.96,[e] 0.007

HR, hazard ratio; max, maximum.
a Probability level for CI around crude death rate not reported in CASH.[81]
b The CASH[81] and SCD-HeFT[105] trials are three-arm trials; however, the two control arms have been combined to provide a single pairwise comparison for the meta-analysis (see *Cochrane Handbook* section 16.5.4[65]) (see *Figure 4*).
c Longer-term follow-up (5.6 years) from one centre of the CIDS study[84] has been excluded from the meta-analysis to avoid double counting of participants.
d HRs for amiodarone vs. placebo are not presented in the summary tables (see *Appendix 7*).
e 97.5% CI.

compared with OPT alone, with a RR 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 cardiomyopathy,[69,82,90] in the early period post MI[95,97] or scheduled for a CABG,[78] found no statistically significant differences between groups for all-cause mortality. The AMIOVIRT trial[69] reported all-cause mortality after a mean follow-up of 2 years, finding that 11.8% of those with an ICD + OPT had died compared with 13.5% of those receiving amiodarone + OPT ($p = 0.8$). The CAT trial[82] reported all-cause mortality at 1 year, showing no significant difference between groups (ICD + OPT 8% vs. OPT 3.7%, $p = 0.3672$). Longer mean follow-up to 5.5 years showed a limited difference between groups, with 26% of the ICD + OPT group and 31.5% of the OPT group dying (*p*-value not stated). The DEFINITE trial[90] found that 12.2% of participants receiving an ICD + OPT and 17.5% of those receiving OPT had died at a mean follow-up of 29 months, a HR of 0.65 (95% CI 0.40 to 1.06, $p = 0.08$) (see *Table 17*). Combining these three cardiomyopathy trials using random-effects meta-analysis confirmed that there was no significant difference between the treatments, with a RR of 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 CHF subgroup of the SCD-HeFT trial[105] is assessed in *Subgroup analyses reported by included randomised controlled trials*. The DINAMIT[95] and IRIS[97] trials assessed the effects of ICDs + OPT compared with OPT in those who were in the early period post MI. The DINAMIT trial[95] reported that 18.7% of participants receiving an ICD + OPT and 17.0% of those receiving OPT had died by 30 months' follow-up, resulting in a HR of 1.08 (95% CI 0.76 to 1.55, $p = 0.66$). Similarly, the IRIS trial[97] found no significant difference in all-cause mortality between the ICD + OPT group (26.1%) and the OPT group (25.8%), reflected in a HR of 1.04 (95% CI 0.81 to 1.35, $p = 0.15$). Meta-analysis of the DINAMIT[95] and IRIS[97] trials confirmed that there was no significant difference between the treatments, with a RR 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,[78] which included people who were scheduled for a CABG, reported a mortality rate of 22.9% for those receiving an ICD + OPT compared with 21.2% for those receiving OPT (*p*-value not stated), a RR of 1.08 (95% CI 0.85 to 1.38, $p = 0.53$) (see *Figure 4*).

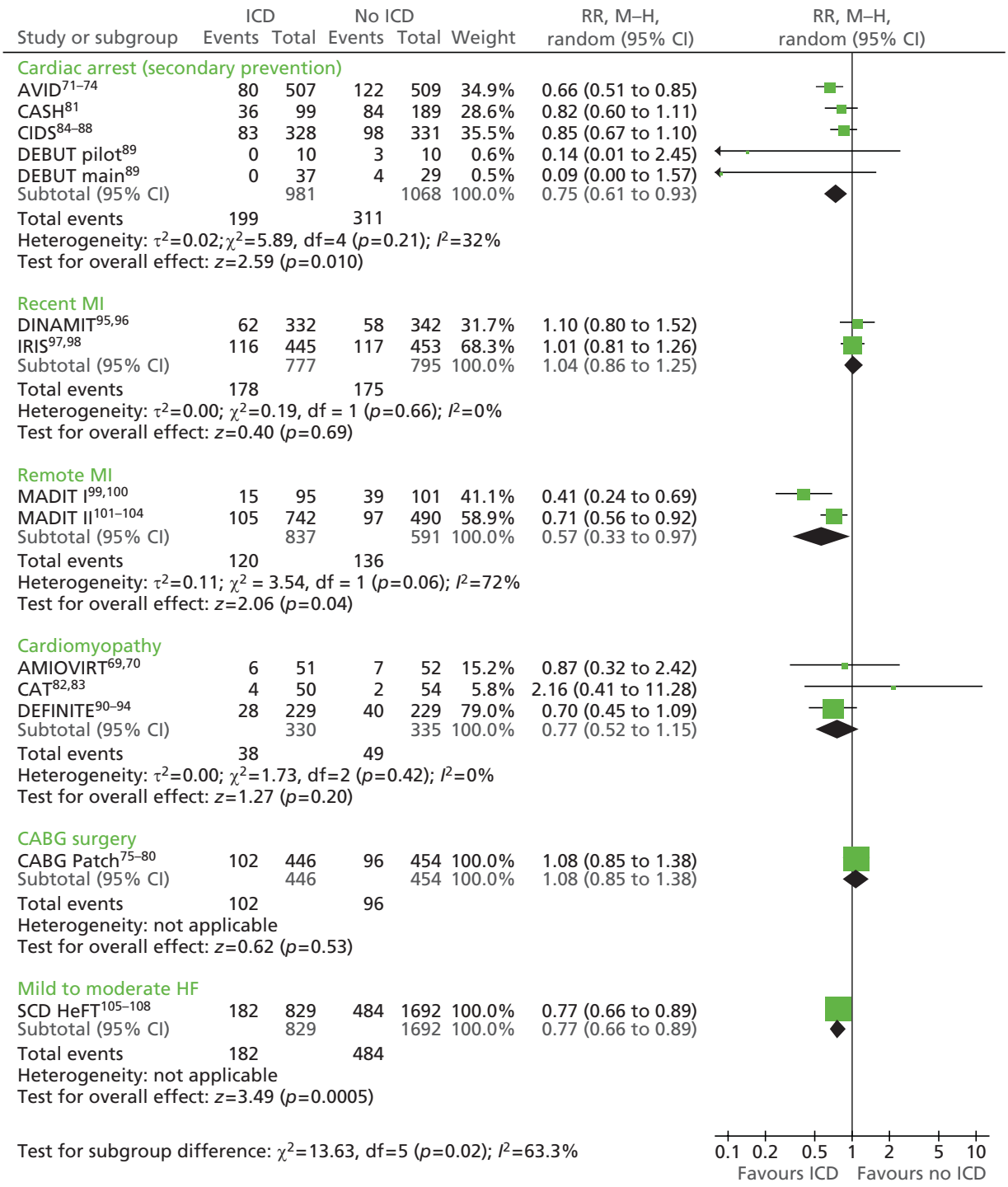

FIGURE 4 All-cause mortality.

Total cardiac deaths

Only two trials in people at increased risk of SCD due to previous ventricular arrhythmias, specifically the AVID[72] and CIDS[84] trials, assessed the effects of ICDs compared with AADs on total cardiac deaths (*Table 18*). Although both studies found lower crude rates for those receiving an ICD, neither reported whether the effect was statistically significant (AVID:[72] ICD 12.4%, AAD 18.5%, *p*-value not stated; CIDS:[84] ICD 20.4%, AAD 25.1%; *p*-value not stated). In addition, the CIDS trial[84] found no statistically significant difference between the interventions with regard to annual crude mortality rates (ICD 6.7%, AAD 8.6%, RRR 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 AADs,

TABLE 18 Total cardiac deaths

Study	Follow-up	ICD, *n*/*N* (%) [rate/year, %]	OPT, *n*/*N* (%) [rate/year, %]	Effect	95% CI, *p*-value
Cardiac arrest					
AVID[72]	Mean 18.2 (SD 12.2) months	63/507 (12.4)	AAD: 94/509 (18.5)		
CIDS[84]	Mean 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[95]	Average 30 (SD 13) months	46/332 (13.9)	49/342 (14.3)		
IRIS[97]	Average 37 months	95/445 (21.3)	99/453 (21.9)		
Remote from MI					
MADIT I[99]	Average 27 months	11/95 (11.6)	27/101 (26.7)		
MADIT II[103]	Average 20 months	79/742 (10.6)	80/490 (16.3)		< 0.01
Cardiomyopathy					
AMIOVIRT[69]	Mean 2.0 (SD 1.3) years	4/51 (7.8)	Amiodarone + OPT: 5/52 (9.6)		
CAT[82]	1 year (primary end point)	4/50 (8.0)	0/54 (0)		
Scheduled for CABG					
CABG Patch[78]	Mean 32 (SD 16) months	76/446 (17.0)	79/454 (17.4)	HR 0.97	0.71 to 1.33, 0.84
HF					
SCD-HeFT[108]	Median for surviving patients 45.5 (range 24 to 72.6) months	122/829 (14.7)	Amiodarone + OPT: 162/845 (19.2), placebo + OPT: 167/847 (19.7)	HR 0.76	0.60 to 0.95, 0.018

with a RR of 0.74 (95% CI 0.61 to 0.91, $p = 0.004$) and no apparent heterogeneity ($\chi^2 = 0.84$, df = 1, $I^2 = 0\%$) (*Figure 5*).

Eight trials[69,78,82,95,97,99,101,108] in people who had not suffered a life-threatening arrhythmia but who were at increased risk assessed the effects of ICDs + OPT compared with either OPT, amiodarone + OPT or placebo + OPT on total cardiac deaths (see *Table 18*). Of these, only the MADIT II trial,[103] which included people remote from MI (ICD + OPT 10.6%, OPT 16.3%, $p < 0.01$), and the SCD-HeFT trial,[108] which included people with mild to moderate HF (ICD + OPT 14.7%, placebo + OPT 19.7%, amiodarone + OPT 19.2%; HR 0.76, 95% CI 0.60 to 0.95, $p = 0.018$), found statistically significant benefit for those receiving an ICD + OPT. A similar difference was identified in the MADIT I trial,[99] which included people remote from MI (ICD + OPT 11.6%, OPT 26.7%); however, statistical significance was not stated. A meta-analysis of the MADIT I[99] and II[103] trials using a random-effects model showed a statistically significant benefit for ICDs + OPT, with a RR 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[95] (ICD + OPT 13.9%, OPT 14.3%, *p*-value not stated) and IRIS[97] (ICD + OPT 21.3%, OPT 21.9%, *p*-value not stated) trials, which included those with a recent MI, the AMIOVIRT trial,[69] which included those with cardiomyopathy (ICD + OPT 7.8%, amiodarone + OPT 9.6%, *p*-value not stated) and the CABG Patch trial,[78] which included people scheduled for a CABG (ICD + OPT 17.0%, OPT 17.4%; HR 0.97, 95% CI 0.71 to 1.33, $p = 0.84$) found limited differences in total cardiac deaths between those receiving ICD + OPT and those receiving either OPT or amiodarone + OPT (see *Table 18*). In contrast,

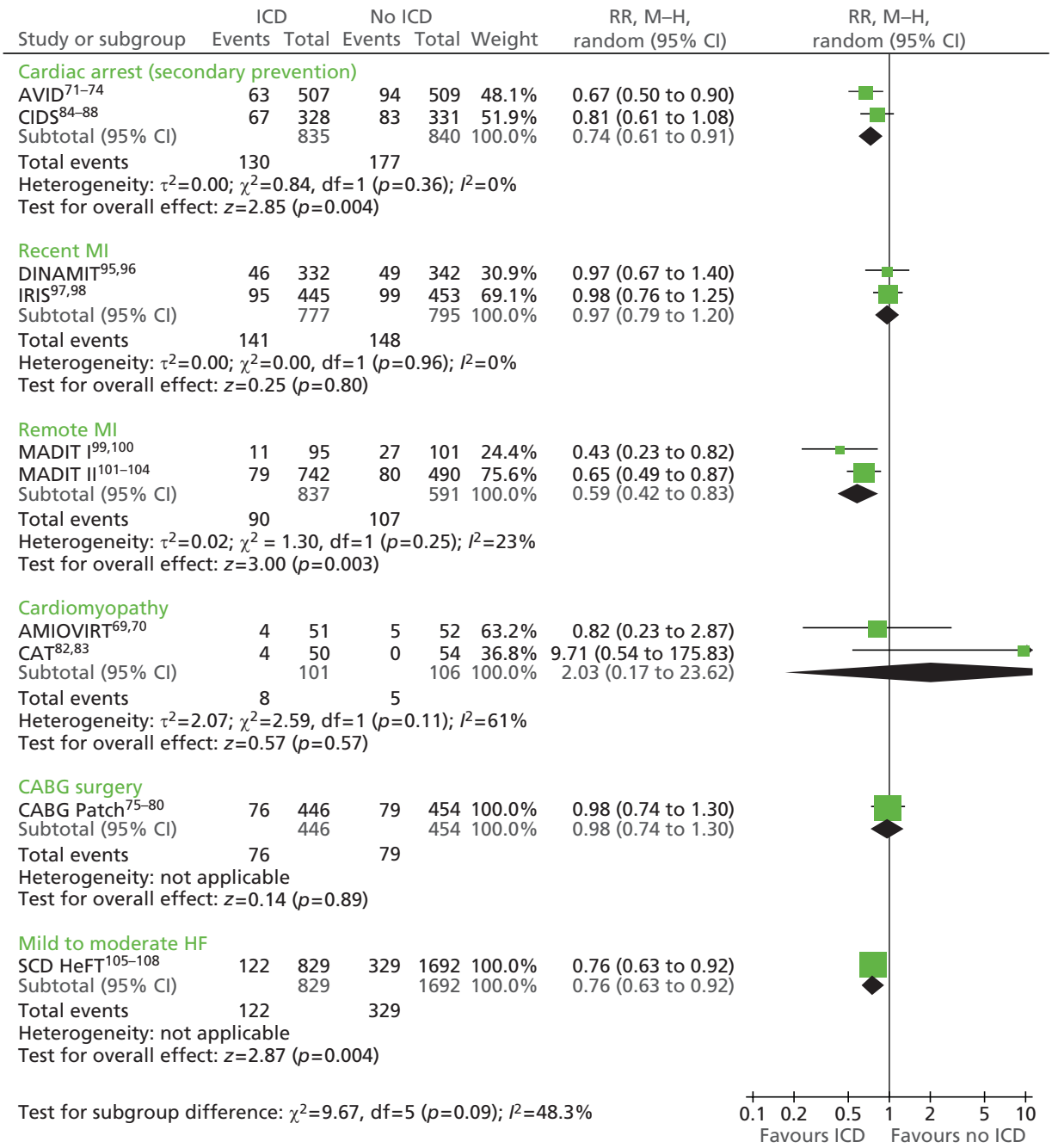

FIGURE 5 Total cardiac deaths.

the CAT trial,[82] which included people with cardiomyopathy, reported higher total cardiac mortality among those receiving an ICD + OPT than among those receiving OPT (ICD + 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[95] and IRIS[97] trials produced a RR 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[69] and CAT[82] trials resulted in a RR 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*).

Sudden cardiac death/arrhythmic deaths

Sudden cardiac and arrhythmic death rates were lower among people receiving an ICD than among those receiving AADs in the four trials[72,81,84,89] that included people at increased risk of SCD as a result of

previous ventricular arrhythmias (*Table 19*). Both the CASH[81] [ICD 13.0%, 95% CI 7.9 to 19.6; AAD (either amiodarone or metoprolol) 32.8%, 95% CI 27.2 to 41.8] and DEBUT[89] (ICD 0%; AAD 13.8%) trials reported lower rates of SCD for those receiving an ICD than for those receiving AADs, although only the CASH trial[81] showed a statistically significant difference. Similarly, the AVID[72] and CIDS[84] studies showed benefit for people receiving an ICD compared with AADs with regard to crude rate of arrhythmic deaths (AVID:[72] ICD 4.7%, AAD 10.8%; CIDS[84]: ICD 9.2%, AAD 13.0%), although neither demonstrated a statistically significant difference. The CIDS trial[84] also showed no statistically significant difference when comparing the interventions for annual crude mortality rate [ICD 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 the ICD group compared with the AAD group, with a RR 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[69,78,82,90,95,97,99,103,108] that included people who had not suffered a life-threatening arrhythmia but who were at increased risk reported sudden cardiac or arrhythmic death as an outcome (see *Table 19*). Although eight of the trials[69,78,90,95,97,99,103,108] showed benefit for those receiving an ICD + OPT compared with OPT, amiodarone + OPT or placebo + OPT, only four[90,95,97,103] identified showed a statistically significant effect. The DINAMIT[95] and IRIS[97] trials highlighted the benefits of ICDs + OPT compared with OPT for people who had had a recent MI, reporting HRs 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 RR 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[99] (ICD + OPT 3.2%, OPT 12.9%, *p*-value not stated) and MADIT II[103] (ICD + OPT 3.8%, OPT 10.0%, $p < 0.01$) trials, which included people remote from MI, showed lower rates of sudden cardiac or arrhythmic death among those receiving an ICD + OPT than among those receiving OPT. Meta-analysis using a random-effects model showed a significant benefit for ICDs + OPT with a RR 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,[69] CAT[82] and DEFINITE[90] trials, which included people with cardiomyopathy, reported differing outcomes. The DEFINITE trial[90] found that significantly fewer people who received an ICD + OPT (1.3%) died from sudden cardiac or arrhythmic death than those receiving OPT (6.1%), reflected in a HR of 0.20 (95% CI 0.06 to 0.71, $p = 0.006$) (see *Table 19*). Although the AMIOVIRT trial[69] also found benefit for those receiving an ICD + OPT (2.0%) compared with those receiving amiodarone + OPT (3.8%), the benefit was not statistically significant ($p = 0.7$). The CAT trial[82] reported no sudden cardiac or arrhythmic deaths in either the ICD + OPT group or the OPT group. A random-effects meta-analysis of the three trials showed an overall statistically significant benefit for participants who received an ICD + OPT compared with the comparator treatment, with a RR of 0.26 (95% CI 0.09 to 0.77, $p = 0.02$) and no heterogeneity ($\chi^2 = 0.41$, df = 1, $I^2 = 0\%$) (see *Figure 6*).

The CABG Patch trial,[78] which included people who were scheduled for CABG surgery, reported lower rates of sudden cardiac and arrhythmic death in the ICD + OPT group (3.4%) than in the OPT (6.2%), although the difference was marginally insignificant (HR 0.55, 95% CI 0.29 to 1.03, $p = 0.06$) (see *Table 19*). In contrast, the SCD-HeFT trial[108] found significantly lower sudden cardiac or arrhythmic mortality in the group receiving an ICD + OPT (4.6%) than in the group receiving amiodarone + OPT (9.5%) or the group receiving placebo + OPT (11.6%), with a RR of 0.44 (95% CI 0.31 to 0.61, $p < 0.00001$) (see *Figure 6*).

Non-arrhythmic cardiac deaths

Two trials[72,84] that included people at increased risk of SCD because of previous ventricular arrhythmias reported rates of non-arrhythmic deaths. The AVID[72] and CIDS[84] trials assessed the effects of ICDs compared with the effects of AADs on crude non-arrhythmic cardiac deaths, with neither stating whether there was any statistically significant benefit (AVID[72]: ICDs 7.7%, AAD 7.7%; CIDS[84]: ICDs 11.3%,

TABLE 19 Sudden cardiac deaths/arrhythmic deaths

Study	Follow-up	ICD, *n*/*N* (%) [rate/year, %]	OPT, *n*/*N* (%) [rate/year, %]	Effect	95% CI, *p*-value
Cardiac arrest					
AVID[72]	Mean 18.2 (SD 12.2) months	24/507 (4.7)	AAD: 55/509 (10.8)		
CASH[81]	57 (SD 34) months	13/99 (13.1, 95% CI 7.9 to 19.6)[a]	Amiodarone: 27/92 (29.3, CI 19.4 to 40.8)[b] Metoprolol: 34/97 (35.1, CI 25.2 to 48.8)[b] Both: 62/189 (32.8, CI 27.2 to 41.8)[a]		
CIDS[84]	Mean 3 years	30/328 (9.1) [3.0]	Amiodarone: 43/331 (13.0) [4.5]	RRR 32.8%	–7.2 to 57.8, 0.094
DEBUT[89] pilot study	Max. 3 years after randomisation	0/10 (0)	Propranolol: 3/10 (30.0)		
DEBUT[89] main study	3 years	0/37 (0)	Propranolol: 4/29 (13.8)		
Early post MI					
DINAMIT[95]	Average 30 (SD 13) months	12/332 (3.6) [1.5]	OPT: 29/342 (8.5) [3.5]	HR 0.42	0.22 to 0.83, 0.009
IRIS[97]	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[99]	Average 27 months	3/95 (3.2)	OPT: 13/101 (12.9)		
MADIT II[103]	Average 20 months	28/742 (3.8)	OPT: 49/490 (10.0)		< 0.01
Cardiomyopathy					
AMIOVIRT[69]	Mean 2.0 (SD 1.3) years	1/51 (2.0)	Amiodarone + OPT: 2/52 (3.8)		0.7
CAT[82]	1 year (primary end point)	0/50 (0)	OPT: 0/54 (0)		
DEFINITE[90]	Mean 29.0 (SD 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[78]	Mean 32 (SD 16) months	15/446 (3.4)	OPT: 28/454 (6.2)	0.55	0.29 to 1.03, 0.06
HF					
SCD-HeFT[108]	Median for surviving patients 45.5 (range 24 to 72.6) months	38/829 (4.6)	Amiodarone + OPT: 80/845 (9.5) Placebo + OPT: 98/847 (11.6)		

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

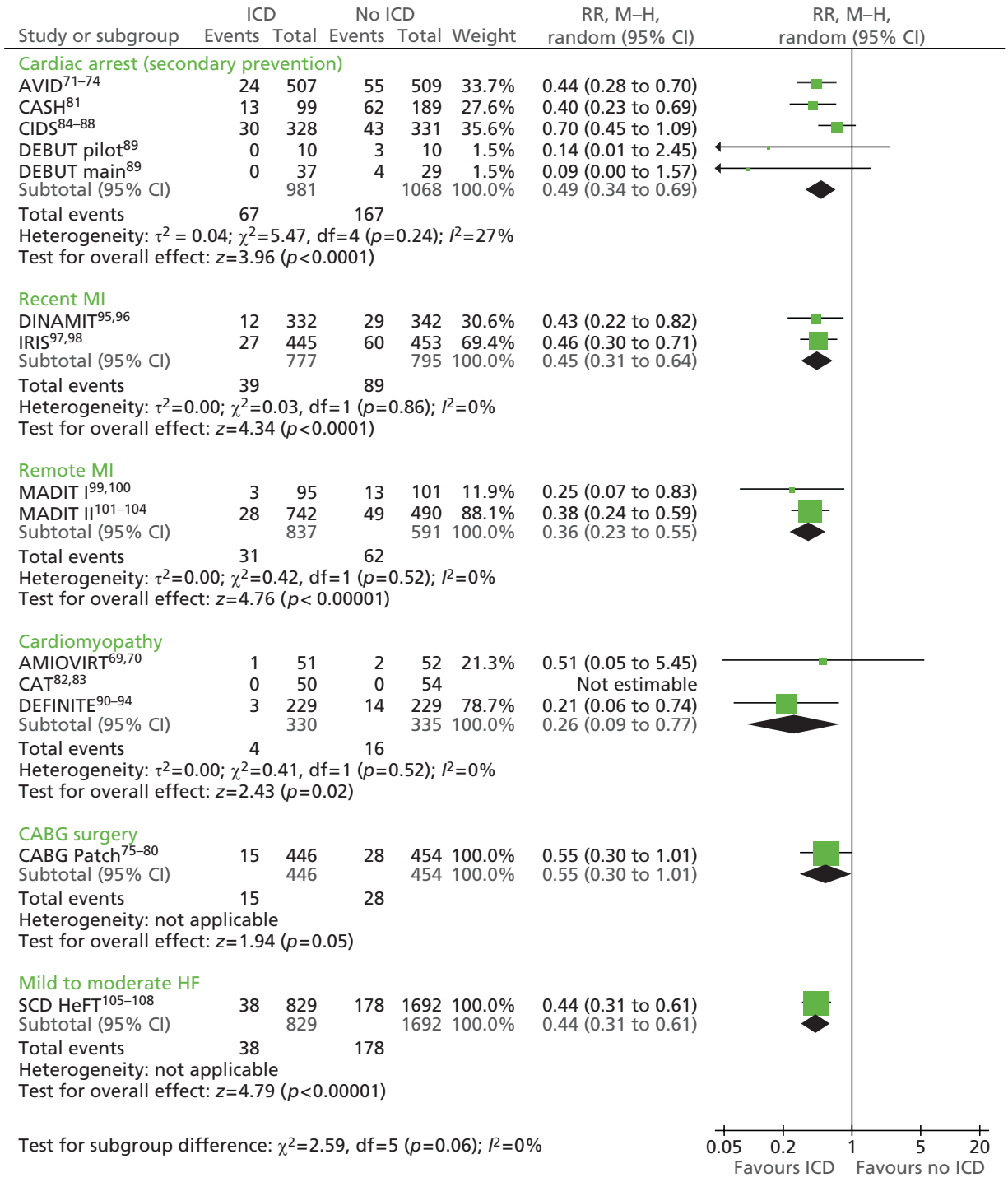

FIGURE 6 Sudden cardiac deaths/arrhythmic deaths.

AAD 12.1%) (*Table 20*). The CIDS trial[84] also reported annual crude mortality rates (ICDs 3.7%, AAD 4.2%), which resulted in a non-significant RRR of 13.5% (95% CI –35.4 to 44.7, $p = 0.526$). A random-effects meta-analysis confirmed the lack of a statistically significant difference between the groups, reporting a RR of 0.97 (95% CI 0.72 to 1.31, $p = 0.83$) and no heterogeneity ($\chi^2 = 0.06$, df = 1, $I^2 = 0\%$) (*Figure 7*).

Implantable cardiac defibrillator + OPT appeared to have a limited effect on the occurrence of non-arrhythmic cardiac deaths compared with OPT, amiodarone + OPT or placebo + OPT in people who had not suffered a life-threatening arrhythmia but who were at increased risk (see *Table 20*). In people

TABLE 20 Non-arrhythmic cardiac deaths

Study	Follow-up	ICD, *n/N* (%) [rate/year, %]	OPT, *n/N* (%) [rate/year, %]	Effect	95% CI, *p*-value
AVID[72]	Mean 18.2 (SD 12.2) months	39/507 (7.7)	AAD: 39/509 (7.7)		
CIDS[84]	Mean 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[95]	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[97]	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[99]	Average 27 months	7/95 (7.4)	13/101 (12.9)		
MADIT II[103]	Average 20 months	43/742 (5.8)	21/490 (4.3)		
Cardiomyopathy					
AMIOVIRT[69]	Mean 2.0 (SD 1.3) years	3/51 (5.9)	Amiodarone + OPT: 3/52 (5.8)		0.7
CAT[82]	1 year (primary end point)	4/50 (8.0)	0/54 (0)		
DEFINITE[90]	Mean 29.0 (SD 14.4) months	9[a]/229 (3.9)	11[a]/229 (4.8)		
Scheduled for CABG					
CABG Patch[78]	Mean 32 (SD 16) months	57/446 (12.8)	46/454 (10.1)	HR 1.24	0.84 to 1.84, 0.28
HF					
SCD-HeFT[108]	Median for surviving patients 45.5 (range 24 to 72.6) months	81/829 (9.8)	Amiodarone + OPT: 77/845 (9.1), placebo + OPT: 68/847 (8.0)		

a Deaths from HF reported only.

who had had a recent MI, the DINAMIT[95] and IRIS trials[97] found a statistically significant benefit for those receiving OPT only compared with those receiving an ICD + OPT, reporting HRs of 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 using a random-effects meta-analysis confirmed the statistically significant benefit for people receiving OPT, with a RR of 1.77 (95% CI 1.30 to 2.40, $p = 0.0002$) and no apparent heterogeneity ($\chi^2 = 0$, df = 1, $I^2 = 0\%$) (see *Figure 7*).

The effect of the different interventions on non-arrhythmic cardiac deaths in other patient subgroups was more equivocal. The MADIT I[99] and MADIT II[103] trials, which included people remote from MI, reported contrasting mortality rates (MADIT I:[99] ICD + OPT 7.4%, OPT 12.9%; MADIT II:[103] ICD + OPT 5.8%, OPT 4.3%). Meta-analysing these data using a random-effects model showed no statistically significant difference between the ICD + OPT group and the OPT group (RR 0.95, 95% CI 0.41 to 2.18, $p = 0.9$; $\chi^2 = 2.77$, df = 1, $I^2 = 64\%$) (see *Figure 7*). Similar variation was reported by the three trials assessing non-arrhythmic cardiac deaths among people with cardiomyopathy. The AMIOVIRT[69] (ICD + OPT 5.9%, amiodarone + OPT 5.8%), CAT[82] (ICD + OPT 8%, OPT 0%) and DEFINITE[90] (ICD + OPT 3.9%, OPT 4.8%) trials reported differing mortality rates; when these data were meta-analysed there were no statistically significant differences between the groups (RR 1.13, 95% CI 0.42 to 3.03, $p = 0.81$; $\chi^2 = 2.71$, df = 2, $I^2 = 26\%$) (see *Figure 7*). Similarly, the CABG Patch trial,[78] which included those who were scheduled for CABG surgery (RR 1.26, 95% CI 0.87 to 1.82, $p = 0.21$), and the SCD-HeFT trial,[108] which included those

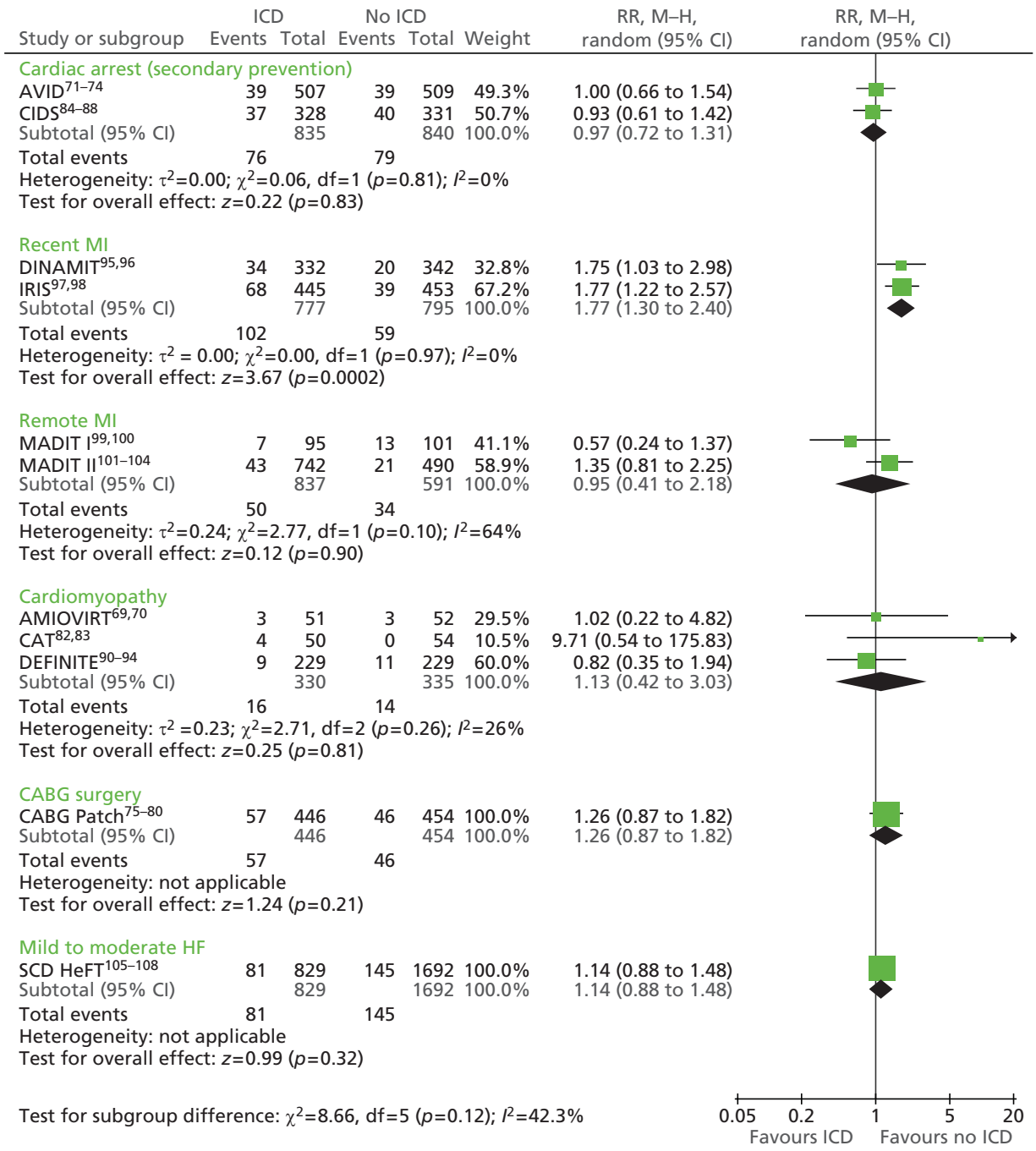

FIGURE 7 Non-arrhythmic cardiac deaths.

with mild to moderate HF (RR 1.14, 95% CI 0.88 to 1.48, $p = 0.32$) found no statistically significant differences between the groups (see *Figure 7*).

Other causes of death: non-cardiac deaths

Two trials[72,84] in people at increased risk of SCD because of previous ventricular arrhythmias assessed non-cardiac causes of death as an outcome (*Table 21*). The AVID[72] and CIDS[84] trials found no statistically significant difference between ICDs and AADs for the outcome of other non-cardiac causes of death (AVID:[72] ICD 3.4%, AAD 5.5%, RR 1.78, 95% CI 0.98 to 3.26, $p = 0.053$; CIDS:[84] non-cardiac vascular: ICD 0.9%, AAD 0.6%, RRR –36.6%, 95% CI –719.8 to 77.2, $p = 0.732$; non-vascular: ICD 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 (RR 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

TABLE 21 Other causes of death (non-cardiac)

Study	Outcome and follow-up	ICD, *n*/*N* (%) [rate/year, %]	OPT, *n*/*N* (%) [rate/year, %]	Effect	95% CI, *p*-value
Cardiac arrest					
AVID[72]	Mean 18.2 (SD 12.2) months	17/507 (3.4)	AAD: 28/509[a] (5.5)	RR 1.78	0.98 to 3.26, 0.053
CIDS[84]	Non-cardiac vascular deaths, mean 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 deaths, mean 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[95]	Non-cardiac vascular deaths, average 30 (SD 13) months	5/332 (1.5) [0.6]	3/342 (0.9) [0.4]	HR 1.69	0.40 to 7.06, 0.47
	Non vascular deaths, average 30 (SD 13) months	11/332 (3.3) [1.3]	6/342 (1.8) [0.7]	HR 1.85	0.68 to 5.01, 0.22
IRIS[97]	Average 37 months	21/445 (4.7)	18/453 (4.0)	HR 1.23	0.51
Remote from MI					
MADIT I[99]	Non-cardiac deaths, average 27 months	4/95 (4.2)	6/101 (5.9)		
	Unknown (cardiac or non-cardiac deaths), average 27 months	0/95 (0)	6/101 (5.9)		
MADIT II[103]	Non-cardiac deaths, average 20 months	22/742 (3.0)	12/490 (2.4)		
	Unknown (cardiac or non-cardiac deaths), average 20 months	4/742 (0.5)	5/490 (1.0)		
Cardiomyopathy					
AMIOVIRT[69]	Mean 2.0 (SD 1.3) years	2/51 (3.9)	Amiodarone + OPT: 2/52 (3.8)		0.9
CAT[82]	1 year (primary end point)	0/50 (0)	2/54 (3.7)		
Scheduled for CABG					
CABG Patch[78]	Non-cardiac deaths, mean 32 (SD 16) months	25/446 (5.6)	17/454 (3.7)	HR 1.49	0.80 to 2.76, 21
	Unknown deaths	1/446 (0.2)	0/454 (0)		
HF					
SCD-HeFT[108]	Non-cardiac deaths, median for surviving patients 45.5 (range 24–72.6) months	48/829 (5.8)	Amiodarone + OPT: 54/845 (6.4)		
			Placebo + OPT: 53/847 (6.3)	HR 0.80[b]	0.57 to 1.12, NS
	Unknown deaths, median for surviving patients 45.5 (range 24–72.6) months	12/829 (1.4)	Amiodarone + OPT: 24/845 (2.8)		NS
			Placebo + OPT 24/847 (2.8)		

NS, not significant.
a Three attributed to amiodarone pulmonary toxicity.
b Comparison for non-cardiac deaths between ICD + OPT and placebo + OPT.

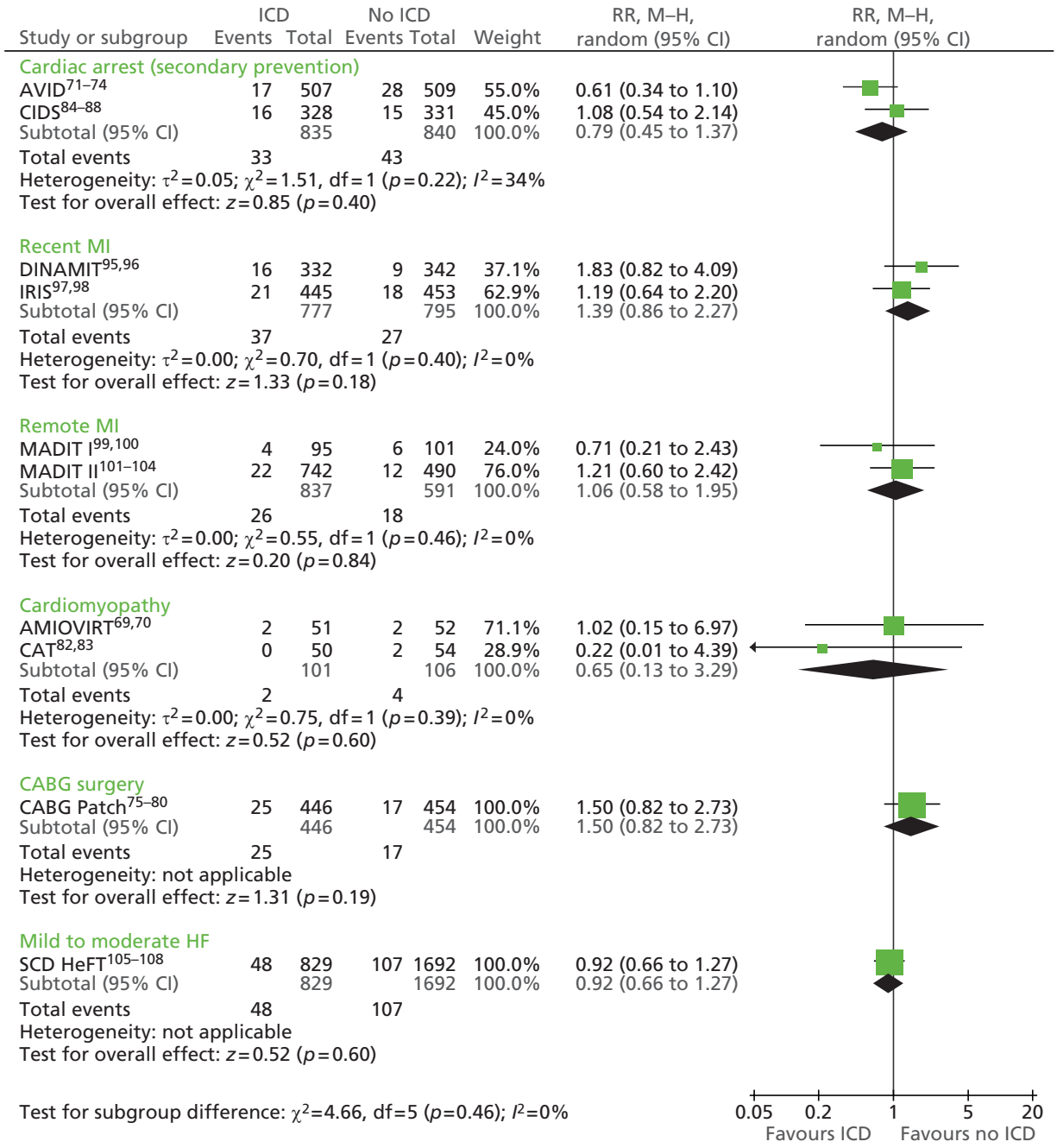

FIGURE 8 Other causes of death: non-cardiac deaths.

trial[84] presented annual crude death rates for the ICD and AAD groups for non-cardiac vascular (ICD 0.3%, AAD 0.2%) and non-vascular (ICD 1.3%, AAD 1.4%) causes,[84] finding limited differences.

Eight trials[69,78,82,95,97,99,103,108] in people who had not suffered a life-threatening arrhythmia but who were at increased risk assessed the effects of ICDs + OPT on other non-cardiac causes of death compared with the different comparator treatments, finding no statistically significant benefit (see *Table 21*). Meta-analyses using random-effects models of the DINAMIT[95] and IRIS[97] 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[99] and MADIT II[103] 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[69] and CAT[82] 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 (see *Figure 8*). Similarly, the CABG Patch trial[78] 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[108] trial, which included people with mild-to moderate HF (RR 0.92, 95% CI 0.66 to 1.27, $p = 0.60$), reported no statistically significant differences between groups in deaths from other non-cardiac causes (see *Figure 8*).

Cumulative mortality

The cumulative mortality risk for both total and arrhythmic mortality was assessed annually for up to 3 years' follow-up in the CIDS trial in people at increased risk of sudden cardiac death as a result of previous ventricular arrhythmias.[84] Rates were consistently lower for those receiving an ICD compared with those receiving AADs, with a RRR for total mortality of 15.4% in year 1, 29.7% in year 2 and 13.7% in year 3 and a RRR for arrhythmic mortality of 29.9% in year 1, 31.4% in year 2 and 17.8% in year 3 (*Table 22*).

Four trials in people who had not suffered a life-threatening arrhythmia but who were at increased risk reported other mortality outcomes.[75,90,97,105] The IRIS trial[97] in people with a recent MI presented cumulative death rates annually up to 3 years (see *Table 22*). Although this trial found lower mortality rates for those

TABLE 22 Cumulative mortality

Study	Outcome	ICD	OPT	Effect
Cardiac arrest				
CIDS[84]	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
Cardiomyopathy				
DEFINITE[90]	All-cause mortality rate at 1 year, %	2.6	6.2	
	All-cause mortality rate at 2 years, %	7.9	14.1	
Early post MI				
IRIS[97]	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	
Scheduled for CABG				
CABG Patch[75]	Actuarial mortality by 4 years' follow-up, %	27	24	*p*-value 0.64
	HR for death per unit time			1.07 (95% CI 0.81 to 1.42)
HF				
SCD-HeFT[105]	Kaplan–Meier estimates of death from any cause, 5-year event rate	0.289	Amiodarone + OPT: 0.340 Placebo + OPT: 0.361	

ARR, absolute risk reduction.
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.

receiving an ICD + OPT (year 1 10.6%, year 2 15.4%, year 3 22.4%) than for those receiving OPT (year 1 12.5%, year 2 18.2%, year 3 22.9%), the differences were not found to be statistically significant ($p = 0.76$). Similarly, the DEFINITE trial,[90] which included people with cardiomyopathy (year 1: ICD + OPT 2.6%, OPT 6.2%; year 2: ICD + OPT 7.9%, OPT 14.1%), and the SCD-HeFT trial,[105] which included people with mild to moderate HF (Kaplan–Meier estimate, 5 years: ICD + OPT 0.289; amiodarone + OPT 0.340; placebo + OPT 0.361), also reported lower all-cause mortality following implantation of an ICD (*p*-values not stated). In contrast, the CABG Patch trial,[75] which included people scheduled for CABG surgery, reported higher actuarial mortality at 4 years' follow-up in those receiving an ICD + OPT (27%) than in those receiving 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*).

Survival

Differences in mortality were reflected in the survival outcomes reported by the AVID[71,72] and CASH[81] trials in people at increased risk of SCD as a result of previous ventricular arrhythmias. The AVID trial reported statistically significant differences in overall survival during the 3 years of follow-up ($p < 0.02$),[71] survival free of cardiac death at 2 years ($p = 0.0042$)[72] and survival to arrhythmic death at 2 years ($p = 0.0002$),[72] favouring ICDs compared with AAD (*Table 23*). Survival free of non-arrhythmic cardiac death did not differ significantly between those receiving ICDs and those receiving AADs ($p = 0.8039$).[72] Despite the CASH trial[81] finding benefits for ICDs compared with AADs for overall survival (HR 0.766, $p = 0.081$) and survival free of cardiac arrest (HR 0.481, $p = 0.072$), the differences were not statistically significant. In contrast, the CASH trial[81] did report a significant benefit for survival free of sudden death for people who received an ICD compared with those who received AADs (HR 0.423, $p = 0.005$). The DEBUT trial[89] reported a mean survival time for the AAD group of 26.2 [standard error of the mean (SEM) 1.4] months (no deaths in the ICD group).

Only the AMIOVIRT[69] and CAT[82] trials, which included people with cardiomyopathy, reported survival (see *Table 23*). The AMIOVIRT trial[69] presented overall and arrhythmia-free survival rates for the ICD + OPT group and the amiodarone + OPT group at 1 and 3 years' follow-up, showing no statistically significant difference (overall survival $p = 0.1$, arrhythmia-free survival $p = 0.8$). The CAT trial[82] presented cumulative survival data for the ICD + OPT group and the OPT group for up to 6 years' follow-up, finding no statistically significant difference between the groups ($p = 0.554$) (see *Table 23*).

Heart failure hospitalisations

Only the AVID study,[71] which included people at increased risk of SCD because of previous ventricular arrhythmias, reported the proportion of patients rehospitalised annually for up to 3 years' follow-up. Significantly higher rates were reported for the ICD group than for the AAD group ($p = 0.04$) (*Table 24*). For both groups, the rehospitalisation rate was > 55% at year 1, > 65% at year 2 and > 75% at year 3.

The MADIT II trial,[101] which included people remote from MI, reported the proportion of hospitalisations because of HF (ICD + OPT 19.9%, OPT 14.9%, *p*-value not stated) and the number of patients hospitalised per 1000 months of follow-up (ICD + OPT 11.3, OPT 9.4, $p = 0.09$), with higher rates among those receiving an ICD + OPT (see *Table 24*).

Symptoms/complications related to arrhythmias

The CAT[82] and AMIOVIRT[69] trials, which included people with cardiomyopathy, reported the occurrence of syncope. Some 12% of people with an ICD + OPT had syncope during VTs in the CAT trial[82] and 3.9% of ICD + OPT patients and 5.8% of amiodarone + OPT patients had syncope in the AMIOVIRT study[69] (*Table 25*). The MADIT II trial,[103] which included people remote from MI, reported the number of adverse cardiac events in the week before SCD (ICD + OPT 28, OPT 49), with comparable rates of syncope and angina pectoris (4% for both), lower rates of MI for the ICD + OPT group (ICD + OPT 4%, OPT 10%) and higher rates of ventricular arrhythmia (ICD + OPT 25%, OPT 10%) and CHF (ICD + OPT 43%, OPT 16%) for the ICD + OPT group.

TABLE 23 Survival

Study	Outcome and follow-up	ICD, *n*/*N* (%)	OPT, *n*/*N* (%)	*p*-value
Cardiac arrest				
AVID[71]	Overall survival, %, mean 18.2 (SD 12.2) months		AAD:	< 0.02
	1 year	89.3	82.3	
	2 years	81.6	74.7	
	3 years	75.4	64.1	
	[a]Survival free of cardiac death, %[72]			0.0042
	At 1 year	90.9	85.1	
	At 2 years	85.0	81.2	
	[b]Survival to arrhythmic death, %[72]			0.0002
	At 1 year	96.6	91.9	
	At 2 years	94.2	89.1	
	Survival free of non-arrhythmic cardiac death[c]	Presented in figure only	Presented in figure only	0.8039
CASH[81]	57 (SD 34) months		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[89] main study	3 years			
	Mean (SEM) survival (months)		26.2 (1.4)	
Cardiomyopathy				
AMIOVIRT[69]	Survival rate, %			0.8[d]
	1 year	96	Amiodarone + OPT: 90	
	3 years	88	Amiodarone + OPT: 87	
	Arrhythmia-free survival rate, %			0.1[e]
	1 year	78	82	
	3 years	63	73	
CAT[82]	Cumulative survival, %			0.554
	2 years	92	93	
	4 years	86	80	
	6 years	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	Outcome	ICD	OPT	*p*-value
Cardiac arrest				
AVID[71]	% of patients rehospitalised (patients at risk $N = 1011$)			0.04
	At 1 year	59.5	55.6	
	At 2 years	74.8	64.7	
	At 3 years	83.3	75.5	
Remote from MI				
MADIT II[101]	Hospitalisation because of HF, *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	ICD	OPT	Effect (HR)
Cardiomyopathy				
CAT[82]	Syncope during VT, *n/N* (%)	6/50 (12)		
AMIOVIRT[69]	Syncope, %	3.9[a]	5.8	0.7
Remote from MI				
MADIT II[103]	Adverse cardiac events in week before SCD, *n*	28	49	
	Syncope, %	4	4	
	Angina pectoris, %	4	4	
	MI, %	4	10	
	Ventricular arrhythmia, %	25	10	
	CHF, %	43	16	

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

Quality of life

Two trials in people at increased risk of SCD because of previous ventricular arrhythmias, the AVID[74] and CIDS[87] trials, reported results from substudies using a range of generic and condition-specific measures of QoL (*Table 26*). The AVID trial[74] assessed QoL using the Short Form questionnaire-36 items (SF-36) physical component summary (PCS) and mental component summary (MCS), the 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 differences between the ICD group and the AAD group (baseline: ICD 37.4, AAD 36.5, $p = 0.3$; 12 months: ICD 40.0, AAD 38.0, $p = 0.3$). In contrast, the ICD group had a lower (worse) mean score on the MCS at baseline than the AAD group, which 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 group and the AAD group at baseline (ICD 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 ICD and AAD groups were similar at baseline (ICD 22.1, AAD 21.9, *p*-value not stated) and at 12 months' follow-up (scores and *p*-values not stated).

TABLE 26 Quality-of-life outcomes

Study	Outcome and follow-up	Intervention	Comparator(s)	95% CI, *p*-value
Cardiac arrest (secondary prevention)				
AVID[74]	1 year	(*n* = 416)	AAD (*n* = 384)	
	SF-36 PCS score, mean (SD)			
	Baseline	37.4 (10.9)	36.5 (11.2)	0.3
	12 months	*40 (10.5)*[a]	*38 (17)*[a]	
	SF-36 MCS score, mean (SD)			
	Baseline	45.9 (11.8)	47.5 (11.5)	0.006
	12 months	*49 (16.5)*[a]	*48 (17)*[a]	
	Patient concerns checklist, mean (SD)			
	Baseline	15.9 (8.6)	16.2 (8.9)	0.06
	12 months	NR	NR	0.1
	QL index, mean (SD)			
	Baseline	22.1 (4.9)	21.9 (5.0)	
	Impact of adverse symptoms on QoL[b]			
	SF-36 PCS score	–2.25 (–3.32 to –1.18), $p < 0.001$	–1.64 (–2.89 to –0.41), $p = 0.009$	
	SF-36 MCS score	–2.32 (–3.76 to –0.88), $p = 0.002$	–0.51 (–1.97 to 0.94), $p = 0.5$	
	Patient concerns	1.84 (0.91 to 2.76), $p < 0.001$	0.91 (0.07 to 1.75), $p = 0.03$	
	Impact of ICD shocks on QoL[b]			
	SF-36 PCS score	–1.45 (–2.74 to –0.18), $p = 0.03$		
	SF-36 MCS score	–1.82 (–3.56 to –0.08), $p = 0.04$		
	Patient concerns	2.15 (1.07 to 3.23), $p < 0.001$		
CIDS[87]		(*n* = 86)	Amiodarone (*n* = 92)	Time by group *p*-value
	Domains of MHI, 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

TABLE 26 Quality-of-life outcomes (*continued*)

Study	Outcome and follow-up	Intervention	Comparator(s)	95% CI, *p*-value
	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

continued

TABLE 26 Quality-of-life outcomes (*continued*)

Study	Outcome and follow-up	Intervention			Comparator(s)	95% CI, *p*-value
	Effects of ICD shocks on HRQoL scores[87]	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 MHI, mean (SD)					
	Total index[c]					
	Baseline	175.9 (26.5)	171.7 (22.7)	171.2 (32.0)	177.9 (27.1)	
	12 months	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	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	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 NHP, 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	19.5 (27.1)[e]	24.8 (33.4)[e]	23.5 (29.5)	37.0 (37.6)	0.003
	Within-group *p*-value	0.02	0.115	0.859		
	Physical mobility[d]	($n = 65$)	($n = 27$)	($n = 15$)	($n = 93$)	
	Baseline	13.1 (15.0)	12.4 (10.2)	7.1 (9.8)	13.18 (20.1)	
	12 months	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		

TABLE 26 Quality-of-life outcomes (*continued*)

Study	Outcome and follow-up	Intervention			Comparator(s)	95% CI, *p*-value
	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	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	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	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	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	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[104]	HUI3 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	

continued

TABLE 26 Quality-of-life outcomes (*continued*)

Study	Outcome and follow-up	Intervention	Comparator(s)	95% CI, *p*-value
	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[69]	1 year	(*n* = 51)	Amiodarone + OPT (*n* = 52)	
	QWBS, mean (SD)	74 (19)	70 (22)	0.5[k]
	State–Trait Anxiety Inventory, mean (SD)	61 (17)	67 (20)	0.4[k]
DEFINITE[94]		(*n* = 227)	(*n* = 226)	
	SF-12			
	Long-term MCS scores			0.89
	Long-term PCS scores			NS
	Long-term MLWHFQ subscale scores			NS

TABLE 26 Quality-of-life outcomes (*continued*)

Study	Outcome and follow-up	Intervention		Comparator(s)	95% CI, *p*-value
Scheduled for CABG					
CABG Patch[80]	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)			
		ICD device did not fire (*n* = 161)	ICD device fired (*n* = 101)	OPT (*n* = 228)	OPT vs. ICD fired (95% CI)[n]
	HRQoL, mean (SD)				
	Perception of health				
	General health status	56.6 (23.3)	52.1 (22.1)	58.3 (23.6)	NS
	Perception of health transition[m]	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

continued

TABLE 26 Quality-of-life outcomes (*continued*)

Study	Outcome and follow-up	Intervention		Comparator(s)	95% CI, *p*-value
	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 completing the 6-month QoL instrument (%)	36.0	55.5	33.8	
HF					
SCD-HeFT[107]		ICD + OPT ($n = 816$)		Amiodarone + OPT ($n = 830$), placebo + OPT ($n = 833$)	Difference (95% CI)[q]
	DASI, mean score (SD)				
	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)
		ICD + OPT ($n = 816$)		Amiodarone + OPT ($n = 830$), placebo + OPT ($n = 833$)	Difference (95% CI),[q] *p*-value
	MHI-5				
	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)
		ICD + OPT		Placebo + OPT	*p*-value

TABLE 26 Quality-of-life outcomes (*continued*)

Study	Outcome and follow-up	Intervention	Comparator(s)	95% CI, *p*-value
	MLWHFQ, median			
	Baseline	41	43	0.77
	3 months	30	36	0.006
	12 months	32	36	0.07
	30 months	32	36	0.05
		ICD + OPT	Placebo + OPT	*p*-value
	Global health status, median			
	3 months	75	70	0.002
	12 months	75	70	0.05
	30 months	70	70	0.18
		ICD + OPT ($n = 816$)		*p*-value
		Received shock within 1 month before a scheduled QoL assessment ($n = 49$)	No shock	
	SF-36 score, mean change			
	General health perceptions	–6.3	3.4	0.002
	Physical function	–8	10.9	< 0.001
	Emotional function	–11	4.5	0.02
	Social function	–5.3	4.6	0.009
	Self-related health	–3.2	6.6	0.009

DASI, Duke Activity Status Index; HUI3, Health Utilities Index 3; MHI, Mental Health Index; MHI-5, Mental Health Index-5; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; NHP, Nottingham Health Profile; QWBS, Quality of Well-Being Scale; NR, not reported; NS, not significant; SF-12, Short Form questionnaire-12 items.

a Values in italics obtained from figure in paper using Engauge Digitizer free software version 5.1 (see http://digitizer.sourceforge.net/).
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 vs. 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 has *p*-value of 0.0507.
p *F*-test for analysis of variance has *p*-value of 0.0549.
q ICD vs. placebo reported here. Amiodarone vs. placebo can be viewed in data extraction forms (see *Appendix 7*).

The effects of adverse symptoms and ICD shocks were assessed in the AVID trial[74] using PCS scores, MCS scores and patient concerns using multivariate analysis including age, sex, race, index arrhythmia, ejection fraction, history of HF and use of beta-blockers at hospital discharge (see *Table 26*). 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 ICD group and 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 of PCS scores ($p = 0.03$), MCS scores ($p = 0.04$) and patient concern scores ($p < 0.001$).

A substudy of the CIDS trial[87] reported the effects of ICDs and AADs 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 (see *Table 26*). At 12 months' follow-up the ICD group had shown a 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 the MHI and the 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[87] on the different domains of the MHI and the NHP through univariate comparisons between groups in terms of the numbers of shocks (i.e. ICD no shocks, ICD one to four shocks, ICD five or more shocks and AAD group without an ICD) (see *Table 26*). It was evident that the ICD five or more shocks group, like the AAD group without an ICD, did not experience the significant improvements in QoL that were reported by the ICD groups with less than five shocks. At 12 months' follow-up the ICD five or more shocks group scored significantly worse ($p < 0.05$) than both the ICD no shocks group and the ICD one to four shocks group on the MHI 'total index' and 'psychological distress' domains, than the ICD one to four shocks group on the MHI 'psychological well-being' domain and than the ICD no shocks group on the NHP 'emotional reactions' domain. Although the ICD five or more shocks group did not differ significantly from the AAD group without an ICD on any of the MHI and NHP domains, the ICD no shocks and ICD one to four shocks groups had significantly better ($p < 0.05$) QoL than the AAD group without an ICD on the MHI 'total index' and 'psychological distress' domains and the NHP 'energy level', 'physical mobility' (ICD no shocks only), 'emotional reactions' and 'lifestyle impairment' domains.

Five trials[69,80,94,104,107] in people who had not suffered a life-threatening arrhythmia but who were at increased risk assessed QoL. The MADIT II trial[104] assessed QoL in those remote from their MI through the Health Utilities Index 3 (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 (see *Table 26*). The mean annual change in HUI3 scores showed a worsening in HRQoL for the ICD + OPT group compared with the OPT group annually, with a statistically significantly change in years 2 ($p = 0.05$) and 3 ($p = 0.10$).[104] 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).[104]

The AMIOVIRT study[69] in people with cardiomyopathy assessed changes in QoL using the Quality of Well-Being Scale (QWBS) and the State–Trait Anxiety Inventory (STAI) (see *Table 26*). Comparison of the ICD + OPT group with the amiodarone + OPT group at 1 year of follow-up showed no statistically significant difference between the groups for well-being on the QWBS ($p = 0.5$) or for anxiety on the STAI ($p = 0.4$). Although the DEFINITE trial[94] in people with cardiomyopathy assessed QoL using the Short Form questionnaire-12 items (SF-12) MCS and PCS and the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), stating that no statistically significant differences were found between the ICD + OPT group and the OPT group, no data were reported.

The CABG Patch trial[80] in people scheduled for a CABG assessed HRQoL using measures of perception of health, ability to function and psychological well-being at 6 months' follow-up (see *Table 26*). On all measures of HRQoL the group receiving OPT reported a higher QoL than the ICD + 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 ($p = 0.040$).[80] With 38.5% of people with an ICD + OPT having received a shock in the 6 months before completing the QoL instrument, the CABG Patch trial[80] assessed the effects on QoL scores. On 10 of the 12 measures the OPT group had a higher QoL than the ICD + OPT group when the device either fired or did not fire. The scores for the ICD + OPT group when the device did not fire were similar to those of the OPT group, with no statistically significant differences (*p*-values not stated). In contrast, the ICD + OPT group when the device did fire had a lower QoL, with statistically significant differences ($p = 0.05$) for perception of health transition, physical limitations, physical role functioning, emotional role functioning, mental health and satisfaction with appearance.

The SCD-HeFT trial[107] in people with HF reported QoL through a comparison of the Duke Activity Status Index (DASI), the Mental Health Inventory 5 (MHI-5), the MLWHFQ and the global health status of the ICD + OPT, amiodarone + OPT and placebo + OPT groups at baseline and 3, 12 and 30 months' follow-up (see *Table 26*). The effects on QoL were compared between those experiencing shocks and those not receiving a shock in the ICD + OPT group using the SF-36. Using the DASI there were no clinical (4-point difference) or statistically significant differences in median or mean scores between the groups at baseline and 3, 12 and 30 months. On the MHI-5, outcomes were more equivocal. Although the differences in the median and mean scores comparing the ICD + OPT group and amiodarone + OPT group separately with the placebo + OPT group were below clinically meaningful levels (i.e. 5-point difference), some were statistically significant. Comparison of the median scores showed that the ICD + OPT group had significantly better scores than the placebo + OPT group at 3 months ($p = 0.01$) and 12 months ($p = 0.003$). By 30 months the scores for the ICD + OPT group had declined to baseline levels. Similarly, the mean scores for the ICD + OPT group differed significantly from those for the placebo + OPT group at 3 and 12 months ($p = 0.05$). Although the amiodarone + OPT group had a significantly higher MHI-5 score at baseline than the placebo + OPT group ($p = 0.05$), these differences disappeared during subsequent follow-up.

Similar improvements for the ICD + OPT group were reported on the MLWHFQ in the SCD-HeFT trial,[107] resulting in significantly better scores for the ICD + OPT group than for the placebo + OPT group at 3 ($p = 0.006$) and 30 ($p = 0.05$) months (see *Table 26*). However, these differences were thought to be clinically insignificant (5-point change). In contrast, a comparison using a time trade-off utility measure showed that the health status of the ICD + OPT group and the placebo + OPT group declined from baseline with no statistically significant difference at 30 months' follow-up ($p = 0.18$).

The effects of ICD shocks on QoL were assessed in the SCD-HeFT trial using the SF-36 (see *Table 26*).[107] A comparison of the changes in scores for those who had received a shock within 1 month of a scheduled QoL assessment and those who had not received a shock showed a significant decrease in the QoL of those who received a shock with regard to 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 ($p = 0.009$).[107]

Adverse events

All four trials[71,81,84,89] comparing the use of ICDs with AADs in people at increased risk of SCD because of previous ventricular arrhythmias reported adverse events (*Table 27*). 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[89] and the AVID[71] and CASH[81] trials respectively. The DEBUT trial[89] reported that 29.7% of the ICD group and 13.8% of the AAD group suffered adverse events (*p*-value not stated). The AVID trial[71] 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

TABLE 27 Adverse events

Study	Outcome and follow-up	ICD, *n*/*N* (%)	OPT, *n*/*N* (%)	*p*-value
Cardiac arrest (secondary prevention)				
AVID[71]	Non-fatal torsade de pointes VT		1/509 (0.2)	
	Suspected pulmonary toxicity, %			
	At 1 year		3	
	At 2 years		5	
	Death from pulmonary toxicity		1/509 (0.2)	
	Thyroid replacement medication, %			
	At 1 year	1	10	
	At 2 years	1	16	
	Death within 30 days of initiation of therapy[a]	12/507 (2.4)	18/509 (3.5)	0.27
	Bleeding requiring reoperation or transfusion	6/507 (1.2)		
	Serious haematoma	13/507 (2.6)		
	Infection	10/507 (2.0)		
	Pneumothorax	8/507 (1.6)		
	Cardiac perforation	1/507 (0.2)		
	Early dislodgement or migration of leads	3/507 (0.6)		
	Unsuccessful first attempt at ICD implantation without thoracotomy	5/507 (1.0)		
	Overall rate of non-fatal complications of implantation, %	5.7		
CASH[81]			Amiodarone Metoprolol	
	Drug-related pulmonary toxicity		0/92 (0)	
	Hyperthyroidism		3/92 (3.3)	
	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) [epicardial ICDs 3/55 (5.4), endocardial ICDs 2/44 (4.5)]	AADs: 2/189 (1.1) [amiodarone 2/92 (2.2), metoprolol 0/97 (0)]	0.029
	Other complications			
	Infection	3/99 (3.0) (explantation required for two)		
	Haematoma or seroma	6/99 (6.1)		
	Pericardial effusion	1/99 (1.0)		
	Pleural effusion	3/99 (3.0)		
	Pneumothorax	1/99 (1.0)		

TABLE 27 Adverse events (*continued*)

Study	Outcome and follow-up	ICD, *n*/*N* (%)	OPT, *n*/*N* (%)	*p*-value
	Dislodgement or migration of system leads	3/99 (3.0)		
	Device dysfunction	5/99 (5.1)		
	Overall complication rate, %	23.0 (including an explantation rate of 2.1)		
CIDS[84]	30-day mortality in implanted patients ($n = 310$)			
	In patients with thoracotomy ($n = 33$)	1/33 (3.0)		
	In patients with non-thoracotomy lead system ($n = 277$)	1/277 (0.4)		
	ICD permanently or temporarily explanted because of infection, heart transplantation or patient preference	16/310 (5.2)		
	Adverse experiences ever reported			
	Pulmonary infiltrate		18/331 (5.7) (1.9% per year)[b]	
	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)[b]	
	Tremor		91/331 (15.4)[b]	
	Insomnia		64/331 (19.3)	
	Peripheral neuropathy		1/331 (0.3)	
	ICD product discomfort	25/328 (7.6)		
	ICD malfunction	2/328 (0.6)		
	ICD pocket infection	15/328 (4.6) (1.4% per year)		
	ICD dislodgement/fracture	8/328 (2.4)		
DEBUT (pilot study)[89]	Operative mortality	0/0 (0)		
	Adverse effects	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)		

continued

TABLE 27 Adverse events (*continued*)

Study	Outcome and follow-up	ICD, *n*/*N* (%)	OPT, *n*/*N* (%)	*p*-value
DEBUT (main study)[89]	Operative mortality	0/0 (0)		
	Adverse effects	11/37 (29.7)	4/29 (13.8)	
	Minor complications, corrected by reprogramming devices without major intervention			
	Defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia	7/37 (19.0)		
	T-wave oversensing	3/37 (8.1)		
	Pocket erosion requiring removal of ICD	1/37 (2.7)		
	Side-effects in beta-blocker group			
	Impotence/decrease in libido		1/29 (3.4)	
	Fatigue		1/29 (3.4)	
	Profound bradycardia		1/29 (3.4)	
	Hypotension plus central nervous system side effect		1/29 (3.4)	
Early post MI				
DINAMIT[95]	Number of deaths related to device implantation	0/310 (0)		
	In-hospital device-related complications	25/310 (8.1)		
IRIS[97]	Died within 30 days of 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)		
	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) (four had lead replacements)		

TABLE 27 Adverse events (*continued*)

Study	Outcome and follow-up	ICD, *n*/*N* (%)	OPT, *n*/*N* (%)	*p*-value
Remote from MI				
MADIT I[99]	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)	
	Problems with defibrillator lead	7/95 (7.4)	0/101 (0)	
	Malfunction of defibrillator generator	3/95 (3.2)	2/101 (2.0)	
	Total no. of patients with adverse events	19/95 (20.0)	12/101 (11.9)	
MADIT II[101]	Adverse effects of treatment, death during implantation	0/742 (0)		
	Lead problems	13/742 (1.8)		
	Non-fatal infections requiring surgical intervention	5/742 (0.7)		
Cardiomyopathy				
AMIOVIRT[69]	Discontinued amiodarone because of adverse effects, mean follow-up 17.8 (SD 13.3) months		25/52 (48.1)	
CAT[82]	Complications caused by ICD therapy			
	Death within 30 days of ICD implantation	0/50 (0)		
	Device dislocation and bleeding requiring revision	2/50 (4.0)		
	Electrode dislocation requiring revision	2/50 (4.0)		
	Complications in 24 months of follow-up	10 in seven patients		
	Electrode dislocation and sensing/isolation defects	7/50 (14.0)		
	Infection with total device replacement	2/50 (4.0)		
	Perforation	1/50 (2.0)		

continued

TABLE 27 Adverse events (*continued*)

Study	Outcome and follow-up	ICD, *n*/*N* (%)	OPT, *n*/*N* (%)	*p*-value
DEFINITE[90]	Complications during implantation of ICD	3/229 (1.3)		
	Haemothorax	1/229 (0.4)		
	Pneumothorax	1/229 (0.4)		
	Cardiac tamponade	1/229 (0.4)		
	Procedure-related deaths	0/229 (0)		
	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 because of development of sinus node dysfunction	2/229 (0.9)		
	Biventricular devices for NYHA class III or IV HF and prolonged QRS interval	11/229 (4.8)		
Scheduled for CABG				
CABG Patch[75]	Death in the first 30 days after randomisation	24/446 (5.4)	20/454 (4.4)	0.60
	Postoperative complications			
	MI	18[c]/446 (4.0)	16[c]/454 (3.5)	
	Sustained VT	26[c]/446 (5.8)	31[c]/454 (6.8)	
	VF	15[c]/446 (3.4)	24[c]/454 (5.3)	
	Bradycardia	13[c]/446 (2.9)	20[c]/454 (4.4)	
	Atrial fibrillation	102[c]/446 (22.9)	94[c]/454 (20.7)	
	Shock	41[c]/446 (9.2)	34[c]/454 (7.5)	
	New or more severe HF	70[c]/446 (15.7)	57[c]/454 (12.6)	
	Conduction defect	63[c]/446 (14.1)	66[c]/454 (14.5)	
	Residual central nervous system deficit	16[c]/446 (3.6)	9[c]/454 (2.0)	
	Bleeding treated with surgery	22[c]/446 (4.9)	14[c]/454 (3.1)	
	Postpericardiotomy syndrome	4[c]/446 (0.9)	3[c]/454 (0.7)	
	Deep sternal wound infection	12[c]/446 (2.7)	2[c]/454 (0.4)	$0.01 < p < 0.05$
	Infection at wound or catheter site	55[c]/446 (12.3)	27[c]/454 (5.9)	$0.01 < p < 0.05$
	Pneumonia	38[c]/446 (8.5)	18[c]/454 (4.0)	$0.01 < p < 0.05$

TABLE 27 Adverse events (*continued*)

Study	Outcome and follow-up	ICD, *n*/*N* (%)	OPT, *n*/*N* (%)	*p*-value
	Other infection	28[c]/446 (6.3)	15[c]/454 (3.3)	
	Renal failure	30[c]/446 (6.7)	22[c]/454 (4.8)	
	Events during long-term follow-up			
	Angina pectoris	120[c]/446 (27.0)	125[c]/454 (27.5)	
	MI	2[c]/446 (0.5)	19[c]/454 (4.2)	$0.01 < p < 0.05$
	New or worsening HF	190[c]/446 (42.5)	193[c]/454 (42.5)	
	Ventricular arrhythmias	87[c]/446 (19.4)	65[c]/454 (14.3)	
	Atrial fibrillation	66[c]/446 (14.7)	46[c]/454 (10.1)	
	Hospitalisation	274[c]/446 (61.4)	251[c]/454 (55.2)	
	Repeat CABG surgery	0/446 (0.0)	3[c]/454 (0.7)	
	PTCA or atherectomy	13[c]/446 (2.9)	10[c]/454 (2.1)	
	Permanent cardiac pacemaker	13[c]/446 (2.9)	22[c]/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)	
HF				
SCD-HeFT[105]		($n = 829$)	Amiodarone + OPT ($n = 845$), placebo + OPT ($n = 847$)	
	Implantation was unsuccessful	1/829 (0.1)		
	ICD removed during follow-up	32/829 (3.9)		
	Clinically significant ICD complications, %[d]			
	At time of implantation	5		
	Later in the course of follow-up	9		
	Increased tremor (amiodarone vs. placebo) at time of last follow-up, %		4	
	Increased hypothyroidism (amiodarone vs. placebo) at time of last follow-up, %		6	

PTCA, percutaneous transluminal coronary angioplasty.
a Or by the time of hospital discharge if discharge occurred later than 30 days after therapy began.
b The numerator, denominator and percentages as reported by the primary publication are incorrect; however, it is not clear where the error lies.
c Calculated from percentages by reviewer.
d Defined as clinical events requiring surgical correction, hospitalisation or new and otherwise unanticipated drug therapy.

ICD group (2.4%) and the AAD group (3.5%) ($p = 0.27$). In contrast, the CASH trial[81] found significantly ($p = 0.029$) higher mortality rates during the perioperative period for the ICD group (5.1%) than for the AAD group (1.1%). The only other comparison between interventions was in the AVID trial,[71] finding that the use of thyroid replacement medication was higher for the AAD group at year 1 (10.0%) and year 2 (16.0%) than in the ICD group (1.0% years 1 and 2) (*p*-value not stated).

Analysis of the adverse events reported for the ICD groups in the four trials[71,81,84,89] showed that these tended to be limited in occurrence (see *Table 27*). 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 (19.0%);[89] T-wave oversensing (8.1%);[89] ICD product discomfort (7.6%);[84] ICD permanently or temporarily explanted because of infection, heart transplantation or patient preference (5.2%);[84] device dysfunction (5.1%);[81] pocket erosion requiring removal of the ICD (2.7%);[89] dislodgement or migration of system leads (3.0%);[81] ICD dislodgement/fracture (2.4%);[84] bleeding requiring reoperation or transfusion (1.2%);[71] and unsuccessful first attempt at ICD implantation without thoracotomy (1.0%).[71] Other adverse events included haematoma or seroma (6.1%);[81] serious haematoma (2.6%);[71] pleural effusion (3.0%);[81] infection (2.0–4.6%);[71,84] and pneumothorax (1.6%).[71]

Adverse events reported for the AAD groups differed between the four trials (see *Table 27*).[71,81,84,89] The CIDs trial[84] found that > 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[84] included skin discolouration (6.3%) and pulmonary infiltrate (5.7%). In the CASH trial[81] 10% of people receiving amiodarone (9.8%) or metoprolol (10.3%) had to discontinue drug treatment. The AVID trial[71] reported that 5% of the AAD group had suspected pulmonary toxicity at 2 years. Other adverse events reported by the AVID,[71] CASH[81] and DEBUT[89] trials affected < 5% of participants (see *Table 27*).

All nine trials[69,75,82,90,95,97,99,101,105] comparing ICDs + OPT with the differing comparator treatments in people who had not suffered a life-threatening arrhythmia but who were at increased risk reported adverse events, with six trials[69,82,90,95,97,101] focused predominantly on those related to the placement of ICDs (see *Table 27*). The type of adverse events reported differed between the trials, making comparisons difficult. Adverse events were thought to affect between 5%[105] and 61%[75] of people receiving an ICD, depending on the definition of an adverse event or complication and the period of follow-up. Only three trials[75,99,105] reported adverse events for the different comparator treatments, with rates varying from 11.9% to 55%.

Mortality rates associated with implantation of an ICD appeared low, with no deaths reported by four trials[82,95,99,101] and crude death rates ranging from 1.6% to 5.4% in the IRIS[97] and CABG Patch[75] trials respectively. Deaths among those receiving the comparator treatments were reported only in the CABG Patch trial,[75] with a crude death rate for the OPT group of 4.4%.

Lead-, electrode- or defibrillator generator-related problems were reported in five trials,[82,90,97,99,101] affecting between 1.8% and 14.0% of people. In the IRIS trial,[97] these led to a surgical revision rate of 2.4%. Surgical or device-related infections were reported in four trials,[75,82,90,99] affecting between 0.4% and 12.3% of people in the ICD group. A further three trials[81,82,101] reported infection leading to surgical intervention or device removal/replacement, which occurred in 0.7–4% of people.

Other non-device-specific adverse events were reported by four trials.[75,82,90,99] In the MADIT I[99] and SCD-HeFT[75] trials only syncope (5%) and hypothyroidism (6%) affected ≥ 5% of people in the comparator groups. The CABG Patch trial[75] reported adverse events in the postoperative period and during long-term follow-up for both the ICD + OPT group and the OPT group, focusing predominantly on changes in underlying cardiac conditions. In the postoperative period the CABG Patch trial[75] reported event rates of ≥ 5% for the ICD + OPT group and ≥ 4% for the OPT group for atrial fibrillation (ICD + OPT 22.9%, OPT 20.7%), new or severe HF (ICD + OPT 15.7%, OPT 12.6%), conduction defect (ICD + OPT 14.1%, OPT 14.5%), sustained VT (ICD + OPT 5.8%, OPT 6.8%), shock (ICD + OPT 9.2%, OPT 7.5%), pneumonia

(ICD + OPT 8.5%, OPT 4.0%) and renal failure (ICD + OPT 6.7%, OPT 4.8%).[75] Events during long-term follow-up that affected ≥ 5% of the ICD + OPT group and the OPT group included new or worsening HF (ICD + OPT 42.5%, OPT 42.5%), angina pectoris (ICD + OPT 27.0%, OPT 27.5%), ventricular arrhythmias (ICD + OPT 19.4%, OPT 14.3%) and atrial fibrillation (ICD + OPT 14.7%, OPT 10.1%).

Subgroup analyses reported by included randomised controlled trials

Six trials[71,75,90,97,103,105] reported prespecified subgroup analyses, although it should be noted that the trials were not powered to detect differences in subgroups.

The report of the AVID trial,[71] which included people at increased risk of SCD because of previous ventricular arrhythmias, presented in a figure four prespecified subgroup analyses for all-cause mortality (age, LVEF, cause of arrhythmia and qualifying arrhythmia). No subgroup differed significantly from the others 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 $n = 561$).[72] ICDs improved survival free of arrhythmic death for people whose presenting arrhythmia was VT ($p = 0.025$) or VF ($p = 0.0019$). For non-arrhythmic cardiac death there were no statistically significant differences in survival between the ICD group and the AAD group for people presenting with either VT ($p = 0.72$) or VF ($p = 0.98$).

The IRIS trial,[97] which included people in the early period post MI, prespecified 13 subgroup analyses for all-cause mortality, nine of which were presented in a figure [age, sex, CHF on admission, criterion of inclusion (for definitions see *Appendix 7*), 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 and number of risk factors). For most of the subgroups the 95% CIs crossed 1.0, apart from those for thrombolytic therapy for early reperfusion for 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[103] reported prespecified subgroup analyses for all-cause mortality using baseline characteristics, five of which were presented in a figure only (age, sex, ejection fraction, NYHA class or QRS interval) and seven of which were not presented (hypertension, diabetes, LBBB, atrial fibrillation, the interval since the most recent MI, type of ICD, and blood urea nitrogen level). The HRs in all of the subgroups were similar, with no statistically significant interactions.

The DEFINITE trial,[90] which included people with cardiomyopathy, presented six prespecified subgroup analyses for all-cause mortality in a figure only (age, sex, LVEF, QRS interval, NHYA class and history of atrial fibrillation). 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,[75] which included people who were scheduled for CABG surgery, evaluated 10 prespecified subgroups (age, sex, HF, NYHA class, LVEF, diabetes mellitus, QRS complex duration, use of ACE inhibitors, use of class I or class III AADs and use of beta-adrenergic-blocking drugs). HRs 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, which included people with mild to moderate HF, reported prespecified subgroup analyses for all-cause mortality[105] and cause of death[108] according to cause of CHF (ischaemic or non-ischaemic) and NYHA class (II or III) and for all-cause mortality according to race.[106] *Table 28* presents the results for ICDs compared with placebo; subgroup results for the comparisons between amiodarone and placebo are reported in *Appendix 7*.

There was no significant interaction between ICD therapy and the cause of CHF for all-cause mortality ($p = 0.68$).[105] The HRs for those with ischaemic and non-ischaemic CHF 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 between ICD therapy and the cause of CHF for each of the specified modes of death[108] (see *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 CHF, whereas no significant reduction in other modes of death was found for either subgroup (see *Table 28*).

TABLE 28 Subgroups in the SCD-HeFT trial

Subgroup and outcome	ICD vs. placebo HR (95% CI), *p*-value
Ischaemic CHF	
All-cause mortality[105]	0.79 (0.60 to 1.04[a]), 0.05
Cause of death[108]	
Cardiac	0.80 (0.60 to 1.05)
Sudden tachyarrhythmic	0.43 (0.27 to 0.67)
HF	1.11 (0.74 to 1.67)
Non-cardiac	0.79 (0.50 to 1.22)
Non-ischaemic CHF	
All-cause mortality[105]	0.73 (0.50 to 1.07[a]), 0.06
Cause of death[108]	
Cardiac	0.68 (0.44 to 1.03)
Sudden tachyarrhythmic	0.34 (0.17 to 0.70)
HF	1.21 (0.67 to 2.18)
Non-cardiac	0.81 (0.48 to 1.37)
NYHA class II	
All-cause mortality[105]	0.54 (0.40 to 0.74[a]), < 0.001
Cause of death[108]	
Cardiac	0.50 (0.36 to 0.70)
Sudden tachyarrhythmic	0.26 (0.15 to 0.44)
HF	0.93 (0.56 to 1.54)
Non-cardiac	0.63 (0.40 to 0.99)
NYHA class III	
All-cause mortality[105]	1.16 (0.84 to 1.61[a]), 0.30
Cause of death[108]	
Cardiac	1.17 (0.84 to 1.64)
Sudden tachyarrhythmic	0.73 (0.41 to 1.29)
HF	1.34 (0.86 to 2.09)
Non-cardiac	1.10 (0.66 to 1.85)
Race African American	
All-cause mortality[106]	0.65 (95% CI 0.43 to 0.99)
Race white	
All-cause mortality[106]	0.73 (95% CI 0.58 to 0.90)

a 97.5% CI.

There was a statistically significant interaction between ICD therapy and NYHA class ($p < 0.001$).[105] Compared with placebo, ICDs reduced the risk of death in people in NYHA class II (HR 0.54, 97.5% CI 0.40 to 0.74, $p < 0.001$), but not in those in 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 HF ($p = 0.29$) or non-cardiac ($p = 0.11$) deaths.[108] 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 in NYHA class II, but not in those in 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 American: HR 0.65, 95% CI 0.43 to 0.99; white: HR 0.73 95% CI 0.58 to 0.90).[106]

Combining data from the SCD-HeFT[105] non-ischaemic CHF subgroup with data from the three cardiomyopathy trials (AMIOVIRT,[69] CAT,[82] DEFINITE[90]) was considered appropriate by clinical experts. SCD-HeFT[105] did not report the number of events for all-cause mortality occurring in each of the ischaemic and non-ischaemic 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-ischaemic subgroup strongly influenced the analysis and a statistically significant effect in favour of ICD therapy with no statistical heterogeneity was found (RR 0.74, 95% CI 0.58 to 0.93, $p = 0.01$). This is in contrast to the non-significant result of the meta-analysis of the three cardiomyopathy trials alone (see *Figure 4*).

Other relevant trials

Two trials[146,147] were excluded as the intervention did not meet the scope of the present review (many participants in the intervention arm did not receive an ICD); however, these trials presented subgroup data comparing ICD therapy with no ICD therapy that may be considered relevant. The MUSTT[146] and MAVERIC[147] trials have not undergone formal data extraction and quality assessment but the data are presented here for information.

The MUSTT study was included in the previous TARs[62,63] although the authors noted that it did not meet their inclusion criteria if strictly applied (in that randomisation determined electrophysiology-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.[62]

The MUSTT study was designed to test the hypothesis that electrophysiology-guided antiarrhythmic therapy reduces SCD. People with sustained, monomorphic VT induced by any method of stimulation and those with sustained polymorphic VT (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 electrophysiological testing or no antiarrhythmic therapy. ICD therapy could be recommended for people randomised to electrophysiological testing after at least one unsuccessful drug

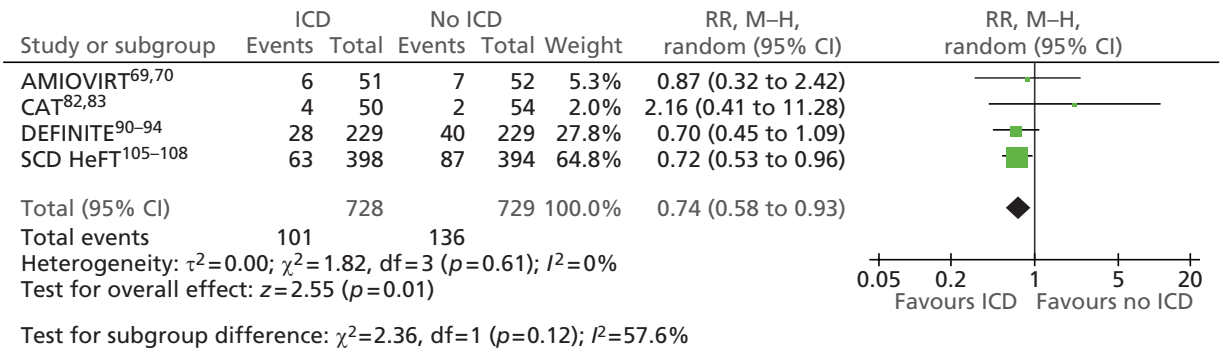

FIGURE 9 All-cause mortality, cardiomyopathy RCTs and SCD-HeFT non-ischaemic CHF subgroup.

test. Median follow-up was 39 months. Beta-blocker use was significantly higher in the no therapy group (electrophysiological testing 29%, no therapy 51%, $p = 0.001$).

All-cause mortality was significantly reduced in the ICD group compared with the electrophysiology-guided therapy without a defibrillator group (RR 0.42, 95% CI 0.29 to 0.61, $p < 0.001$) and the no therapy group (RR 0.49, 95% CI 0.35 to 0.69, $p < 0.001$).[146] The overall mortality rate at 5 years was 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 receiving electrophysiology-guided therapy without a defibrillator (RR 0.24, 95% CI 0.13 to 0.43, $p < 0.001$) and those receiving no therapy (RR 0.28, 95% CI 0.16 to 0.49, $p < 0.001$).[146]

The MAVERIC trial was in progress at the time of the previous TAR.[62] This multicentre UK study was designed to test the possibility of prospectively identifying, using electrophysiological testing, patients who would benefit most from ICD therapy in the context of the secondary prevention of SCD. Survivors of sustained VT, VF or SCD were randomised to electrophysiology-guided interventions (AADs, coronary revascularisation and ICD therapy) or empirical amiodarone therapy, with prestratification for haemodynamic status at the index event. Median follow-up was 60 months.

Subgroup analysis was presented for ICD recipients compared with non-ICD recipients, regardless of allocated treatment. As with the MUSTT trial, these results must be viewed with caution because of the lack of randomisation and the possibility of bias and confounding. An ICD was received by 31 of 108 (29%) patients randomised to electrophysiological testing [14/60 (23%) patients haemodynamically stable and 17/48 (35%) patients haemodynamically unstable at the 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 the index event]. ICD recipients were significantly younger [62.7 (SD 9.0) years vs. 68.1 (SD 9.8) years, $p = 0.002$] 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 in non-ICD recipients [HR 0.54, 0.30 to 0.97 (definition of interval not stated), $p = 0.0391$]. Comparisons between ICD recipients and non-ICD recipients were also presented separately for haemodynamically stable patients [HR 0.71, 0.29 to 1.75 (definition of interval not stated), $p = 0.4537$] and haemodynamically unstable patients [HR 0.42, 0.20 to 0.92 (definition of interval not stated), $p = 0.0299$] at the index event. Multivariate analysis of factors affecting survival found that ICD implantation was associated with a non-statistically significant reduction in the risk of death [OR 0.43, 0.17 to 1.11 (definition of interval not stated), $p = 0.080$].

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

- A total of 13 RCTs were included that compared ICDs with medical therapy in people at risk of SCD because of arrhythmias. The trials were synthesised according to the criteria that they used to identify people at risk of SCD.
- 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 because of inadequate reporting.

Ventricular arrhythmia/cardiac arrest (secondary prevention)

- Four RCTs compared the effectiveness of ICDs and AADs. Average length of follow-up ranged from 18 months to 57 months and sample size ranged from 66 to 1016. The proportion of participants with

CHF differed in the trials. In two trials 100% of participants had CHF, with > 80% in NYHA classes I and II. In the other two trials between 60% and 90% had CHF with approximately 50% in both trials in NYHA classes I and II. LVEF also varied, ranging 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 showed a statistically significant benefit for ICDs compared with AADs (RR 0.75, 95% CI 0.61 to 0.93, $p = 0.01$). Differences were found in the four RCTs for the outcome of sudden cardiac/arrhythmic deaths, with a statistically significant benefit for ICDs compared with AADs when combined through meta-analysis (RR 0.49, 95% CI 0.34 to 0.69, $p < 0.0001$).
- Meta-analysis of two trials showed a statistically significant benefit for ICDs compared with AAD for the outcome of total cardiac deaths (RR 0.74, 95% CI 0.61 to 0.91, $p = 0.004$); however, no differences were found for the outcomes of 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 a statistically significant benefit for ICDs compared with AADs for 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 in one trial (difference 5%, $p = 0.0002$) and survival free of sudden death at 57 months in the other trial (HR 0.423, $p = 0.005$). One RCT found lower cumulative mortality annually over 3 years' follow-up with ICDs (difference: year 1 14.5%, year 2 1.7%, year 3 4.1%).
- Two RCTs assessed QoL through separate substudies using a range of measures. In one RCT there were no significant between-group differences at follow-up. A second RCT found that QoL improved significantly in the ICD group on three domains of the MHI and five domains of the NHP, whereas there were no changes in the OPT group. In this trial the QoL of those experiencing five or more ICD shocks did not differ significantly from that of the OPT group when analysed using the MHI and the NHP. The no shocks and one to four shocks ICD groups showed significant improvements on the 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 6–41 days or ≤ 31 days)

- Two RCTs compared ICDs + OPT with OPT. Length of follow-up was 30 or 37 months and sample size ranged 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 between the groups 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, $p = 0.8$) and non-cardiac deaths (RR 1.39, 95% CI 0.86 to 2.27, $p = 0.18$). Those who received an ICD + OPT 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 between the groups. QoL was not reported.
- One trial reported prespecified subgroup analyses for all cause-mortality. No significant differences were found for the 13 prespecified subgroups.

People with remote myocardial infarction (> 3 weeks or > 1 month previously)

- Two RCTs compared ICDs + 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 27 and 20 months and sample size was 196 and 1232 respectively. 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 SCD (RR 0.36, 95% CI 0.23 to 0.55, $p < 0.00001$) in the ICD + OPT group compared with the OPT group. 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 the groups. One trial reporting hospitalisations found a higher rate per 1000 months' follow-up among those who received an ICD (11.3 vs. 9.4, $p = 0.09$), with higher HF hospitalisations (19.9% vs. 14.9%, *p*-value not reported).
- In one trial that assessed QoL using the HUI3, scores were lower in the ICD + OPT group than in the OPT group at baseline. Differences between the groups were not statistically significant at 3 years' follow-up.
- One trial reported prespecified subgroup analyses for all-cause mortality. The HRs in all 12 of the subgroups were similar, with no statistically significant interactions.

People with non-ischaemic or idiopathic dilated cardiomyopathy

- Three RCTs compared ICD + OPT with OPT or ICD + OPT with amiodarone + OPT. Mean follow-up was between 24 months (two RCTs) and 29 months and sample size ranged from 103 to 458. 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 15–21% were in NYHA class I. Mean LVEF ranged from 21% to 25%.
- Meta-analysis found no significant difference between ICDs and OPT or amiodarone 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 rate of SCDs (RR 0.26, 95% CI 0.09 to 0.77, $p = 0.02$) with ICDs.
- Two trials reported no significant difference in survival between groups.
- Two trials reported no significant differences in QoL, assessed using the QWBS and STAI or the SF-12 MCS and PCS and MLWHFQ.
- One trial reported six prespecified subgroup analyses for all-cause mortality. None of the differences between subgroups was statistically significant.
- Meta-analysis of the three cardiomyopathy trials and the non-ischaemic CHF subgroup of the SCD-HeFT trial found a statistically significant reduction in all-cause mortality (RR 0.74, 95% CI 0.58 to 0.93, $p = 0.01$) with ICDs compared with OPT or amiodarone.

People scheduled for coronary artery bypass graft surgery

- One trial compared ICD + OPT with 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 between groups in all-cause mortality (RR 1.08, 95% CI 0.85 to 1.38, $p = 0.53$), total cardiac deaths (HR 0.97, 95% CI 0.71 to 1.33, $p = 0.84$), non-arrhythmic cardiac death (HR 1.24, 95% CI 0.84 to 1.84, $p = 0.28$), non-cardiac death (RR 1.50, 95% CI 0.82 to 2.73, $p = 0.19$) or actuarial mortality at 4 years' follow-up (HR 1.07, 95% CI 0.81 to 1.42, $p = 0.64$). The rate of SCD was lower in the ICD group but this did not reach statistical significance (HR 0.55, 95% CI 0.29 to 1.03, $p = 0.06$).
- HRQoL was higher among those receiving OPT than among those receiving an ICD + 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.
- HRs for the ICD group compared with the control group for all-cause mortality were found to be similar among 10 prespecified subgroups.

A broad population of people with mild to moderate heart failure

- One three-arm trial compared ICDs, 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 in the ICD + OPT group than in the placebo + OPT group (HR 0.77, 97.5% CI 0.62 to 0.96, $p = 0.007$). A significant reduction in total cardiac deaths (HR 0.76, 95% CI 0.60 to 0.95, $p = 0.018$) and SCD (compared with the 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 between the ICD group and the placebo and amiodarone groups combined in the number of non-arrhythmic cardiac deaths (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, $p = 0.60$).
- Little difference was found in QoL assessed using the DASI. Statistically significant differences in MHI scores 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 between ICD therapy ($p = 0.68$) and the cause of CHF (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 HF ($p = 0.29$) or non-cardiac ($p = 0.11$) deaths.

Adverse events

- Adverse events were reported by all four RCTs that included those with previous ventricular arrhythmias. Up to 30% of people in the ICD groups reported adverse events, with most related to the placement and operation of the device. Rates in the OPT group appeared lower.
- The nine RCTs that included people who had not suffered a life-threating arrhythmia reported adverse event rates in the ICD group of between 5% and 61%, depending on the definition of adverse event and length of follow-up. Adverse event rates for the comparator treatment group were between 11.9% and 55% in the three RCTs reporting this. Lead-, electrode- or defibrillator generator-related problems affected 1.8–14% of people in the five trials that reported this.

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony

Quantity and quality of research available

Four RCTs[109,116,121,125] comparing CRT-P and OPT in people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT met the inclusion criteria. In addition, one of these RCTs, the Comparison of Medical Therapy, Pacing, and Defibrillation in Patients with Left Ventricular Systolic Dysfunction (COMPANION) trial,[116] compared CRT-P and CRT-D with OPT.

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 TAR,[64] which also included the RCT of the CONTAK-CD device.[126] This trial is discussed later in *People with both conditions*.

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 8*.

TABLE 29 Included RCTs for people with HF

Study	Publication[a]
CARE-HF	**Cleland *et al.* 2005,[109]** 2001,[110] 2006,[111] 2008[112] and 2009,[113] Gras *et al.* 2007,[36] Gervais *et al.* 2009,[114] Ghio *et al.* 2009[115]
COMPANION	**Bristow *et al.* 2004[116]** and 2000,[117] US Food and Drug Administration 2004,[118] Carson *et al.* 2005,[119] Anand *et al.* 2009[120]
MIRACLE	**Abraham *et al.* 2002[121]** and 2000,[122] US Food and Drug Administration 2001,[123] St John Sutton *et al.* 2003[124]
MUSTIC	**Cazeau *et al.* 2001[125]**

CARE-HF, CArdiac REsynchronization in Heart Failure; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies.
a Bold text indicates primary or key publication.

TABLE 30 Study characteristics

Parameter	CARE-HF[109]	COMPANION[116]	MIRACLE[121]	MUSTIC[125]
Study design	RCT	RCT	RCT	Randomised crossover trial
Target population	NYHA class III or IV as a result of LVSD and cardiac dyssynchrony	Advanced chronic HF and intraventricular conduction delays	Moderate to severe HF	Severe HF and major intraventricular delay
Intervention	CRT-P + 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 the UK)	USA (128)	USA and Canada (45)	Europe (15) (France, Germany, Italy, Sweden, Switzerland and the 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 11.9–16.2 months	6 months	3 months
Key inclusion criteria	HF for ≥ 6 weeks; NYHA class III or IV despite standard pharmacological therapy; LVEF ≤ 35%; LVEDD ≥ 30 mm;[a] QRS interval ≥ 120 milliseconds;[b] aortic pre-ejection delay > 140 milliseconds, interventricular mechanical delay > 40 milliseconds, delayed activation of posterolateral left ventricular wall	Sinus rhythm; NYHA class III or IV; LVEF ≤ 35%; LVEDD ≥ 60 mm; QRS ≥ 120 milliseconds; PR interval > 150 milliseconds	HF due to ischaemic or non-ischaemic cardiomyopathy for > 1 month; NYHA class III or IV; LVEF ≤ 35%; LVEDD ≥ 55 mm; QRS interval ≥ 130 milliseconds; 6-minute walk distance ≤ 450 m	Severe HF due to idiopathic or ischaemic LVSD; sinus rhythm; NYHA class III for ≥ 1 month whilst on OPT; LVEF < 35%; LVEDD > 60 mm; QRS interval > 150 milliseconds; No standard indication for a pacemaker

CARE-HF, CArdiac REsynchronization in Heart Failure; LVEDD, left ventricular end-diastolic diameter; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies.
a Indexed to height.
b QRS interval of 120–149 milliseconds: patients need to meet two-thirds of additional criteria for dyssynchrony.

TABLE 31 Key participant characteristics

	CARE-HF[109]		COMPANION[116]			MIRACLE[121]		MUSTIC[125]	
Parameter	CRT-P	OPT	CRT-P	CRT-D	OPT	CRT-P on	CRT-P off	CRT-P on	CRT-P off
Sample size, *n*	409	404	617	595	308	228	225	29	29
Age (years), 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
Ischaemic heart disease, %	40	36	54	55	59	50	58		
Dilated cardiomyopathy, %	43	48							
NYHA class, %									
I	0	0	0	0	0	0	0	0	0
II	0	0	0	0	0	0	0	0	0
III	94	93	87	86	82	90	91	100	100
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 (milliseconds), mean (SD)	160[b] (152–180)[a]	160[b] (152–180)[a]	160[b]	160[b]	158[b]	167 (21)	165 (20)	172 (22)	175 (19)
LBBB/RBBB, %			69/12	73/10	70/9				
6-minute walk test (m), mean			274[b]	258[b]	244[b]	305	291	354 (110)	346 (111)
Peak VO_2 (ml/kg/minute), 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)

bpm, beats per minute; RBBB, right bundle branch block; VO_2, oxygen consumption.
a Range.
b Median.

Intervention and comparators

In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE)[121] and Multisite Stimulation in Cardiomyopathies (MUSTIC)[125] trials, all participants were implanted with a CRT-P device and pacing was inactivated in the control group. Participants in the CArdiac REsynchronization in Heart Failure (CARE-HF)[109] and COMPANION[116] trials received either a device + 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 HF, with the majority of participants in NYHA class III (ranging from 82% in CARE-HF[109] to 100% in MUSTIC[125]). All of the trials included participants with LVEF < 35%; average LVEF was about 22% in the MIRACLE[121] and COMPANION trials[116] and 25% in the CARE-HF trial.[109]

The trials differed in their eligibility criteria with regard to the QRS interval, with the CARE-HF[109] and COMPANION[116] trials requiring a QRS interval of ≥ 120 milliseconds, the MIRACLE trial[121] requiring a QRS

interval of ≥ 130 milliseconds and the MUSTIC trial[125] requiring a QR interval of > 150 milliseconds. This is reflected in the average QRS interval at baseline in these studies, with the longest average QRS interval seen in the MUSTIC trial[125] (see *Table 31*). When reported, the proportion of participants with ischaemic heart disease ranged from 36% (CARE-HF[109]) to 59% (COMPANION[116]).

The mean age of the participants in the studies was similar, ranging from around 64 years in the MIRACLE[121] and MUSTIC[125] trials to 68 years in the COMPANION trial[116] (see *Table 31*). The majority of participants were men (73% and 74% in the CARE-HF trial arms,[109] 67%, 67% and 69% in the three COMPANION trial arms,[116] 68% in both of the MIRACLE trial arms[121] and 66% and 83% in the MUSTIC trial arms[125]).

Pharmacological therapy

Optimal pharmacological therapy was used in all of the trials (*Table 32*). At least 90% of all participants received ACE inhibitors or ARBs. Less than one-third (28%) of participants used beta-blockers in the MUSTIC study,[125] between 55% and 62% used beta-blockers in the MIRACLE trial,[121] between 66% and 68% used beta-blockers in the COMPANION trial[116] and between 70% and 74% used beta-blockers in the CARE-HF trial.[109] Spironolactone use was not reported by the MIRACLE study[121] but was 22% in the MUSTIC trial,[125] and between 53% and 55% in the COMPANION trial[109] and between 54% and 59% in the CARE-HF trial.[109] Less than half of the participants in the CARE-HF trial[109] used diuretics, with around 94% of participants in the other studies using them. Both the CARE-HF trial[109] and the MUSTIC trial[125] reported that less than half of the participants used digoxin, and around one-third of participants in the MUSTIC trial[125] used amiodarone. In the MIRACLE trial[121] around three-quarters of participants used digitalis medication.

Outcomes

Although all four trials reported all-cause mortality, it was not a primary outcome. The primary outcome of two trials was a composite end point: all-cause mortality and all-cause hospitalisation in the COMPANION trial[116] and all-cause mortality and unplanned hospitalisation for a major cardiovascular event in the CARE-HF trial.[109] Composite outcomes can be seen in the data extraction forms (see *Appendix 8*) but have not been discussed in this report. The primary outcome of the MIRACLE[121] and MUSTIC[125] trials was distance walked in 6 minutes; changes in NYHA class and QoL were also primary outcomes in the MIRACLE trial.[125]

TABLE 32 Medication at baseline

	CARE-HF[109]		COMPANION[116]			MIRACLE[121]		MUSTIC[125]	
Medication	CRT-P	OPT	CRT-P	CRT-D	OPT	CRT-P on	CRT-P off	CRT-P on	CRT-P off
Sample size, *n*	409	404	617	595	308	228	225	67[a]	
Aldosterone antagonist (spironolactone), %	54	59	53	55	55			22	
Amiodarone, %								31	
ACE inhibitor, %			70	69	69				
ACE inhibitor or ARB, %	95	95	89	90	89	93	90	96	
Beta-blockers, %	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.

All four trials reported mortality from SCD. In addition, the COMPANION[116] and MUSTIC[125] trials reported total cardiac deaths and the CARE-HF[109] and COMPANION[116] trials reported death from HF. HF hospitalisation was reported by all four trials. The CARE-HF,[109] MIRACLE[121] and MUSTIC[125] trials reported details on worsening HF whereas arrhythmias were reported by the CARE-HF[109] and MUSTIC[125] trials. All trials except for the MUSTIC trial[125] reported change in NYHA class, but only the CARE-HF[109] and MIRACLE[121] trials reported changes in LVEF. HRQoL and adverse events were reported by all trials.

Setting

All four studies were multicentre trials, with the number of centres ranging from 15 (MUSTIC[125]) to 128 (COMPANION[116]). The CARE-HF[109] and MUSTIC[125] trials were undertaken in Europe, with both including centres in the UK. The COMPANION study[116] was undertaken in the USA whereas the MIRACLE[121] trial included centres in the USA and Canada.

The MUSTIC study[125] used a randomised crossover design, with 3 months' follow-up for each of the two crossover periods. The length of follow-up for the MIRACLE study[121] was 6 months. The mean length of follow-up in the CARE-HF study[109] was 29.4 months, plus an 8-month extension (total mean follow-up 37.4 months). The COMPANION trial[116] reported a median follow-up for the composite end point 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 months for CRT-D and 16.5 months for CRT-P.

Risk of bias

Details of the risk of bias for each study can be found in the data extraction tables in *Appendix 8*, with a summary in *Table 33*.

TABLE 33 Risk of bias

	Judgement			
Domain	**CARE-HF[109]**	**COMPANION[116]**	**MIRACLE[121]**	**MUSTIC[125]**
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[a] – low; secondary[b] – high or unclear	Low	Low	High
Attrition bias				
Incomplete outcome data addressed	Composite[a] and echocardiographic outcomes – low; left ventricular 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 Morality and hospitalisation.
b Echocardiographic outcomes – high risk; adverse events – unclear risk.

Because of a lack of reported details on randomisation methods and allocation concealment methods, the risk of selection bias for the COMPANION,[116] MIRACLE[121] and MUSTIC[125] trials was unclear. The risk of selection bias was low in the CARE-HF trial.[109]

The MIRACLE trial[121] 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). The MUSTIC trial[125] was at high risk of performance and detection bias, with only participants blinded to the treatment order (CRT-P on or off). Both the CARE-HF trial[109] and the COMPANION trial[116] were unblinded trials, placing them at high risk of performance bias. For detection bias, the CARE-HF trial[109] was judged to be at low risk of bias for the composite end point 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 end-points committee but others by an unblinded independent expert. The risk of detection bias in the COMPANION trial[116] was low, with a steering committee and end-points committee unaware of treatment assignment.

Both the COMPANION trial[116] and the MUSTIC trial[125] were at low risk of attrition bias. The MUSTIC trial[125] reported both numbers and reasons for withdrawals, whereas the COMPANION trial[116] censored data in the ITT analysis for participants who withdrew and for whom data could not be obtained. The CARE-HF trial[109] 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 left ventricular reverse remodelling was unclear because of unexplained differences in numbers. The risk of attrition bias in the MIRACLE study[121] was unclear for both primary and secondary outcomes. Although ITT analysis was used and attrition reported, the low numbers reported for the primary outcome of NYHA class and differences in sample size between the primary outcome and the secondary outcome were unexplained. Both the CARE-HF trial[109] and the COMPANION study[116] were at low risk of selective reporting bias. For both studies the protocol or rationale/design papers have been published and there was no evidence of missing outcomes. However, the MIRACLE[121] and MUSTIC[125] trials were at high risk of selective reporting bias. The MIRACLE trial[121] assessed change in NYHA class but failed to report the data, and the MUSTIC trial[125] included the SF-36 in the study protocol[122] but did not report any data.

There was an additional risk of bias in the MUSTIC trial[125] because of the use of block randomisation without blinding. However, the use of the crossover design appears appropriate.

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 trials included a statistical power calculation. The CARE-HF,[109] MIRACLE[121] and MUSTIC[125] trials appeared to be adequately powered to detect a difference in the relevant primary outcome measure. The MUSTIC trial[125] randomised 58 participants, the MIRACLE trial[121] randomised 453 participants and the CARE-HF trial[109] randomised 813 participants. The COMPANION trial[116] 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 end point.

Crossovers

By the end of the extension period in the CARE-HF trial,[109] 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. The MIRACLE trial[121] reported that 4% of participants crossed over from OPT to the CRT-P treatment group, but reported no details for the CRT-P treatment group. The COMPANION trial[120] reported

that, out of 78 cardiac procedures in the OPT group, 33 (42%) were for CRT implants. In addition, this trial reported that there were substantial withdrawals in the OPT group (26%) to receive commercially available implants, whereas the withdrawal rates in the CRT-P and CRT-D groups were 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 before implantation. In the CARE-HF study[109] baseline measures were taken before randomisation and implantation, whereas in the COMPANION study[116] randomisation occurred before implantation but baseline measures were taken 1 week after successful implantation. The remaining two studies (MIRACLE[121] and MUSTIC[125]) randomised participants after implantation. In the MIRACLE study[121] baseline measures were taken before implantation and randomisation whereas in the MUSTIC study[125] baseline measures were taken after randomisation, which occurred 2 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 the studies.

The MUSTIC trial[125] does not report all outcomes for both crossover periods. In addition, 10 participants did not complete both crossover periods (including five who did not complete the first period). The COMPANION trial[116] had substantial withdrawals from the OPT group (see *Crossovers*).

Funding

All four trials received funding grants from the device manufacturers, with three trials funded by Medtronic[109,121,125] and one by the Guidant Corporation.[116] In addition, three of the trials, the MIRACLE,[121] MUSTIC[125] and CARE-HF[109] trials, reported conflicts of interests, as some/all authors were consultants or investigators for, or employees of, the company providing the funding. Both the CARE-HF trial[109] and the COMPANION trial[116] stated that sponsors had no role in data analysis, whereas the MIRACLE trial[121] stated that sponsors placed no restrictions or limitation on the investigators performing the data analyses.

Assessment of effectiveness

All-cause mortality

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

CRT-P compared with optimal pharmacological therapy

The CARE-HF trial[109] reported a statistically significant difference in all-cause mortality between the groups after a mean follow-up of 37.4 months, which included an 8-month 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 11.5 percentage points lower for the CRT-P group (CRT-P 23.6% vs. OPT 35.1%), although no statistical comparison was reported. After completion of the CARE-HF trial, long-term follow-up of people who survived and reconsented (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 > 95% of those originally assigned to the control group (ITT analysis undertaken, with participants remaining in their assigned group regardless of subsequent treatment).[150] In contrast, the MIRACLE trial[121] found no statistically significant difference in all-cause mortality between the groups after 6 months' follow-up (CRT-P 5.3% vs. OPT 7.1%, HR 0.73, 95% CI 0.34 to 1.54, $p = 0.40$), and the difference in the 12-month all-cause mortality rate between the CRT-P and OPT groups in the COMPANION trial[116] did not reach statistical significance (CRT-P 15% vs. OPT 19%, HR 0.76, 95% CI 0.58 to 1.01, $p = 0.059$). The MUSTIC trial[125] reported one death in the first crossover period (1/29, 3.4%) and two in the second crossover period (2/29, 6.9%) among those receiving CRT-P and none during the OPT period. No statistical comparison was reported.

TABLE 34 All-cause mortality

Study	Follow-up	CRT-P, *n/N* (%)	OPT, *n/N* (%)	Effect	95% CI, *p*-value
CARE-HF[109]	First 90 days of trial	12/409 (2.9)	15/404 (3.7)		
	29.4 months[a]	82/409 (20.0)	120/404 (29.7)	HR 0.64	0.48 to 0.85, < 0.002
	[a]37.4 months[111]	101/409 (24.7)	154/404 (38.1)	HR 0.60	0.47 to 0.77, < 0.0001
	Mortality rate 1 year,[111] %	9.7	12.6		
	Mortality rate 2 year, %	18	25.1		
	Mortality rate 3 year, %	23.6	35.1		
MIRACLE[121]	6 months	12/228 (5.3)	16/225 (7.1)	HR 0.73	0.34 to 1.54, 0.40
MUSTIC[125]	6 months	First period: 1/29 (3.4[b]), second period: 2/29 (6.9[b])	First period: 0/29 (0), second period: 0/29 (0)	RR 7.00[b]	0.37 to 132.56, 0.19[b]
		CRT-P, *n/N* (%)	**OPT, *n/N* (%)**		
COMPANION[116]	CRT-P 16.5 months, OPT 14.8 months[c]	131/617 (21.2)	77/308 (25.0)		
	12-month 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 months, OPT 14.8 months[c]	105/595 (17.6)	77/308 (25.0)	RR 0.71[b]	0.54 to 0.92, 0.009[b]
	12-month rate	71[b]/595 (12)	59[b]/308 (19)	HR 0.64	0.48 to 0.86, 0.003
		CRT-P, *n/N* (%)	**CRT-D, *n/N* (%)**		
	CRT-P 16.5 months, CRT-D 16.0 months[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.

The studies were considered sufficiently similar to combine in a meta-analysis (*Figure 10*). For meta-analysis of the MUSTIC crossover trial,[125] all deaths in those receiving CRT-P or OPT from both crossover periods were included. This method provides a conservative analysis, with the study being underweighted rather than overweighted.[65] There was evidence of moderate statistical heterogeneity between the studies ($\chi^2 = 4.99$, df = 3, $I^2 = 40\%$). The RR for CRT-P compared with OPT for all-cause mortality using the random-effects method was 0.75 (95% CI 0.58 to 0.96, $p = 0.02$) (see *Figure 10*). Excluding the MUSTIC trial[125] from the meta-analysis had little effect (RR 0.73, 95% CI 0.60 to 0.89, $p = 0.002$).

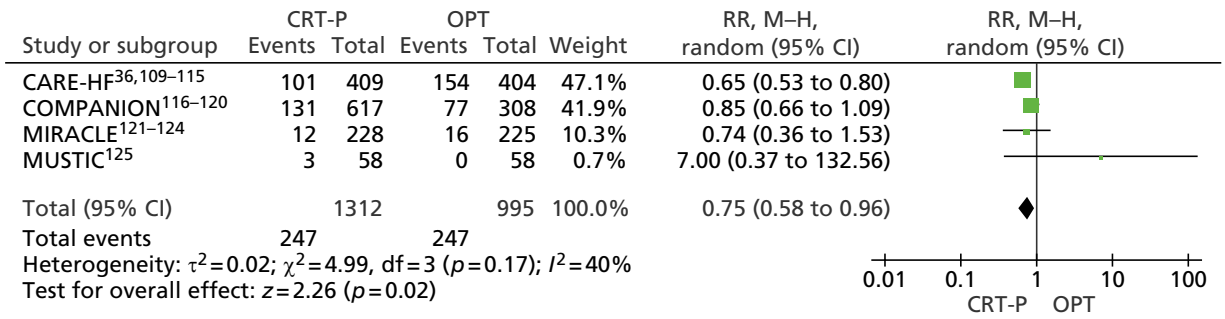

FIGURE 10 All-cause mortality: CRT-P vs. OPT.

CRT-D compared with optimal pharmacological therapy

The COMPANION trial[116] 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 pacer compared with CRT-D

The COMPANION trial[116] included three treatment arms (CRT-P, CRT-D and OPT). The difference in all-cause mortality between the CRT-P group (21%) and the CRT-D group (18%) was not statistically significant (RR 1.20, 95% CI 0.96 to 1.52, $p = 0.12$). However, all comparisons between CRT-P and CRT-D should be treated with caution as the trial was not powered for this comparison.

Total cardiac deaths

Both the COMPANION trial[119] and the MUSTIC trial[125] reported total cardiac deaths.

CRT-P compared with optimal pharmacological therapy

The COMPANION trial[119] found no statistically significant difference in total cardiac deaths between CRT-P and OPT (CRT-P 17.7% vs. OPT 18.8%, $p = 0.334$), 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 the MUSTIC trial[125] were from 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 compared with optimal pharmacological therapy

The COMPANION trial[119] found that the number of cardiac deaths was statistically significantly lower in the CRT-D group than in the OPT group (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, $p = 0.02$) (see *Table 35*).

CRT-P compared with CRT-D

The number of cardiac deaths in the COMPANION trial[119] was statistically significantly higher in the CRT-P group than in the CRT-D (RR 1.38, 95% CI 1.06 to 1.81, $p = 0.02$). However, all comparisons between CRT-P and CRT-D should be treated with caution as the trial was not powered for this comparison.

TABLE 35 Total cardiac deaths

Study	Follow-up	CRT-P, *n*/*N* (%)	OPT, *n*/*N* (%)	Effect	95% CI, *p*-value
MUSTIC[125]	6 months	First period: 1/29 (3.4[a]), second period: 2/29 (6.9[a])	First period 0/29 (0), second period 0/29 (0)	RR 7.00[a]	0.37 to 132.56, 0.19[a]
COMPANION[119]	CRT-P 16.5 months, OPT 14.8 months[b]	109/617 (17.7[c])	58[d]/308 (18.8)	RR 0.94[a]	0.70 to 1.25, 0.66[a] (0.334[e])
	% of deaths	83.2	75.3		
		CRT-D, *n*/*N* (%)	**OPT, *n*/*N* (%)**		
	CRT-D 16.0 months, OPT 14.8 months[b]	76/595 (12.8)	58[d]/308 (18.8)	RR 0.68[a]	0.50 to 0.93, 0.02[a] (0.006[e])
	% of deaths	72.4	75.3		
		CRT-P, *n*/*N* (%)	**CRT-D, *n*/*N* (%)**		
	CRT-P 16.5 months, CRT-D 16.0 months[b]	109/617 (17.7[c])	76/595 (12.8)	RR 1.38[a]	1.06 to 1.81, 0.02[a]
	% of deaths	83.2	72.4		

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.

Heart failure deaths

Both the CARE-HF trial[109] and the COMPANION trial[119] reported mortality from HF.

CRT-P compared with optimal pharmacological therapy

The CARE-HF trial[109] found that mortality attributed to worsening HF was statistically significantly lower in the CRT-P group than in the OPT group (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' follow-up. The risk of HF was reported to be 3.0% per annum for those receiving CRT-P compared with 5.1% per annum for those receiving OPT. The COMPANION trial[119] found no statistically significant differences between those receiving CRT-P and those receiving OPT (8.6% vs. 11.0% respectively, HR 0.71, 95% CI 0.46 to 1.09, $p = 0.112$), with follow-up of 16.5 months for those receiving CRT-P and 14.8 months for those receiving OPT (*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 RR for HF deaths for the comparison between CRT-P and OPT was 0.67 (95% CI 0.51 to 0.88, $p = 0.004$) (*Figure 11*).

CRT-D compared with optimal pharmacological therapy

The COMPANION trial[119] found no statistically significant difference in HF 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 receiving CRT-D and 14.8 months' follow-up for those receiving OPT (see *Table 36*).

CRT-P compared with CRT-D

The HF death rates in the CRT-P and CRT-D groups in the COMPANION trial[119] were similar (8.6% vs. 8.7% respectively), with a RR of 0.98 (95% CI 0.68 to 1.42, $p = 0.93$).

TABLE 36 Heart failure deaths

Study	Follow-up	CRT-P, *n/N* (%)	OPT, *n/N* (%)	Effect	95% CI, *p*-value
CARE-HF[109]	29.4 months[a]	33/409 (8.1)	56/404 (13.9)	RR 0.58	0.39 to 0.87, 0.009
	[a]37.4 months (with extension)[111]	38/409 (9.3)	64/404 (15.8)	HR 0.55	0.37 to 0.82, 0.003
	Per annum (%)	3.0	5.1		
COMPANION[119]	CRT-P 16.5 months, OPT 14.8 months[b]	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 months, OPT 14.8 months[b]	52/595 (8.7)	34/308 (11.0)	HR 0.73	0.47 to 1.11, 0.143
	% of deaths	49.5	44.2		
		CRT-P, *n/N* (%)	CRT-D, *n/N* (%)		
	CRT-P 16.5 months, CRT-D 16.0 months[b]	53/617 (8.6)	52/595 (8.7)	RR 0.98[c]	0.68 to 1.42, 0.93[c]
	% of deaths	40.5	49.5		

a Mean.
b Median.
c Calculated by reviewer.

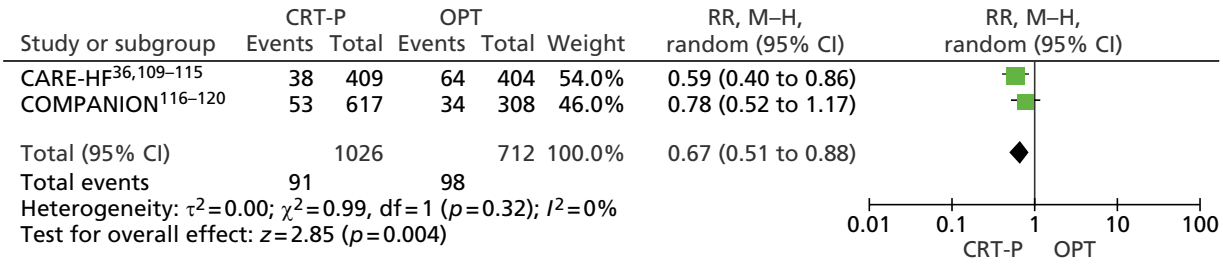

FIGURE 11 Heart failure deaths: CRT-P vs. OPT.

Sudden cardiac death

All trials reported SCDs, although there were uncertainties within the MIRACLE trial data.[121]

CRT-P compared with optimal pharmacological therapy

The CARE-HF trial[109] found the rate of SCDs to be statistically significantly lower in the CRT-P group than in the OPT group (7.8% vs. 13.4% respectively, HR 0.54, 95% CI 0.35 to 0.84, $p = 0.005$) at a mean follow-up of 37.4 months. The proportion of SCDs per year was reported to be 2.5% for those receiving CRT-P and 4.3% for those receiving OPT. There were two reported SCDs in the MUSTIC trial,[125] 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 (2 hours after switching from inactive to active pacing). No statistical comparison was reported. CRT-P failed to reduce the risk of SCD in the COMPANION trial,[119] with more sudden deaths in the group receiving CRT-P than in the group receiving 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 receiving CRT-P and 14.8 months' follow-up

for those receiving OPT. The study also reported the proportion of deaths classified as SCD as 36.6% for those receiving CRT-P and 23.4% for those receiving OPT (*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 the rates of SCD between CRT-P and OPT were not statistically significant, with a random-effects RR of 0.97 (95% CI 0.44 to 2.14, $p = 0.94$) (*Figure 12*).

TABLE 37 Sudden cardiac death

Study	Follow-up	CRT-P, *n*/*N* (%)	OPT, *n*/*N* (%)	Effect	95% CI, *p*-value
CARE-HF[109]	29.4 months[a]	29/409 (7.1)	38/404 (9.4)	RR 0.75[b]	0.47 to 1.20, 0.23[b]
	[a]37.4 months[111]	32/409 (7.8)	54/404 (13.4)	HR 0.54	0.35 to 0.84, 0.005
	Per annum (%)	2.5	4.3		
MUSTIC[125]	6 months	First crossover: 1/29 (3.4[b]), second crossover: 1/29 (3.4[b])	First crossover: 0/29 (0), second crossover: 0/29 (0)	RR 5.00[b]	0.25 to 99.82, 0.29[b]
COMPANION[119]	CRT-P 16.5 months, OPT 14.8 months[c]	48/617 (7.8)	18/308 (5.8)	HR 1.21	0.70 to 2.07, 0.485
	% of deaths	36.6	23.4		
		CRT-D, *n*/*N* (%)	**OPT, *n*/*N* (%)**		
	CRT-D 16.0 months, OPT 14.8 months[c]	17/595 (2.9)	18/308 (5.8)	HR 0.44	0.23 to 0.86, 0.020
	% of deaths	16.2	23.4		
		CRT-P, *n*/*N* (%)	**CRT-D, *n*/*N* (%)**		
	CRT-P 16.5 months, CTR-D 16.0 months[c]	48/617 (7.8)	17/595 (2.9)	RR 2.72[b]	1.58 to 4.68, 0.0003[b]
	% of deaths	36.6	16.2		

a Mean.
b Calculated by reviewer.
c Median.

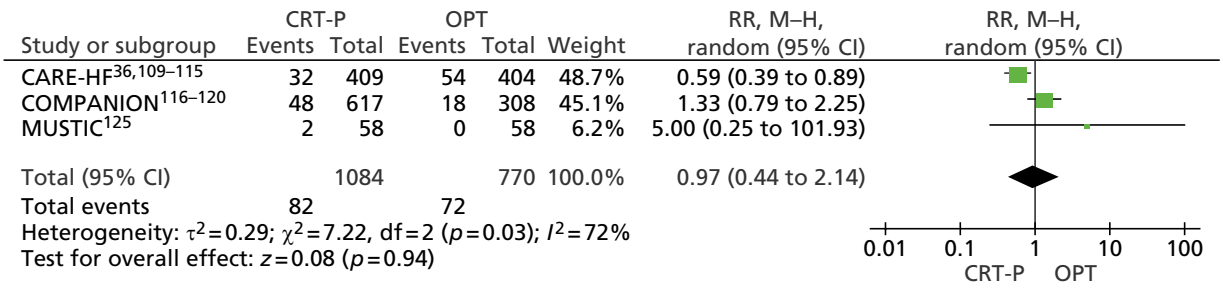

FIGURE 12 Sudden cardiac death: CRT-P vs. OPT.

The FDA report[123] associated with the MIRACLE trial reported the numbers of SCDs in each arm at 9 months' follow-up (CRT-P $n = 7$, OPT $n = 5$) (the main publication[121] reported outcomes at 6 months); 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 ($n = 453$).[121] 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 these data with the CARE-HF, COMPANION and MUSTIC data in a meta-analysis gives an overall RR of 1.02 (95% CI 0.54 to 1.94).

CRT-D compared with optimal pharmacological therapy

The COMPANION trial[119] found the rate of SCD to be statistically significantly lower in the group receiving CRT-D than in the group receiving 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 receiving CRT-D and 14.8 months' follow-up for those receiving OPT.

CRT-P compared with CRT-D

In the COMPANION trial[119] the rate of SCD was statistically significantly higher in the group receiving CRT-P than in the group receiving CRT-D (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 and CRT-D should be treated with caution as the trial was not powered for this comparison.

Other causes of death

The COMPANION trial[119] found no statistically significant difference in the number of non-cardiac deaths between those receiving CRT-P and those receiving OPT ($p = 0.122$) or between those receiving CRT-D and those receiving OPT ($p = 0.717$). The numbers of vascular, non-cardiac and unknown deaths appear to be similar between those receiving CRT-P and those receiving CRT-D (*Table 38*).

Hospitalisations because of heart failure

All four trials reported hospitalisations because of HF. Additional hospitalisation outcomes reported by the trials, including cardiac and non-cardiac hospitalisations, are summarised in *Appendix 6*.

Number of people hospitalised because of heart failure

CRT-P compared with optimal pharmacological therapy The CARE-HF trial[109] found that fewer people were hospitalised because of HF in the CRT-P group (CRT-P 17.9% vs. OPT 32.9%; HR 0.48, 95% CI 0.36 to 0.64, $p < 0.001$) at 29.4 months' mean follow-up. Similar results were found in the MIRACLE trial[121] at 6 months' follow-up (CRT-P 7.9% vs. OPT 15.1%, HR 0.50, 95% CI 0.28 to 0.88, $p = 0.02$) and in the COMPANION trial[116] at 16.2 months' follow-up for CRT-P and 11.9 months' follow-up for OPT (CRT-P 29% vs. OPT 36%, RR 0.80, 95% CI 0.66 to 0.97, $p = 0.02$) (*Table 39*). In the MUSTIC trial,[125] hospitalisations related to decompensated HF were lower in the group receiving CRT-P (CRT-P 10.3% vs. OPT 31.0%), but this 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, the MUSTIC trial[125] 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 RR of hospitalisation because of HF for CRT-P compared with OPT was 0.61 (95% CI 0.44 to 0.83, $p = 0.002$), giving a RRR for hospitalisation related to HF with CRT-P of 39% (*Figure 13*).

CRT-D compared with optimal pharmacological therapy In the COMPANION trial[119] there were significantly fewer people admitted to hospital with HF in the CRT-D group than in the OPT group (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 receiving CTR-D and 11.9 months for those receiving OPT.

TABLE 38 Other causes of death

Study	Outcome and follow-up	CRT-P, *n/N* (%)	OPT, *n/N* (%)	Effect	95% CI, *p*-value
COMPANION[119]	Vascular deaths, CRT-P 16.5 months, OPT 14.8 months[a]	5/617 (0.8)	0		
	% of deaths	3.8			
	Non-cardiac deaths	14/617 (2.3)	11/308 (3.6)		0.122
	% of deaths	10.7	14.3		
	Unknown deaths	3/617 (0.5)	8/308 (2.6)		
	% of deaths	2.3	10.4		
		CRT-D, *n/N* (%)	OPT, *n/N* (%)		
	Vascular deaths, CRT-D 16.0, OPT 14.8 months[a]	3/595 (0.5)	0		
	% of deaths	2.8			
	Non-cardiac deaths	21/595 (3.5)	11/308 (3.6)		0.717
	% of deaths	10.7	14.3		
	Unknown deaths	5/595 (0.8)	8/308 (2.6)		
	% of deaths	4.8	10.4		

a Median.

TABLE 39 Hospitalisations related to HF

Study	Outcome and follow-up	CRT-P, *n/N* (%)	OPT, *n/N* (%)	Effect	95% CI, *p*-value
CARE-HF[109]	Unplanned hospitalisation with worsening HF, 29.4 months[a]	72/409 (17.6)	133/404 (32.9)	HR 0.48	0.36 to 0.64, < 0.001
MIRACLE[121]	Hospitalisation for worsening HF, 6 months	18/228 (7.9)	34/225 (15.1)	HR 0.50	0.28 to 0.88, 0.02
MUSTIC[125]	Hospital admission because of decompensated HF, 3 months[b]	3/29 (10.3)	9/29 (31.0)	RR 0.33[c]	0.10 to 1.11, 0.07[c,d]
COMPANION[116]	Hospitalised one or more times with HF, CRT-P 16.2 months, OPT 11.9 months[e]	179/617 (29)	112/308 (36)	RR 0.80[c]	0.66 to 0.97, 0.02[c]
		CRT-D, *n/N* (%)	OPT, *n/N* (%)		
	Hospitalised one or more times with HF, CRT-D 15.7 months, OPT 11.9 months[e]	166/595 (28)	112/308 (36)	RR 0.77[c]	0.63 to 0.93, 0.008[c]

a Mean.
b Data reported for first crossover period only.
c Calculated by the reviewer.
d Analyses reported by paper, $p < 0.05$.[125]
e Median.
Note: The COMPANION trial[116] states that no significant differences were found for any of the end points between CRT-P and CRT-D (no *p*-values reported).

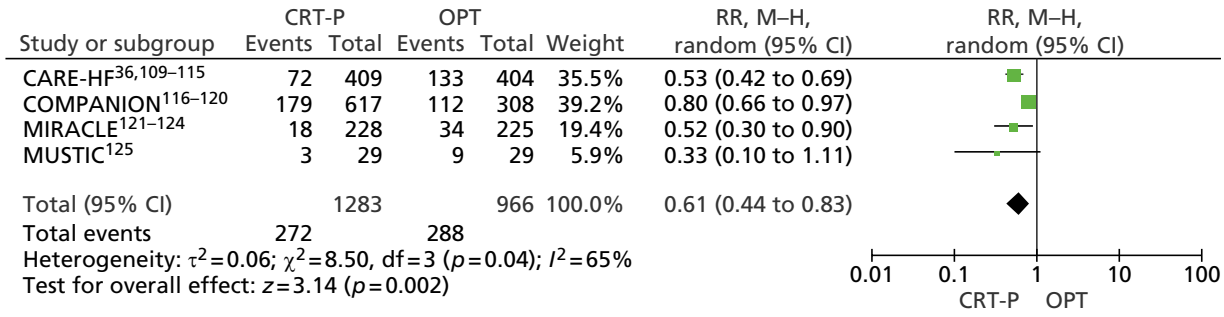

FIGURE 13 Hospitalisations related to HF: CRT-P vs. OPT.

CRT-P compared with CRT-D The COMPANION trial report[116] states that no significant differences were found in any of the end points between those receiving CRT-P and those receiving CRT-D. In addition, the proportions of people hospitalised at least once with HF were similar in the two groups (28% vs. 29% respectively).

Number of hospitalisation events for heart failure

The CARE-HF,[109] COMPANION[120] and MIRACLE[121] trials reported the number of hospitalisation events and/or number of days hospitalised because of HF. The CARE-HF trial[109] reported the number of unplanned hospitalisations of patients because of worsening HF. The COMPANION trial[120] reported the number of admissions, the percentage of total admissions and the average number of days hospitalised per patient year of follow-up, whereas the MIRACLE trial[121] reported the total number of days hospitalised because of HF (*Table 40*).

TABLE 40 Hospitalisations related to HF: number of events and/or days of admission

Study	Outcome and follow-up	CRT-P	OPT	Effect	95% CI, *p*-value
CARE-HF[109]	Hospitalisation events, 29.4 months[a]	122	252		
MIRACLE[121]	Total no. of days hospitalised, 6 months	83	363		
	No. of hospitalisations	25	50		
COMPANION[120]	CRT-P 16.2 months, OPT 11.9 months[b]				
	No. of admissions (% of total admissions)	329 (33)	235 (46)		
	Average no. of 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		
	CRT-D 15.7 months, OPT 11.9 months[b]				
	No. of admissions (% of total admissions)	333 (36)	235 (46)		
	Average no. of 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.
Note: The COMPANION trial[116] reports that no significant differences were found in any of the hospitalisation end points between the CRT-P group and the CRT-D group (no *p*-values reported).

CRT-P compared with optimal pharmacological therapy In the CARE-HF trial,[109] the 72 participants in the CRT-P group ($n = 409$) who were hospitalised with worsening HF had a total of 122 hospitalisations, compared with a total of 252 hospitalisations for 133 patients in the OPT group ($n = 404$). In the COMPANION trial,[120] 33% of the total admissions were due to HF among patients receiving CRT-P compared with 46% of the total admissions among patients receiving OPT, at a median 16.2 months' follow-up for those with CRT-P and median 11.9 months' follow-up for those with OPT. The average number of admissions per patient year of follow-up was also lower in the group receiving CRT-P (CRT-P 0.41 vs. OPT 0.73). The average length of stay per admission was similar between the treatment groups (CRT-P 8.6 days vs. OPT 8.2 days). Similarly, the MIRACLE trial[121] found that the total number of days hospitalised because of HF was lower in the CRT-P group than in the OPT group at 6 months' follow-up (83 days vs. 363 days respectively), but no statistical comparison was reported. However, hospitalisation occurred twice as often in those receiving OPT (OPT 50 events vs. CRT-P 25 events) (see *Table 40*).

The rate of events was calculated for each trial (no. of events/N × follow-up) and combined in a meta-analysis using the inverse variance method. Although statistical heterogeneity was present ($\chi^2 = 28.27$, df = 3, $I^2 = 89\%$), the direction of the effect was fairly consistent (*Figure 14*). A significant reduction in the rate of HF hospitalisations was found in the CRT-P group (RR 0.58, 95% CI 0.35 to 0.96, $p = 0.03$).

CRT-D compared with optimal pharmacological therapy In the COMPANION trial[120] the proportion of admissions that were related to HF was lower in the CRT-D group (CRT-P 36% vs. OPT 46%), at a median of 15.7 months' follow-up for those receiving CRT-P and 11.9 months' follow-up for those receiving OPT. The average number of admissions per patient year of follow-up was lower in those receiving CRT-D (CRT-D 0.43 vs. OPT 0.73). The average length of stay per admission was similar in both treatment groups (CRT-D 8.8 days vs. OPT 8.2 days) (see *Table 40*).

CRT-P compared with CRT-D The COMPANION trial[120] found that there were no significant differences between those receiving CRT-P and those receiving CRT-D for any of the hospitalisation end points; in addition, the proportion of admissions that were related to HF was similar between the groups (33% vs. 36% respectively). This was reflected in both the average number of admissions per patient year of follow-up (CRT-P 0.41 vs. CRT-D 0.43) and the average length of stay per admission (CRT-P 8.6 days vs. 8.8 CRT-D days) (see *Table 40*).

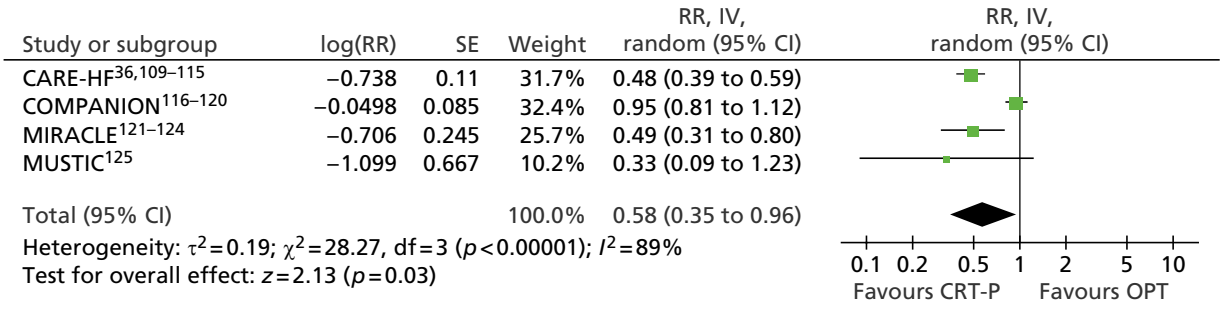

FIGURE 14 Number of hospitalisations because of HF: CRT-P vs. OPT.

Arrhythmias

The CARE-HF trial[109] reported atrial arrhythmias or ectopy whereas the MUSTIC trial[125] reported decompensation due to persistent atrial fibrillation. Because of the different outcome measures used in the two trials, data were not pooled. No comparisons between CRT-D and OPT or between CRT-P and CRT-D were reported.

CRT-P compared with optimal pharmacological therapy

In the CARE-HF trial,[109] the risk of arrhythmias or ectopy was significantly higher in the CRT-P group than in the OPT group (15.6% vs. 10.1% respectively; RR 1.54, 95% CI 1.07 to 2.23, $p = 0.02$). One case of decompensation due to persistent atrial fibrillation occurred in the OPT treatment group during the first crossover period of the MUSTIC trial[125] (RR 0.33, 95% CI 0.01 to 8.02, $p = 0.50$) (*Table 41*).

Worsening heart failure

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

CRT-P compared with optimal pharmacological therapy

In the CARE-HF trial,[109] fewer people receiving CRT-P experienced worsening HF than those receiving OPT (CRT-P 46.7% vs. OPT 64.9%; RR 0.72, 95% CI 0.63 to 0.82, $p < 0.001$) (*Table 42*). In the MIRACLE trial,[121] there were fewer people with HF requiring intravenous diuretics (CRT-P 5.7% vs. OPT 10.7%; HR 0.51, 95% CI 0.26 to 1.00, $p = 0.05$), vasodilators or positive inotropic agents (CRT-P 2.6% vs. OPT 6.2%; HR 0.41, 95% CI 0.16 to 1.08, $p = 0.06$) or medication for HF (CRT-P 7.0% vs. OPT 15.6%; HR 0.43, 95% CI 0.24 to 0.77, $p = 0.004$) in the CRT-P group than in the OPT group (see *Table 42*). The MUSTIC trial[125] 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, $p = 0.50$). Despite the different definitions used by the trials, the risk of worsening HF 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.

Change in New York Heart Association class

The CARE-HF,[109] COMPANION[116] and MIRACLE[121] trials reported improvement in NYHA class. The three trials included people in NYHA classes III and IV at baseline. The CARE-HF trial[109] reported NYHA class at 18 months and mean NYHA class at 90 days; the MIRACLE trial[121] reported improvements in NYHA class at 6 months; and the COMPANION trial[116] reported NYHA class at 3 and 6 months. NYHA class was one of three reported primary end points in the MIRACLE trial.[121]

TABLE 41 Arrhythmias

Study	Outcome and follow-up	CRT-P, *n*/*N* (%)	OPT, *n*/*N* (%)	Effect	95% CI, *p*-value
CARE-HF[109]	Atrial arrhythmias or ectopy, 29.4 months[a]	64/409 (15.6)	41/404 (10.1)	RR 1.54[b]	1.07 to 2.23, 0.02[b]
MUSTIC[125]	Decompensation due to persistent atrial fibrillation, 6 months	First period: 0/29, second period: 0/29	First period: 1/29 (3.4), second period: 0/29	RR 0.33[b]	0.01 to 8.02, 0.50[b]

a Mean.
b Calculated by reviewer.

TABLE 42 Worsening HF

Study	Outcome and follow-up	CRT-P, *n/N* (%)	OPT, *n/N* (%)	Effect	95% CI, *p*-value
CARE-HF[109]	Worsening HF, 29.4 months[a]	191/409 (46.7)	263/405 (64.9)	RR 0.72[b]	0.63 to 0.82,[b] < 0.001
MIRACLE[121]	HF requiring intravenous medication, 6 months				
	Diuretic agents	13/228 (5.7)	24/225 (10.7)	HR 0.51	0.26 to 1.00, 0.05
	Vasodilators or positive inotropic agents	6/228 (2.6)	14/225 (6.2)	HR 0.41	0.16 to 1.08, 0.06
	Medication for HF	16/228 (7.0)	35/225 (15.6)	HR 0.43	0.24 to 0.77, 0.004
MUSTIC[125]	Severe decompensation, 6 months	First period: 0/29 (0), second period: 0/29 (0)	First period: 1/29 (3.4), second period: 0/29 (0)	RR 0.33[b]	0.01 to 8.02, 0.50[b]

a Mean.
b Calculated by reviewer.

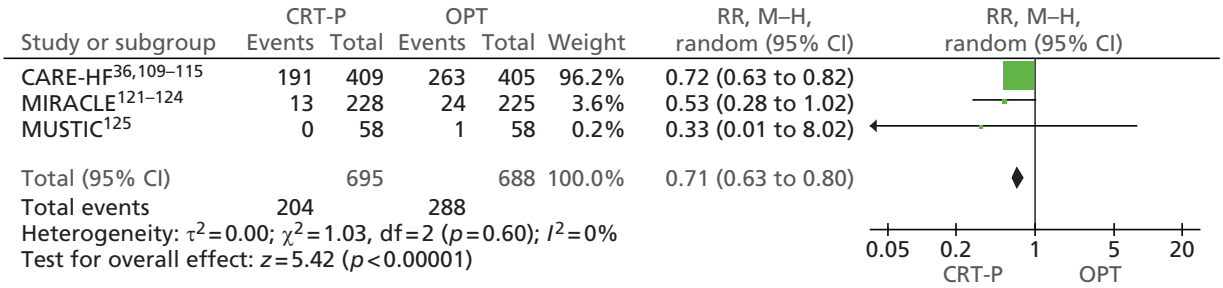

FIGURE 15 Worsening HF: CRT-P vs. OPT.

CRT-P compared with optimal pharmacological therapy

All three trials reported a statistically significant greater proportion of participants with improvement in NYHA class with CRT-P than with OPT (*Table 43*). The CARE-HF trial[109] also reported an improvement in mean NYHA class with CRT-P [CRT-P 2.1 (SD 1.0) vs. OPT 2.7 (SD 0.9), $p < 0.001$]. There was no evidence of statistical heterogeneity between the studies when the data were pooled in a random-effects meta-analysis ($\chi^2 = 70$, df = 2, $I^2 = 0\%$) (*Figure 16*). The pooled data from all three trials showed an increase in the proportion of people with an improvement of one or more NYHA class in the CRT-P group compared with the OPT group (RR 1.68, 95% CI 1.52 to 1.86, $p < 0.00001$).

CRT-D compared with optimal pharmacological therapy

In the COMPANION trial,[116] the proportion of people with an improvement in NYHA class was statistically significantly greater in the CRT-D group than in the OPT group at both 3 months (CRT-D 55% vs. OPT 24%, $p < 0.001$) and 6 months (CRT-D 57% vs. OPT 38%, $p < 0.001$) (see *Table 43*).

CRT-P compared with CRT-D

In the COMPANION trial[116] the proportion of people with an improvement in NYHA class was similar between the CRT-P group and the CRT-D group at both 3 months (58% vs. 55% respectively) and 6 months (61% vs. 57% respectively; RR 0.93, 95% CI 0.84 to 1.04, $p = 0.20$) (see *Table 43*). However, this comparison should be treated with caution as the trial was not powered for this comparison.

TABLE 43 Changes in NYHA class

Study	Outcome and follow-up	CRT-P, *n*/*N* (%)	OPT, *n*/*N* (%)	Effect	95% CI, *p*-value
CARE-HF[109]	NYHA class, 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 at 90 days, mean (SD)	2.1 (1.0)	2.7 (0.9)	MD 0.6	0.4 to 0.7, < 0.001
MIRACLE[121]	6 months				
	Improved by two or more classes	34/211 (16)	12/196 (6)	RR 1.80[b]	1.47 to 2.20, < 0.00001[b]
	Improved by one class	109/211 (52)	62/196 (32)		
	No change	64/211 (30)	115/196 (59)		
	Worsened	4/211 (2)	7/196 (4)		
COMPANION[116]	Improvement in NYHA class symptoms				
	3 months	320[c]/551 (58)	58[c]/242 (24)		< 0.001
	6 months	298[c]/489 (61)	76[b]/199 (38)	RR 1.60[b]	1.32 to 1.93, < 0.00001[b,d]
		CRT-D	**OPT**		
	3 months	299[c]/543 (55)	58[c]/242 (24)		< 0.001
	6 months	283[c]/497 (57)	76[c]/199 (38)	RR 2.14[b]	2.14 to 1.53, < 0.00001[b,d]
		CRT-P	**CRT-D**		
	3 months	320[c]/551 (58)	299[c]/543 (55)		
	6 months	298[c]/489 (61)	283[c]/497 (57)	RR 0.93[b]	0.84 to 1.04, 0.20[b]

MD, mean difference.
a RR, 95% CI and *p*-value for classes I and II combined.
b Calculated by reviewer.
c Numerators calculated by reviewer.
d Analysis reported in paper: $p < 0.001$.[116]

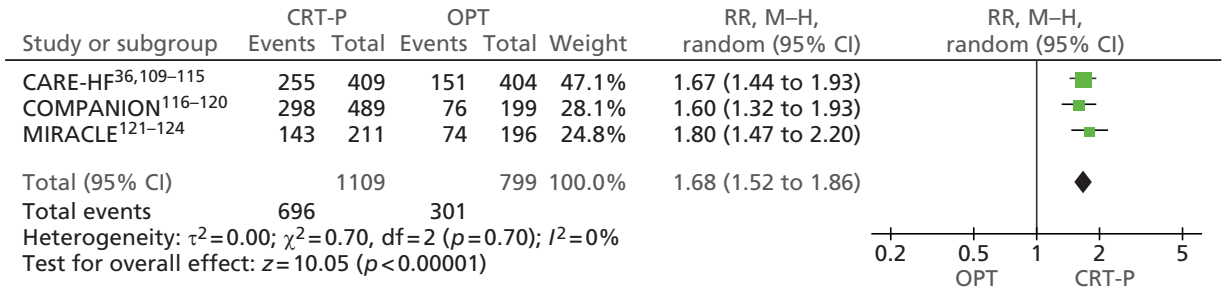

FIGURE 16 Participants with improvement by one or more NYHA class: CRT-P vs. OPT.

Change in left ventricular ejaculation fraction

Only one trial reported LVEF. The MIRACLE trial[121] reported absolute change in median LVEF at 6 months for those receiving CRT-P and those receiving OPT. No comparisons between CRT-D and OPT or between CRT-P and CRT-D were reported.

CRT-P compared with optimal pharmacological therapy

The MIRACLE trial[121] reported an improvement in median LVEF with CRT-P (+4.6, 95% CI 3.2 to 6.4), but LVEF decreased 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 ($p < 0.001$).

Exercise capacity

The COMPANION trial[116] reported the mean increase in 6-minute walk distance at 3 and 6 months, whereas the MIRACLE trial[121] reported the median change from baseline in 6-minute walk distance and median change in total exercise time. Change in 6-minute walk distance was one of three primary end points in this trial. The MUSTIC trial[125] reported mean distance walked in 6 minutes at 3 months (*Table 44*). The CARE-HF trial[109] did not report 6-minute walk distance. Only two trials reported change in peak oxygen consumption. The MIRACLE trial[121] reported the median change in oxygen consumption (VO_2) and the MUSTIC trial[125] reported mean VO_2 (*Table 45*). No comparisons between CRT-D and OPT or between CRT-P and CRT-D were reported.

CRT-P compared with optimal pharmacological therapy

In all three trials, the distance walked in 6 minutes was statistically significantly greater for the CRT-P group than the OPT group (see *Table 44*). In the MIRACLE trial,[121] the CRT-P group also had a superior outcome for change in total exercise time (CRT-P 81 seconds vs. OPT 19 seconds, $p = 0.001$).

The trials were combined in a meta-analysis. For meta-analysis of the MUSTIC crossover trial,[125] data were combined from both periods. This method provides a conservative analysis, with the study being underweighted rather than overweighted.[65] 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 the MUSTIC trial[125] ($\chi^2 = 2.93$, df = 2, $I^2 = 32\%$). The improvement in distance walked in 6 minutes was statistically significantly greater for those receiving CRT-P than for those receiving OPT [mean difference (MD) 38.14, 95% CI 21.74 to 54.54, $p < 0.00001$] (*Figure 17*).

The MIRACLE trial[121] reported statistically significantly greater improvements in VO_2 with CRT-P than with OPT (+1.1 units vs. +0.2 units respectively, $p = 0.009$). In the MUSTIC trial,[125] the authors combined the data from both crossover periods for the statistical analysis, which demonstrated a significantly greater VO_2 in those receiving CRT-P (CRT-P 16.2 units vs. OPT 15 units, $p = 0.029$).

CRT-D compared with optimal pharmacological therapy

In the COMPANION trial,[116] the improvement in 6-minute walk distance was statistically significantly greater with CRT-D than with OPT at 3 months (44 m vs. 9 m respectively, $p < 0.001$) and 6 months (46 m vs. 1 m respectively, $p < 0.001$).

CRT-D compared with CRT-P

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

TABLE 44 Change in 6-minute walk distance

Study	Outcome and follow-up	CRT-P	OPT	Effect	95% CI, *p*-value
MIRACLE[121]	6 months				
	Change in 6-minute walk distance (m), median (95% CI, SD)	+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 (seconds), median (95% CI)	+81 (62 to 119) (*n* = 159)	+19 (–1 to 47) (*n* = 146)		0.001
MUSTIC[125]	Distance walked in 6 minutes (m), mean (SD)				
	Group 1 (CRT-P on, CTR-P off) (*n* = 22)	384.1 (78.9)	336.1 (128.3)		
	Group 2 (CRT-P off, CRT-P on) (*n* = 24)	412.9 (116.9)	316.2 (141.8)		
	Both groups (*n* = 46)	399.2 (100.5)	325.7 (134.4)		< 0.001
COMPANION[116]	Change in 6-minute walk distance (m), mean (SD)				
	3 months	33 (99) (*n* = 422)	9 (84) (*n* = 170)		< 0.001
	6 months	40 (96) (*n* = 373)	1 (93) (*n* = 142)		< 0.001
		CRT-D	**OPT**		
	Change in 6-minute walk distance (m), mean (SD)				
	3 months	44 (109) (*n* = 420)	9 (84) (*n* = 170)		< 0.001
	6 months	46 (98) (*n* = 378)	1 (93) (*n* = 142)		< 0.001
		CRT-P	**CRT-D**		
	Change in 6-minute walk, m, mean change (SD)				
	3 months	33 (99) (*n* = 422)	44 (109) (*n* = 420)		
	6 months	40 (96) (*n* = 373)	46 (98) (*n* = 378)	MD –6.0[a]	–19.87 to 7.87, 0.40[a]

a Calculated by reviewer.

TABLE 45 Change in VO_2

Study	Outcome and follow-up	CRT-P	OPT	Effect	*p*-value
MIRACLE[121]	Change in VO_2 (ml/kg/minute), median (95% CI), 6 months	+1.1 (0.6 to 1.7) (*n* = 158)	+0.2 (–0.2 to 0.8) (*n* = 145)		0.009
MUSTIC[125]	VO_2 (ml/kg/minute), mean (SD), 3 months				
	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

Study or subgroup	CRT-P Mean	CRT-P SD	CRT-P Total	OPT Mean	OPT SD	OPT Total	Weight	MD IV, random (95% CI)
Change value								
COMPANION[116–120]	40	96	373	1	93	142	45.6%	39.00 (20.86 to 57.14)
MIRACLE[121–124]	39	103.9	214	10	89.2	198	44.1%	29.00 (10.34 to 47.66)
Subtotal (95% CI)			587			340	89.7%	34.14 (21.14 to 47.15)
Heterogeneity: τ^2=0.00; χ^2=0.57, df=1 (p=0.45); I^2=0%								
Test for overall effect: z=5.15 (p<0.00001)								
Final value								
MUSTIC[125]	399.2	100.5	46	325.7	134.4	46	10.3%	73.50 (25.00 to 122.00)
Subtotal (95% CI)			46			46	10.3%	73.50 (25.00 to 122.00)
Heterogeneity: not applicable								
Test for overall effect: z=2.97 (p=0.003)								
Total (95% CI)			633			386	100.0%	38.14 (21.74 to 54.54)
Heterogeneity: τ^2=68.04; χ^2=2.93, df=2 (p=0.23); I^2=32%								
Test for overall effect: z=4.56 (p<0.00001)								
Test for subgroup difference: χ^2=2.36, df=1 (p=0.12); I^2=57.6%								

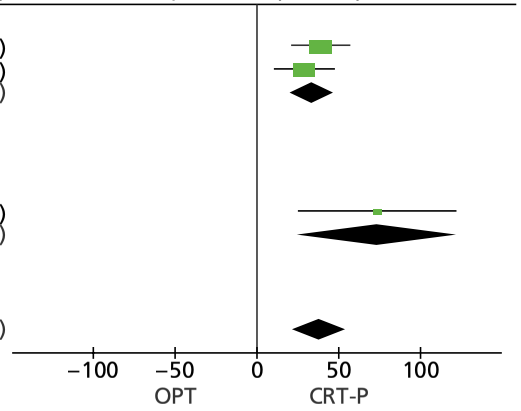

FIGURE 17 Change in 6-minute walk distance at 6 months.

Quality of life

All four studies reported change in QoL assessed using the MLWHFQ. Change in MLWHFQ score was the primary outcome in the MUSTIC trial.[125] The CARE-HF trial[113] also reported EQ-5D scores, mean quality-adjusted life-years (QALYs) and mean life-years (*Table 46*).

TABLE 46 Quality-of-life measures

Study	Outcome and follow-up	CRT-P	OPT	MD (95% CI), *p*-value
CARE-HF[113]	QALYs, mean (95% CI)	(*n* = 409)	(*n* = 404)	
	3 months	0.16 (0.15 to 0.16)	0.15 (0.14 to 0.15)	0.01 (0.001 to 0.018), 0.285
	18 months	0.95 (0.91 to 0.99)	0.82 (0.78 to 0.86)	0.13 (0.07 to 0.018), < 0.0001
	End of study, mean 37.4 months	1.45 (1.38 to 1.53)	1.22 (1.15 to 1.29)	0.23 (0.13 to 0.33), < 0.0001
	Life-years, mean (95% CI)			
	3 months	0.241 (0.238 to 0.244)	0.241 (0.238 to 0.244)	0.0003 (–0.004 to 0.0045), 0.90
	18 months	1.37 (1.34 to 1.40)	1.33 (1.29 to 1.37)	0.04 (–0.01 to 0.09), 0.13
	End of study, mean 37.4 months	2.07 (1.99 to 2.15)	1.96 (1.88 to 2.05)	0.10 (–0.01 to 0.22), 0.07[a]
	EQ-5D, mean (95% CI)			
	Baseline	0.60 (0.58 to 0.63)	0.60 (0.57 to 0.63)	–
	90 days[109]	0.70 (SD 28)	0.63 (SD 0.29)	0.08 (0.04 to 0.12), 0.001
	3 months	0.69 (0.66 to 0.72)	0.61 (0.59 to 0.64)	0.08 (0.04 to 0.11), < 0.0001
	18 months	0.61 (0.58 to 0.64)	0.51 (0.48 to 0.54)	0.10 (0.06 to 0.15), < 0.0001
	End of study, mean 37.4 months	0.56 (0.52 to 0.59)	0.43 (0.39 to 0.46)	0.13 (0.08 to 0.18), < 0.0001[b]
	MLWHFQ,[c] mean (95% CI)			
	Baseline	44.6 (42.5 to 46.7)	43.7 (41.5 to 45.8)	–
	90 days[109]	31 (SD 22)	40 (SD 22)	–10 (–8 to –12), < 0.001
	3 months	30.1 (27.9 to 32.3)	38.9 (36.6 to 41.2)	–10.6 (–8.1 to –13.1), < 0.0001[d]
	18 months	28.4 (26.2 to 30.5)	36.0 (33.5 to 38.5)	–10.7 (–7.6 to –13.8), < 0.0001[d]
	End of study, mean 37.4 months	27.2 (24.9–29.5) (SD 23.7)	35.1 (32.6–37.6) (SD 25.6)	–10.1 (–6.8 to –13.3), < 0.0001[d]

continued

TABLE 46 Quality-of-life measures (*continued*)

Study	Outcome and follow-up	CRT-P	OPT	MD (95% CI), *p*-value
MIRACLE[121]	Change in MLWHFQ score[c]	(*n* = 213)	(*n* = 193)	
	6 months, median (95% CI), SD	–18 (–22 to –12), 37	–9 (–12 to –5), 24.7	0.001
MUSTIC[125]	MLWHFQ score,[c] mean (SD)			
	Group 1 (CRT-P on, CRT-P off) (*n* = 23)	33.3 (22)	42.6 (20.9)	
	Group 2 (CRT-P 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[116]	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
		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
		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[e]

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 section on all-cause mortality.
c MLWHFQ includes 21 questions rated on a 6-point scale (total score 105), with higher scores indicating poorer QoL.
d Decline in EQ-5D despite maintained effect on MLWHFQ is because death has a score of 0 on the EQ-5D and is not included in the MLWHFQ.
e 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.

CRT-P compared with optimal pharmacological therapy

All four trials showed statistically significant improvements in MLWHFQ scores in the CRT-P group compared with the OPT group (lower scores indicate better QoL). The trials were combined in a meta-analysis. The COMPANION trial[116] and the MIRACLE trial[121] reported mean change in MLWHFQ score from baseline whereas the CARE-HF trial[113] and the MUSTIC trial[125] reported final mean values. The MUSTIC trial[125] reported data per crossover period and combined data for both crossover periods (*Figure 18*).

For meta-analysis of the MUSTIC crossover trial,[125] the combined data from both crossover periods were included, as this method provides a conservative analysis, with the study being underweighted rather than overweighted.[65] 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 MD was –10.33 (95% CI –13.31 to –7.36) and MLWHFQ scores were statistically significantly lower in the CRT-P group than in the OPT group ($p = 0.00001$), indicating improved QoL.

Other QoL measures with statistically significant improvements in the CARE-HF trial[113] were the EQ-5D and QALYs. The mean value of the EQ-5D was statistically significantly higher in the CRT-P group at each follow-up (90 days: CRT-P 0.70 vs. OPT 0.63, $p < 0.001$; 3 months: CRT-P 0.69 vs. OPT 0.61, $p < 0.0001$; 18 months: CRT-P 0.61 vs. OPT 0.51, $p < 0.0001$; end of study CRT-P 0.56 vs. OPT 0.43, $p < 0.0001$), although scores appeared to be lower by the end of the study (37.4 months) than at baseline in both treatment arms. The mean QALYs were statistically significantly higher in the CRT-P group at 18 months (CRT-P 0.95 vs. OPT 0.82, $p < 0.0001$) and at the end of the study (CRT-P 1.45 vs. OPT 1.22, $p < 0.0001$).

CRT-D compared with optimal pharmacological therapy

The reduction in MLWHFQ score, indicating improved QoL, in the COMPANION trial[116] was statistically significantly greater in the CRT-D group at both 3 months (CRT-D –24 vs. OPT –9, $p < 0.001$) and 6 months (CRT-D –26 vs. OPT –12, $p < 0.001$).

CRT-P compared with CRT-D

In the COMPANION trial,[116] improvements in MLWHFQ scores were similar in the CRT-P group and the CRT-D group at 6 months (–25 vs. –26 respectively, MD 1.00, 95% CI –2.46 to 4.46, $p = 0.57$).

Study or subgroup	CRT-P Mean	CRT-P SD	CRT-P Total	OPT Mean	OPT SD	OPT Total	Weight	MD IV, random (95% CI)
Change value								
COMPANION[116–120]	– 25	26	460	– 12	23	207	33.2%	–13.00 (–16.93 to – 9.07)
MIRACLE[121–124]	– 18	37	213	– 9	24.7	193	18.4%	–9.00 (–15.07 to – 2.93)
Subtotal (95% CI)			673			400	51.6%	–11.70 (–15.37 to – 8.02)
Heterogeneity: $\tau^2 = 1.19$; $\chi^2 = 1.18$, df = 1 ($p = 0.28$); $I^2 = 15\%$								
Test for overall effect: $z = 6.24$ ($p < 0.00001$)								
Final value								
CARE-HF[36,109–115]	27.2	23.73	409	35.1	25.6	404	39.0%	–7.90 (–11.29 to – 4.51)
MUSTIC[125]	29.6	21.3	45	43.2	22.8	45	9.4%	–13.60 (–22.72 to – 4.48)
Subtotal (95% CI)			454			449	48.4%	–9.12 (–13.69 to – 4.54)
Heterogeneity: $\tau^2 = 3.93$; $\chi^2 = 1.32$, df = 1 ($p = 0.25$); $I^2 = 24\%$								
Test for overall effect: $z = 3.90$ ($p < 0.0001$)								
Total (95% CI)			1127			849	100.0%	–10.33 (–13.31 to –7.36)
Heterogeneity: $\tau^2 = 2.91$; $\chi^2 = 4.39$, df = 3 ($p = 0.22$); $I^2 = 32\%$								
Test for overall effect: $z = 6.81$ ($p < 0.00001$)								
Test for subgroup difference: $\chi^2 = 0.74$, df = 1 ($p = 0.39$); $I^2 = 0\%$								

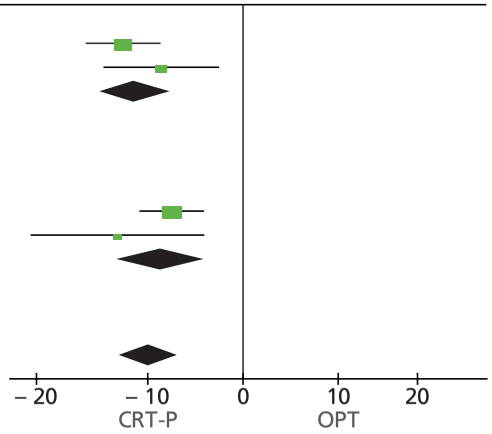

FIGURE 18 Change in MLWHFQ scores.

Adverse events

Reporting of adverse events was limited, as can be seen in *Tables 47* and *48*. All participants in the MIRACLE trial[121] and the MUSTIC trial[125] 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 the MIRACLE trial[121] 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) (see *Table 47*).

TABLE 47 Adverse events in participants with a CRT device (randomised to CRT-P on or off)

Study	Adverse events	CRT device, *n*/*N* (%)
MIRACLE[121] (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 from 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 left ventricular lead	
	CRT-P on	11/228 (4.8)
	CRT-P off	3/225 (1.3)
MUSTIC[125] (enrolled $n = 67$; randomised $n = 58$: CRT-P 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 Three of these participants recovered and continued in the study.

TABLE 48 Adverse events in 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[109] [enrolled and randomised *n* = 813: CRT-P *n* = 409, OPT *n* = 404 (CRT-P off)]	Unsuccessful implantation	19/409 (4.6)		
	Device-related death			
	HF 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[116] (enrolled and randomised *n* = 1520: CRT-P *n* = 617, CRT-D *n* = 595, OPT *n* = 308)	Unsuccessful implantation	78/617 (12.6)		
	Deaths from procedural complications	5/615 (0.8)		
	Mortality rate 30 days after randomisation	6[b]/617 (1.0)	4[b]/308 (1.3)	0.34
	Moderate or severe adverse event from any cause	407[b]/617 (66)	188[b]/308 (61)	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)		
	Deaths from procedural complications	3/595 (0.5)		
	Mortality rate 30 days after randomisation	11[b]/595 (1.8)	4/308 (1.3)	0.97
	Moderate or severe adverse event from any cause	411[b]/595 (69)	188/308 (61)	0.03
	Moderate or severe adverse event related to implantation procedure	48[b]/595 (8)		

TABLE 48 Adverse events in participants randomised to CRT-P or OPT (no device) (*continued*)

Study	Adverse events	CRT-P, *n/N* (%)	OPT, *n/N* (%)	RR (95% CI), *p*-value
	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[b]
	Moderate or severe adverse event from any cause	407[b]/617 (66)	411[b]/595 (69)	0.95 (0.88, 1.03), 0.25[b]

a Number of patients per treatment arm not reported.
b Calculated by reviewer.

The CARE-HF[109] and COMPANION[116] trials randomised participants to receive either a CRT-P (or CRT-D) device or OPT only (see *Table 48*). However, the CARE-HF[109] trial limited reporting of adverse events to device-related complications. Only the COMPANION trial[116] reported any statistical comparison between CRT-P or CRT-D and OPT for adverse events.

Between 4.6%[109] and 12.6%[116] of device implantations were unsuccessful in the trials (see *Tables 47* and *48*). Death from adverse clinical events during the implantation procedure occurred among 0.4% of all participants in the MIRACLE trial,[121] whereas in the COMPANION trial[116] 0.8% of CRT-P recipients and 0.5% of CRT-D recipients died from procedural complications. The mortality rate 30 days after randomisation was not statistically significantly different between the OPT group (1.2%), the CRT-P group (1.0%, $p = 0.34$) and the CRT-D group (1.8%, $p = 0.97$),[116] or between CRT-P and CRT-D (RR 0.53, 95% CI 0.20 to 4.41, $p = 0.2$). Device-related deaths occurred among 0.2% of participants randomised to CRT-P in the CARE-HF trial[109] and among 0.2% of those randomised to OPT (after receiving a device), although the time period was not reported.

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 the COMPANION trial.[116] The most commonly reported adverse events were coronary sinus/venous dissection (0.3% CRT-P, 0.5% CRT-D;[116] 4.0%;[121] 2.4%[109]) or perforation (1.1% CRT-P, 0.8% CRT-D;[116] 2.1%[121]) and lead-related events (6%;[109,121] 13.8%[125]). In the MIRACLE trial,[121] hospitalisation for repositioning or replacement of the left ventricular lead was more frequent in those in the CRT-P on group (4.8%) than those in the CRT-P off group (1.3%).

In the COMPANION trial,[116] the proportion of moderate or severe adverse events from any cause was statistically significantly higher in the CRT-D group than in the OPT group (69% vs. 61% respectively, $p = 0.03$), but there was no statistically significant difference between the CRT-P group and the OPT group (66% vs. 61% respectively, $p = 0.15$) or between the CRT-P group and the CRT-D group (RR 0.95, 95% CI 0.88 to 1.03, $p = 0.25$). The CARE-HF trial[109] reported that the frequency of respiratory tract infections, hypotension, falls or syncope, acute coronary syndromes, renal dysfunction, ventricular arrhythmias or ectopy, and neurological events was similar in the CRT-P and OPT only groups.

Subgroup analyses reported by included randomised control trials

Only the CARE-HF trial[109] presented subgroup analyses that were clearly predefined (*Tables 49* and *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 (see *Table 49*).

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

Summary of clinical effectiveness: people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony

- Four RCTs, with a combined total of 2844 participants, comparing CRT-P (and CRT-D in one trial) with OPT in people with HF as a result of LVSD and cardiac dyssynchrony were included. 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 between CRT-D and CRT-P.
- There was some risk of bias in the trials in relation to performance, detection and reporting bias, although risk was unclear in some cases because of inadequate reporting.
- Length of follow-up in the trials varied and included 3 months, 6 months, a median of 11.9–15.7 months and a mean of 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 compared with optimal pharmacological therapy

- Meta-analysis found that CRT-P significantly reduced the risk of all-cause mortality (four trials; RR 0.75, 95% CI 0.58 to 0.96, $p = 0.02$), HF deaths (two trials; RR 0.67, 95% CI 0.51 to 0.88, $p = 0.004$) and HF hospitalisations (four 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 number of SCDs between the groups (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 receiving 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.

TABLE 49 Changes in LVEF for ischaemic or non-ischaemic heart disease

Study	Outcome and follow-up	CRT-P		OPT		*p*-value
		IHD ($n = 168$)	non-IHD ($n = 197$)	IHD ($n = 135$)	non-IHD ($n = 235$)	
CARE-HF[115]	LVEF (%) at baseline, median (IQR)	25 (22 to 29)	24 (21 to 29)	26 (22 to 30)	24 (21 to 29)	0.1867 (IHD vs. non-IHD)
	Mean (SD) change in LVEF 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, ischaemic heart disease; IQR, interquartile range.
a Values estimated by reviewer from figure using Engauge digitising software (not stated but error bars presumed to show SD).[115]

TABLE 50 Effect of CRT-P on death from any cause or unplanned hospitalisation for a major cardiovascular event in predefined subgroups

Study	Subgroup	Patients with event/total no. of patients[a]	HR (95% CI)
CARE-HF[109]	Overall with primary end point	383/813	0.63 (0.51 to 0.77)
	Age (years)[b]		
	< 66.4	163/406	0.55 (0.40 to 0.75)
	≥ 66.4	220/407	0.68 (0.52 to 0.89)
	Sex		
	Male	290/597	0.62 (0.49 to 0.79)
	Female	93/215	0.64 (0.42 to 0.97)
	NYHA class		
	III	349/763	0.64 (0.52 to 0.80)
	IV	34/50	0.50 (0.25 to 1.01)
	Dilated cardiomyopathy		
	No	238/443	0.68 (0.53 to 0.88)
	Yes	145/370	0.51 (0.36 to 0.73)
	Systolic blood pressure (mmHg)[b]		
	< 117	208/401	0.60 (0.46 to 0.80)
	≥ 117	170/402	0.66 (0.48 to 0.89)
	NT-proBNP (pg/ml)[c]		
	< 214.5	122/366	0.53 (0.36 to 0.76)
	≥ 214.5	224/366	0.70 (0.54 to 0.91)
	Ejection fraction (%)[b]		
	< 24.7	205/372	0.65 (0.49 to 0.86)
	≥ 24.7	152/373	0.62 (0.44 to 0.85)
	End-systolic volume index (ml/m^2)[b]		
	< 119.2	156/366	0.71 (0.52 to 0.98)
	≥ 119.2	193/366	0.54 (0.40 to 0.73)
	QRS interval (milliseconds)		
	< 160	152/290	0.74 (0.54 to 1.02)
	≥ 160	222/505	0.60 (0.46 to 0.79)
	Interventricular mechanical delay (milliseconds)[b]		
	< 49.2	199/367	0.77 (0.58 to 1.02)
	≥ 49.2	147/368	0.50 (0.36 to 0.70)
	Mitral regurgitation area (cm^2)[b]		
	< 0.218	114/302	0.86 (0.60 to 1.25)
	≥ 0.218	175/303	0.56 (0.41 to 0.75)

continued

TABLE 50 Effect of CRT-P on death from any cause or unplanned hospitalisation for a major cardiovascular event in predefined subgroups (*continued*)

Study	Subgroup	Patients with event/total no. of patients[a]	HR (95% CI)
	Glomerular filtration rate (ml/minute/1.73 m^2)[b]		
	< 60.3	196/369	0.67 (0.50 to 0.89)
	≥ 60.3	142/370	0.57 (0.40 to 0.80)
	Beta-blockers		
	No	131/227	0.72 (0.51 to 1.02)
	Yes	252/586	0.59 (0.46 to 0.76)
	Spironolactone		
	No	166/356	0.58 (0.43 to 0.79)
	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)
	≥ 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)
	Yes	165/346	0.59 (0.43 to 0.81)

NT-proBNP, N-terminal pro-B-type natriuretic peptide.
a Authors state that, because of missing baseline data, not all subgroup numbers sum to 813.
b Divided according to the median value in the study population; this lead to some inequality in the sizes of the subgroups.

- One RCT reported change in LVEF, showing a statistically significant improvement in LVEF with CRT-P compared with OPT (4.6% vs. –0.2%, $p < 0.001$) at 6 months.
- There was a greater improvement in exercise capacity with CRT-P, as measured by the distance walked in 6 minutes (meta-analysis of three trials; change from baseline or final values, MD 38.14 m, 95% CI 21.74 to 54.54 m, $p < 0.00001$). A statistically significant improvement in peak oxygen consumption was also reported by two of the RCTs.
- All four RCTs found statistically significant improvements in QoL (MLWHFQ) in the CRT-P group (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 the CRT-P group in the EQ-5D (MD 0.13, 95% CI 0.08 to 0.18, $p < 0.0001$) and in QALYs (MD 0.23, 95% CI 0.13 to 0.33, $p < 0.00001$) at the end of the 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-ischaemic heart disease 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 predefined subgroups.

CRT-D compared with optimal pharmacological therapy

- 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, $p = 0.02$), SCDs (HR 0.44, 95% CI 0.23 to 0.86, $p = 0.02$) and HF 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 HF 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%, $p = 0.717$) between the groups.
- The proportions of people with an improvement of one or more NYHA class (CRT-D 57% vs. OPT 38%, $p < 0.001$), improvement in exercise capacity (change in 6-minute walk distance: CRT-D 46 m vs. OPT 1 m, $p < 0.001$) and improvement in QoL (MLWHFQ) score (CRT-D –26 vs. OPT –12, $p < 0.001$) at 6 months were statistically significantly greater in the CRT-D group.

CRT-P compared with 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 between CRT-P and CRT-D. Statistical comparisons between CRT-P and 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 SCDs (RR 2.72, 95% CI 1.58 to 4.68, $p = 0.0003$) were higher in the CRT-P group than in the CRT-D group. All-cause mortality (RR 1.20, 95% CI 0.96 to 1.52, $p = 0.12$), HF deaths (RR 0.98, 95% CI 0.68 to 1.42, $p = 0.93$) and HF hospitalisations (28% vs. 29%) were similar in the CRT-P group and the CRT-D group.
- Changes in NYHA class, exercise capacity and QoL were similar in the CRT-P group and the CRT-D group.

Adverse events

- Two trials randomised people with successful implantation only. The other two trials reported device-related deaths of between 0.2% and 0.8% for those receiving CRT-P and 0.5% for those receiving CRT-D. Moderate or severe adverse events related to the implantation procedure were reported in 10% of the CRT-P group and 8% of the CRT-D group in one trial, with 13% and 9% of CRT-P and CRT-D implantations, respectively, unsuccessful. Moderate or severe adverse events from any cause were more common among those receiving CRT-D than among those receiving 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

Quantity and quality of research available

Nine RCTs comparing CRT-D and ICDs in people at risk of SCD as a result of ventricular arrhythmias and with HF 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[126]) was included in the 2007 TAR on CRT;[64] however, participants in the CONTAK-CD trial[126] were required to have VT as an indication for ICD and defibrillating capacity was available to the control group and it is therefore discussed here rather than in the previous section.

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

TABLE 51 Included RCTs for people with both conditions

Study	Publication[a]
CONTAK-CD	**Higgins *et al.* 2003,**[126] Lozano *et al.* 2000,[128] US Food and Drug Administration 2002,[129] Saxon *et al.* 1999[127]
MADIT-CRT	**Moss *et al.* 2009**[130] and 2005,[131] Solomon *et al.* 2010,[132] Goldenberg *et al.* 2011,[134,145] Arshad *et al.* 2011[135]
MIRACLE ICD	**Young *et al.* 2003**[136]
MIRACLE ICD II	**Abraham *et al.* 2004**[137]
Piccirillo 2006	**Piccirillo *et al.* 2006**[138]
Pinter 2009	**Pinter *et al.* 2009**[139]
RAFT	**Tang *et al.* 2010**[140] and 2009[141]
RethinQ	**Beshai *et al.* 2007,**[142] Beshai and Grimm 2007[143]
RHYTHM ICD	**US Food and Drug Administration 2004,**[144] US Food and Drug Administration 2005[145]

MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE ICD, Multicenter InSync ICD Randomized Clinical Evaluation; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RethinQ, Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS; RHYTHM ICD, Resynchronization for the HemodYnamic Treatment for Heart failure Management Implantable Cardioverter Defibrillator.
Bold text indicates primary or key publication.

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 9*.

Intervention and comparators

The participants in six of these trials[126,136,137,139,142,144] 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[130,138,140] the comparator group received an ICD only device. Participants in both groups of all trials also received OPT (discussed further in *Pharmacological therapy*).

Participants

Participants in eight of these studies were required to have guideline indications for ICD therapy (see *Table 52*). Piccirillo and colleagues[138] state that the participants were undergoing prophylactic treatment with the ICD or CRT-D. Pinter and colleagues[139] enrolled people who 'were not candidates for CRT therapy based on guidelines at the time of the study' (p. 1510); however, such patients would now be considered to have a conventional indication for CRT.

The trials differed in their eligibility criteria for severity of HF (see *Table 52*). The majority of participants in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT),[130] the Multicenter InSync ICD II Randomized Clinical Evaluation (MIRACLE ICD II)[137] and the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT)[140] were in NYHA class II; in the CONTAK-CD RCT,[126] the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD),[136] the Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) trial[142] and the Resynchronization for the HemodYnamic Treatment for Heart failure Management Implantable Cardioverter Defibrillator (RHYTHM ICD) trial[144] the majority of participants were in NYHA class III; and the majority of participants in the study by Piccirillo and colleagues[138] were in NYHA class IV (see *Table 53*). NYHA class was not reported by Pinter and colleagues[139] although the eligibility criteria required mild to moderate HF. The proportion of participants with ischaemic heart disease varied between the trials, from

TABLE 52 Study characteristics

Parameter	CONTAK-CD[126]	MADIT-CRT[130]	MIRACLE ICD[136]	MIRACLE ICD II[137]	Piccirillo[138]	Pinter[139]	RAFT[140]	RethinQ[142]	Rhythm ICD[144]
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 and 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 (SD 20) months	6 months	Average 12.1 (3.4) months
Key inclusion criteria	Intraventricular conduction delay and malignant VT/VF; NYHA classes II–IV; LVEF ≤ 35%; QRS interval ≥ 120 milliseconds; conventional indications for an ICD	Ischaemic or non-ischaemic CM; NYHA class I or II; LVEF ≤ 30%; ≥ QRS interval ≥ 130 milliseconds; sinus rhythm; met guideline indication for ICD therapy	CHF; stable drug regimen for ≥ 1 month; NYHA class III or IV; LVEF ≤ 35%; ≥QRS interval ≥ 130 milliseconds; LVEDD ≥ 55 mm; cardiac arrest due to VT or VF	Chronic HF; NYHA class II; LVEF ≤ 35%; ≥QRS interval ≥ 130 milliseconds; LVEDD ≥ 55 mm; indication for ICD therapy	Chronic HF secondary to ischaemic DCM; LVEF ≤ 35%; QRS interval > 120 milliseconds; sinus rhythm; prophylactic treatment with an ICD or CRT-D	Symptoms of dyspnoea or fatigue on climbing one or two flights or 6-MWD ≤ 450 m; ≥ 2 weeks drugs;[a] LVEF ≤ 35%; QRS interval > 120 milliseconds; sinus rhythm; high risk of sudden death and eligible for an ICD	Ischaemic or non-ischaemic causes; OPT; NYHA class II or III; LVEF ≤ 30%; QRS interval ≥ 120 or paced ≥ 200 milliseconds; sinus rhythm or permanent atrial fibrillation;[b] planned ICD implantation, primary or secondary prevention	Ischaemic or non-ischaemic CM; narrow QRS interval; intraventricular dyssynchrony; OPT; NYHA class III; LVEF ≤ 35%; QRS interval < 130 milliseconds; approved indication for an ICD	Symptomatic HF for ≥ 6 months; ≥ 90 of days OPT; NYHA class III or IV; LVEF ≤ 35%; QRS interval ≥ 150 milliseconds; ICD indication for VT

6-MWD, 6-minute walk distance; CM, cardiomyopathy. DCM, dilated cardiomyopathy; LVEDD, left ventricular end-diastolic diameter; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; Max, maximum; MIRACLE ICD, Multicenter InSync ICD Randomized Clinical Evaluation; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RethinQ, Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS; RHYTHM ICD, Resynchronization for the HemodYnamic Treatment for Heart failure Management Implantable Cardioverter Defibrillator.

a Max. dose of ACE inhibitors or beta-blockers.

b Or flutter, controlled ventricular rate or planned atrioventricular junction ablation.

TABLE 53 Key participant characteristics

	CONTAK-CD[126]		MADIT-CRT[130]		MIRACLE ICD[136]		MIRACLE ICD II[137]		Piccirillo[138]		Pinter[139]		RAFT[140]		RethinQ[142]		Rhythm ICD[144]	
Parameter	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 (years), 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 class, %																		
I	0	0	14.0	15.5	0	0	0	0	0	0	NR	NR	0	0	0	0	0.8	3.4
II	32	33	86	84.5	0	0	100	100	0	0	NR	NR	79.2	80.8	0	0	5.0	6.8
III	60	57	0	0	88.2	89.6	0	0	31.3	33.3	NR	NR	20.8	19.2	100	99[a]	87.4	84.7
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)[b]	24.0 (8.3)[b]	22.6 (5.4)	22.6 (5.1)	25 (5)	26 (6)	25.6 (8.3)	23.3 (6.4)
QRS interval (milliseconds)																		
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				

IHD, ischaemic heart disease; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE ICD, Multicenter InSync ICD Randomized Clinical Evaluation; NR, not reported; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RBBB, right bundle branch block; RethinQ, Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS; RHYTHM ICD, Resynchronization for the HemodYnamic Treatment for Heart failure Management Implantable Cardioverter Defibrillator.

a NYHA class of one participant not reported.

b Measured by ECG; also measured by quantitative resting radionuclide angiogram (MUGA): CRT-D 24.2% (SD 7.5%), ICD 26.8% (SD 8.4%).

around 52% (RethinQ[142]) to 100% (Piccirillo and colleagues[138]). The RethinQ trial[142] enrolled people with ischaemic or non-ischaemic cardiomyopathy and the study by Piccirillo and colleagues[138] enrolled people with ischaemic dilated cardiomyopathy.

The RethinQ trial[142] differed from the other trials in the criteria used to define cardiac dyssynchrony. Conventionally, a wide QRS interval indicates electrical dyssynchrony. This trial, however, recruited people with a narrow QRS interval (< 130 milliseconds) and evidence of mechanical dyssynchrony on echocardiography. Mean QRS interval in this trial was about 107 milliseconds and approximately one-quarter of participants had a QRS duration of ≥ 120 milliseconds.

Mean QRS interval in the other eight trials, when reported, ranged from 156 milliseconds (CONTAK-CD[126]) to 169 milliseconds (RHYTHM ICD[144]). Pinter and colleagues[139] did not report baseline QRS duration but required a minimum duration of 120 milliseconds for study eligibility. The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT trial)[130] required participants to have a QRS duration of at least 130 milliseconds and reported that around 65% of participants had a QRS interval of ≥ 150 milliseconds at baseline. Mean LVEF ranged from 21% (CONTAK-CD[126]) to 26% (RethinQ[142]).

The mean age of the participants in the trials was similar, ranging from 63 years (MIRACLE ICD II[137]) to 67 years (MIRACLE ICD[136]). The majority of participants (from 75% in MADIT-CRT[130] to 90% in MIRACLE ICD II[137]) were men.

Pharmacological therapy

Table 54 displays medication at baseline. The majority of participants in all studies received ACE inhibitors and/or ARBs, although the proportion receiving beta-blockers varied between studies. Less than half of participants in the CONTAK-CD study,[126] around 60% of participants in the MIRACLE ICD[136] and MIRACLE ICD II[137] trials and around 80–95% of participants in the MADIT-CRT,[130] Piccirillo and colleagues,[138] RAFT,[140] RethinQ[142] and RHYTHM ICD[144] trials received beta-blockers. AAD use also varied between the studies: around 33–35% of participants in the MIRACLE ICD II study,[137] 33–42% of participants in the MIRACLE ICD study,[136] less than one-quarter of participants in the RHYTHM ICD trial,[144] around 15% of participants in the RAFT trial,[140] 8–12% in the RethinQ trial[142] and around 7% in the MADIT-CRT trial[130] were receiving AADs. 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.

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[126,137–140,142,144]), death from HF (four trials[126,137–139]), SCD (six trials[126,136–138,142,144]) and death from other causes (six trials[126,137–139,142,144]). Three trials[126,138,140] reported hospitalisation because of HF, six trials[126,136–138,142,144] reported NYHA class and eight trials[126,130,136–139,142,144] reported LVEF. Six trials[126,136,137,139,142,144] reported exercise capacity assessed by the 6-minute walk test and/or peak oxygen consumption, and QoL assessed by the MLWHFQ. The primary outcome of three trials[126,130,140] was a composite outcome; these can be seen in the data extraction forms in *Appendix 9* but have not been presented here.

Setting

Other than the single-centre study by Piccirillo and colleagues,[138] the trials were multicentre with the majority of the centres in the USA and Canada. Only one of the studies[130] had a centre in the UK.

The number of participants randomised ranged from 31[138] to 1820.[130] The length of follow-up was 6 months in the CONTAK-CD,[126] MIRACE ICD,[136] MIRACLE ICD II,[137] Pinter and colleagues[139] and RethinQ[142] studies, 12 months in the Piccirillo and colleagues[139] and RHYTHM ICD[144] studies and an average of 2.4 years in the MADIT-CRT study[130] and 40 months in the RAFT study.[140]

TABLE 54 Medication at baseline

	CONTAK-CD[126]		MADIT-CRT[130]		MIRACLE ICD[136]		MIRACLE ICD II[137]		Piccirillo[138]		RAFT[140]		RethinQ[142]		Rhythm ICD[144]	
Medication	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	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
ARB, %			20.8	20.2											20.2	16.9
AADs, %					42.3	33.0	35.3	32.7					8	12	24.4	22.0
Amiodarone			7.2	7.0							15.7	13.7				
Other AAD											1.3	0.9				
Class I AAD			1.1	0.4												
Anticoagulants and antiplatelets, %															85.7	81.4
Acetylsalicylic acid (aspirin)									100	93	65.3	68.8				
Clopidogrel											15.0	16.0				
Warfarin											34.7	33.0				
Beta-blockers, %	48	46	93.3	93.2	62.0	58.2	63.5	63.4			90.4	89.0	97	93	79.8	88.1
Biskoprolol									13	7						
Carvedilol									81	80						
Calcium channel blockers, %											11.3	9.2			9.2	15.3
Diuretics, %	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

Medication	CONTAK-CD[126]		MADIT-CRT[130]		MIRACLE ICD[136]		MIRACLE ICD II[137]		Piccirillo[138]		RAFT[140]		RethinQ[142]		Rhythm ICD[144]	
	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD	CRT-D	ICD
Positive inotropics/glycoside, %															61.3	66.1
Digitalis			26.7	24.2												
Digoxin	69	68							75	73						
Statins, %			67.5	67.2							67.9	68.4				

Note: the study by Pinter *et al.*[139] did not report baseline medication but inclusion criteria state ≥ 2 weeks' treatment with maximal tolerated doses of ACE inhibitors or beta-blockers unless adverse effects or contraindicated.

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 9*. Only three of the studies[136,137,142] were at low risk of selection bias. The MADIT-CRT study[130] 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 the 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 the MADIT-CRT study;[130] treating physicians were aware of study group assignments, and diagnosis of HF and decisions about therapy or hospital admission were made by physicians aware of assignments, although members of the mortality and HF committees were unaware of study group assignments. Details of blinding of participants and personnel were not reported by Piccirillo and colleagues[138] and, although spectral recording assessment was blinded, details of blinding of other outcomes were not reported. The RethinQ[142] and RHYTHM ICD[144] studies 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 the RethinQ trial.[142] There was a low risk of performance bias and detection bias in the other studies.[126,136,137,139,140]

Risk of attrition bias in the CONTAK-CD trial[126] was low for the primary outcome but high for other outcomes. MADIT-CRT[130] was judged to have a low risk of bias for survival but a 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[136] and unclear in MIRACLE ICD II.[137] The RethinQ trial[142] was judged to have a low risk of attrition bias for primary and secondary outcomes but a high risk of bias for additional outcomes when missing data were not accounted for. The other studies[138–140,144] had a low risk of attrition bias.

The RAFT study[140] was considered to have a high risk of selective reporting bias as outcomes included in the protocol (e.g. QoL) were not reported in the trial publication. However, it is noted that this was a recent study and data may have been published after the completion of this report. The RHYTHM ICD study report was available only 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. The other studies[126,130,136–139,142] 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,[126] but the potential for these issues to introduce bias into the results is unknown. Because of a lack of details in the RHYTHM ICD report,[144] the risk of other sources of bias is unclear. The sponsors (Medtronic Inc.) of the MIRACLE ICD study[136] appear to have been involved in all aspects of the study, although the risk of bias from this is unclear. The other studies[130,137–140,142] were judged to have a low risk of bias.

Methodological comments

Similarity of groups at baseline

The groups were generally well balanced at baseline (see *Table 53*). However, the ICD group of the MIRACLE ICD study[136] had a higher proportion of participants with ischaemic heart disease. In the RHYTHM ICD study,[144] the ICD group performed significantly better in the exercise test for peak VO_2 (a primary outcome) and included a lower proportion of men, although the authors state that none of the differences was significant (statistical analysis not presented).

TABLE 55 Risk of bias

Domain	Judgement								
	CONTAK-CD[126]	MADIT-CRT[130]	MIRACLE ICD[136]	MIRACLE ICD II[137]	Piccirillo[138]	Pinter[139]	RAFT[140]	RethinQ[142]	Rhythm ICD[144]
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 and 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[a] – 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 Also QoL, NYHA and mortality.

Sample size

Four of the trials were adequately powered to show a difference in their primary outcome(s). These were the MIRACLE ICD trial[136] (a difference in NYHA class of 0.75, in QoL of 13 points or in 6-minute walk distance of 50 m), the trial by Pinter and colleagues[139] (a 12% decrease in end-systolic volume), the RAFT study[140] (a 25% relative reduction in the composite outcome) and the RethinQ trial[142] (a difference of 23% in the proportion of patients who achieved the primary end point).

The actual event rate observed in the CONTAK-CD trial[126] 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. The MADIT-CRT study[130] 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. The MIRACLE ICD study[136] was not powered to detect a morbidity or mortality difference. The study by Piccirillo and colleagues[138] was a small study of 31 participants. The study report does not include details of a sample size calculation, and mortality and NYHA were not primary outcomes and therefore it is assumed that the trial was not powered to detect these outcomes. The MIRACLE ICD II[137] and RHYTHM ICD[144] studies do not report sample size calculations.

Crossovers

Crossovers between groups were reported by six of the trials. Crossover from the ICD group to the CRT-D group occurred in 2.8%[139]–12.4%[130] of participants, the most common reason being for HF events (*Table 56*). Crossover from the CRT-D group to the ICD group occurred in 0%[142]–7.5%[130] of participants, most commonly because of difficulties with the left ventricular/CRT pacing lead (see *Table 56*).

Other issues

There were some differences between studies in the timing of implantation, baseline evaluation and randomisation. The MADIT-CRT,[130] Piccirillo and colleagues[138] and RAFT[140] studies randomised participants before or at the time of implantation. The CONTAK-CD trial[126] implanted the device first because of the immediate need for ICD therapy and then programmed the randomised therapy after a minimum 30-day period with no CRT, during which time investigators were permitted to optimise pharmacological therapy.

The other studies[136,137,139,142,144] randomised only those participants who were successfully implanted. In the MIRACLE ICD study[136] randomisation occurred within 7 days of successful implantation; in the study by Pinter and colleagues[139] participants were randomly assigned following completion of baseline procedures

TABLE 56 Crossovers to the alternative device

Study	CRT-D, *n/N* (%)	ICD, *n/N* (%)
MADIT-CRT[130]	82/1089 (7.5) (technical difficulties positioning CRT pacing lead)	91/731 (12.4) (30 before reaching an end point, 61 after HF event)
MIRACLE ICD[136]	10/187 (5) (two ventricular lead dislodgement, two diaphragmatic stimulation, six programming errors)	14/182 (8) (11 worsening HF, two bradycardia, one programming error)
MIRACLE ICD II[137]	2/85 (2) (left ventricular lead dislodgement in one patient and diaphragmatic stimulation in biventricular and right ventricular pacing modes in one patient)	5/101 (5) (bradycardia in three patients, centre error in one patient and pacemaker dependency after atrioventricular node ablation for atrial flutter in one patient)
Pinter[139]	1/36 (2.8) (late left ventricular capture failure)	1/36 (2.8) (worsening CHF)
RAFT[140]	Not reported	96/904 (10.6) (36 before primary outcome, 60 after HF hospitalisation)
RethinQ[142]	0/87 (0)	3/85 (3.5) (because of worsening HF)

14–28 days post implant; and in the RethinQ[142] and RHYTHM ICD[144] studies baseline evaluation occurred 14 days post implant, followed by randomisation.

The study design of the CONTAK-CD trial[126] was modified because of 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.

The study by Piccarillo and colleagues[138] 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.

The RAFT study[140] initially enrolled both NYHA class II and NYHA class III patients; however, after a protocol revision in February 2006 the study enrolled only NYHA class II patients. Primary and secondary outcomes for patients with NYHA class II or NYHA class III HF were therefore analysed separately.

The RHYTHM ICD study[144] 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. The RHYTHM ICD study[144] formed the basis of a FDA report by St Jude Medical (Sunnyvale, CA, USA). The study by Piccarillo and colleagues[138] did not report funding or competing interests.

Assessment of effectiveness

All-cause mortality

All nine trials reported data on all-cause mortality, although only two[130,140] compared events between groups statistically (*Table 57*). The MADIT-CRT study[130] 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, $p = 0.99$), whereas the RAFT study[140] 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:[126] CRT-D 4.5% vs. ICD 6.5%, RR 0.69, 95% CI 0.33 to 1.45, $p = 0.33$;

TABLE 57 All-cause mortality

Study	Follow-up (months)	CRT-D *n/N* (%)	ICD *n/N* (%)	Effect	95% CI, *p*-value
CONTAK-CD[126]	3–6	11/245 (4.5)	16/245 (6.5)	RR 0.69[a]	0.33 to 1.45,[a] 0.33
MADIT-CRT[130]	Average 2.4 years	74/1089 (6.8)	53/731 (7.3)	HR 1.00	0.69 to 1.44, 0.99
MIRACLE ICD[136]	6	14/187 (7.5)	15/182 (8.2)	RR 0.91[a]	0.45 to 1.83, 0.79[a]
MIRACLE ICD II[137]	6	2/85 (2.4)	2/101 (2.0)	RR 1.19[a]	0.17 to 8.26, 0.86[a]
Piccirillo[138]	12	0/16 (0)	0/15 (0)		
Pinter[139]	6	1/36 (2.8)	1/36 (2.8)	RR 1.00[a]	0.07 to 15.38, 1.00[a]
RAFT[140]	Mean 40 (SD 20)	186/894 (20.8)	236/904 (26.1)	HR 0.75	0.62 to 0.91, 0.003
RethinQ[142]	6	5/87 (5.7)	1/85 (1.2)	RR 4.89[a]	0.58 to 40.95, 0.14[a]
RHYTHM ICD[144]	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.

MIRACLE ICD:[136] CRT-D 7.5% vs. ICD 8.2%, RR 0.91, 95% CI 0.45 to 1.83, $p = 0.79$; MIRACLE ICD II:[137] CRT-D 2.4% vs. ICD 2.0%, RR 1.19, 95% CI 0.17 to 8.26, $p = 0.86$; Piccirillo and colleagues:[138] CRT-D 0% vs. ICD 0%; Pinter and colleagues:[139] CRT-D 2.8% vs. ICD 2.8%, RR 1.00, 95% CI 0.07 to 15.38, $p = 1.00$; RethinQ:[142] CRT-D 5.7% vs. ICD 1.2%, RR 4.89, 95% CI 0.58 to 40.95, $p = 0.14$; RHYTHM ICD:[144] 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,[126,136,137,139,142,144] 12 months in the study by Piccirillo and colleagues[138] and an average of 28.8 months in the MADIT-CRT study[130] and 40 months in the RAFT study.[140]

The trials were considered sufficiently similar to combine in a random-effects meta-analysis and were grouped according to the NYHA class of the majority of the participants in each trial. There was no evidence of significant statistical heterogeneity between the studies ($\chi^2 = 4.82$, df = 7, $I^2 = 0\%$). Note that the study by Piccirillo and colleagues[138] was not estimable within the meta-analysis as zero events were observed in both groups. The RR for CRT-D compared with ICD was 0.84 (95% CI 0.73 to 0.96, $p = 0.01$) (*Figure 19*), giving a RRR of 16% with CRT-D for all-cause mortality. The results were strongly influenced by the large RAFT study[140] 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, $p = 0.69$).

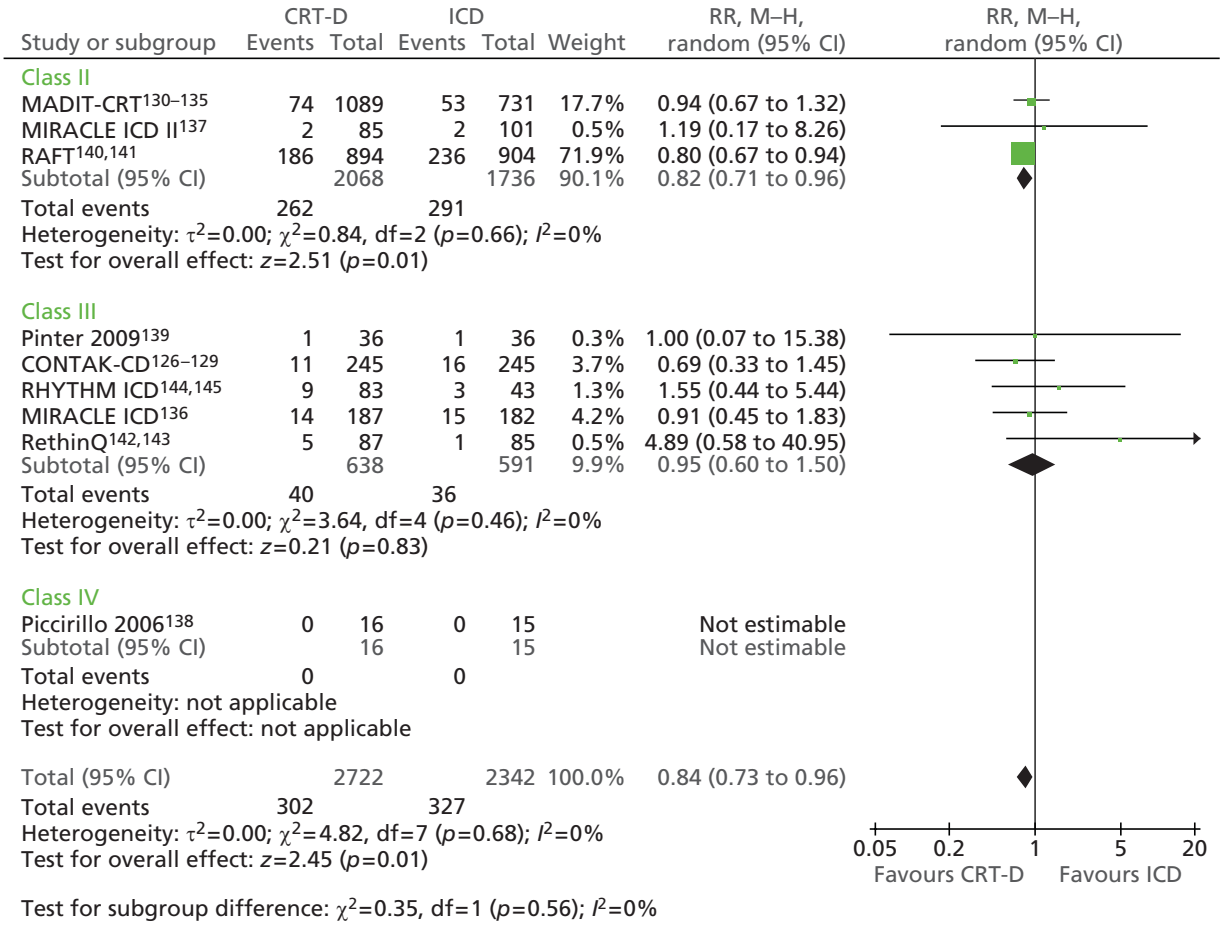

FIGURE 19 All-cause mortality.

Total cardiac deaths

Seven trials reported data on total cardiac deaths, although only one of these compared events between groups statistically (*Table 58*). The RAFT study[140] 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 RR was 0.82 (95% CI 0.67 to 1.00, $p = 0.05$) in favour of CRT-D (*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[140] 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[126]	3–6	7/245 (2.9)	10/245 (4.1)	RR 0.70[a]	0.27 to 1.81[a]
MIRACLE ICD II[137]	6	2/85 (2.4)	2/101 (2.0)	RR 1.19[a]	0.17 to 8.26[a]
Piccirillo[138]	12	0/16 (0)	0/15 (0)		
Pinter[139]	6	1/36 (2.8)	1/36 (2.8)	RR 1.00[a]	0.07 to 15.38[a]
RAFT[140]	Mean 40 (SD 20)	130/894 (14.5)	162/904 (17.9)	HR 0.76	0.60 to 0.96, 0.02
RethinQ[142]	6	4/87 (4.6)	1/85 (1.2)	RR 3.91[a]	0.45 to 34.26[a]
RHYTHM ICD[144]	6	1/83 (1.2)	1/43 (2.3)	RR 0.52[a]	0.03 to 8.08[a]

a Calculated by reviewer.

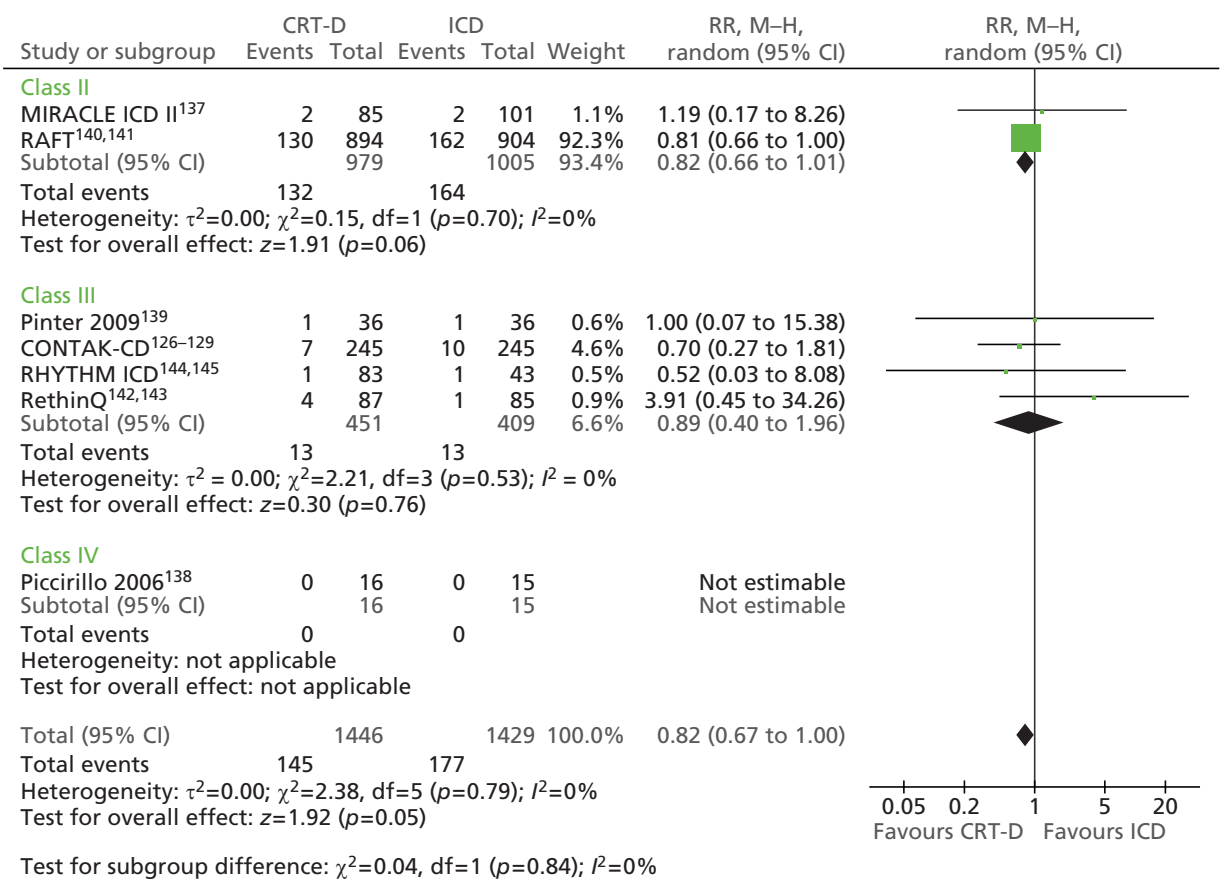

FIGURE 20 Total cardiac deaths.

Heart failure deaths

There were no deaths from HF in the MIRACLE ICD II study[137] of people with mild NYHA class II HF or in the small study by Piccirillo and colleagues[138] of people in NYHA class IV or III. The CONTAK-CD study,[126] in which the majority of participants had NYHA class III or II HF, reported deaths from HF 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[142] died from HF (*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	95% CI, *p*-value
CONTAK-CD[126]	3–6	4/245 (1.6)	9/245 (3.7)	RR 0.44[a]	0.14 to 1.42, 0.17[a]
MIRACLE ICD II[137]	6	0/85 (0)	0/101 (0)		
Piccirillo[138]	12	0/16 (0)	0/15 (0)		
RethinQ[142]	6	2/87 (2.3)	1/85 (1.2)	RR 1.95[a]	0.18 to 21.15, 0.58[a]

a Calculated by reviewer.

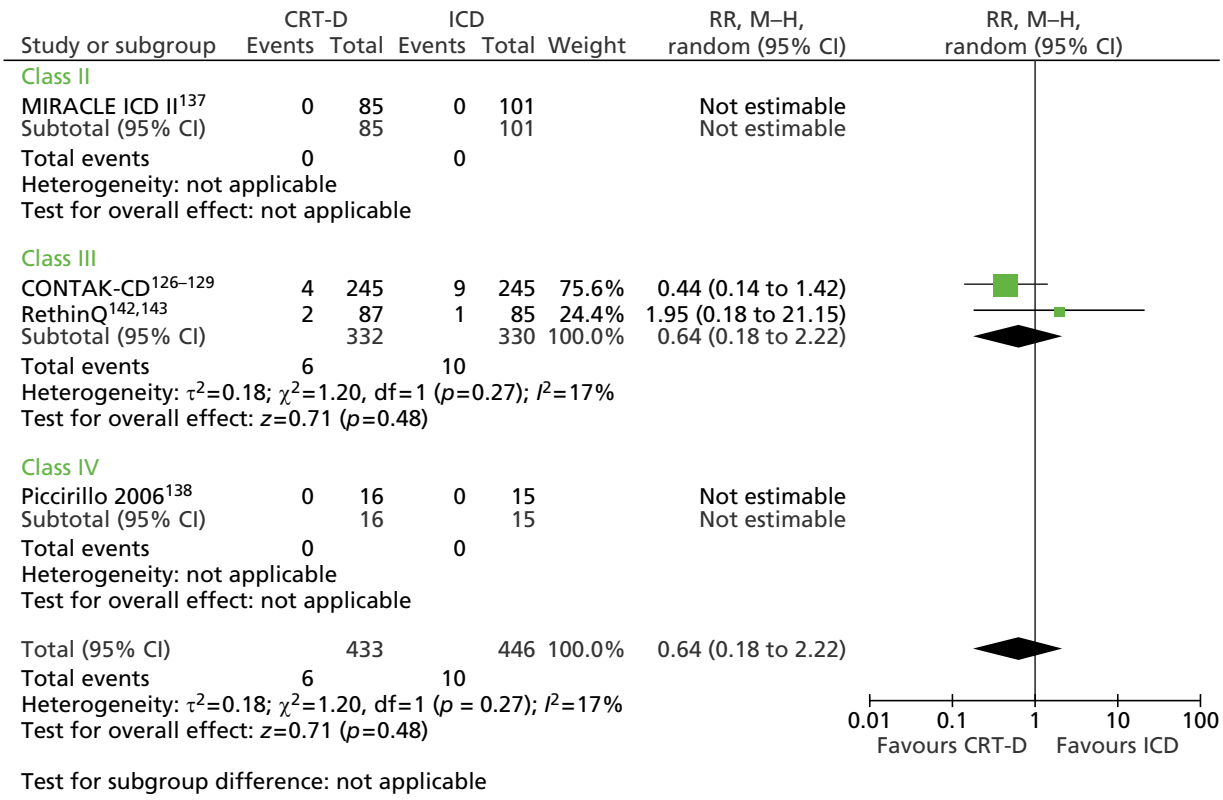

FIGURE 21 Heart failure deaths.

Sudden cardiac death

Six trials reported data on SCD (*Table 60*). No SCDs occurred in the small study by Piccirillo and colleagues[138] or in the RethinQ[142] or RHYTHM ICD[144] studies. Combining the other three trials[129,136,137] in a meta-analysis gives an overall RR of 1.45 (95% CI 0.43 to 4.92, $p = 0.55$), with no important statistical heterogeneity ($\chi^2 = 0.61$, df = 2, $I^2 = 0$) (*Figure 22*).

TABLE 60 Sudden cardiac death

Study	Follow-up (months)	CRT-D, *n/N* (%)	ICD, *n/N* (%)	Effect	95% CI, *p*-value
CONTAK-CD[129]	3–6	1/245 (0.4)	0/245 (0)	RR 3.00	0.12 to 73.28, 0.5[a]
MIRACLE ICD[136]	6	3/187 (1.6)	3/182 (1.6)	RR 0.97	0.2 to 4.76, 0.97[a]
MIRACLE ICD II[137]	6	2/85 (2.4)	1/101 (1.0)	RR 2.38	0.22 to 25.76, 0.48[a]
Piccirillo[138]	12	0/16 (0)	0/15 (0)		
RethinQ[143]	6	0/87 (0)	0/85 (0)		
RHYTHM ICD[144]	6	0/83 (0)	0/43 (0)		

a Calculated by reviewer.

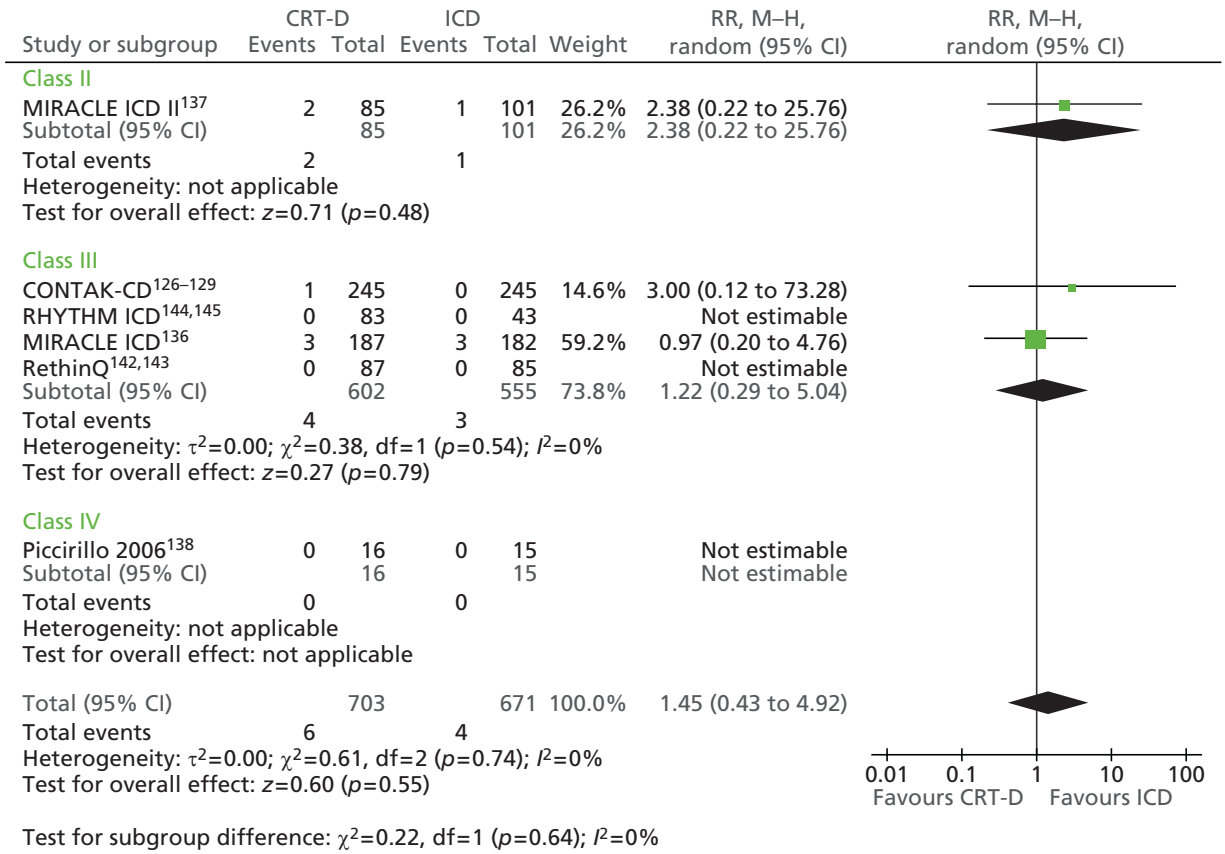

FIGURE 22 Sudden cardiac deaths.

Other causes of death

Deaths from non-cardiac causes were reported in the CONTAK-CD trial[129] (CRT-D 0.8% vs. ICD 1.2%) and the RHYTHM ICD study[144] (CRT-D 8.4% vs. ICD 4.7%). One (1.1%) death of unknown cause occurred in the CRT-D group of the RethinQ trial.[142] No deaths from non-cardiac causes occurred in the studies by Piccirillo and colleagues[138] or Pinter and colleagues[139] (*Table 61*).

Survival

No statistically significant difference in 6-month cumulative survival was found in the MIRACLE ICD study[136] (CRT-D 92.4% vs. ICD 92.2%, $p = 0.96$) or the RethinQ study[142] (CRT-D 94.2% vs. ICD 98.8%, $p = 0.11$), or in cumulative freedom from death caused by worsening HF in the RethinQ study[142] (CRT-D 97.7% vs. 98.9%, $p = 0.58$) (*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;[140] statistical significance was not reported.

TABLE 61 Other causes of death

Study	Follow-up (months)	Cause of death	CRT-D, *n/N* (%)	ICD, *n/N* (%)
CONTAK-CD[129]	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[137]	6	MI with cardiogenic shock	0/85 (0)	1/101 (1.0)
Piccirillo[138]	12	Non-cardiac	0/16 (0)	0/15 (0)
Pinter[139]	6	Non-cardiac	0/36 (0)	0/36 (0)
RethinQ[142]	6	Unknown	1/87 (1.1)	0/85 (0)
		Unknown cardiac	1/87 (1.1)	0/85 (0)
RHYTHM ICD[144]	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)

TABLE 62 Survival

Study	Outcome and follow-up	CRT-D	ICD	*p*-value
MIRACLE ICD[136]	6-month cumulative survival (95% CI), %	92.4 (87.5 to 95.4)	92.2 (87.2 to 95.3)	0.96
RAFT[140]	Probability of event-free survival at 5 years, %	57.6	48.7	
	5-year actuarial rate of death, %	28.6	34.6	
RethinQ[142]	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

Hospitalisations related to heart failure

The CONTAK-CD,[126] Piccirillo and colleagues[138] and RAFT[140] studies reported hospitalisations related to HF (*Table 63*); the MIRACLE ICD,[136] Pinter and colleagues[139] and RAFT[140] studies reported all-cause hospitalisations (see *Appendix 6*). The RAFT study[140] found a statistically significant reduction in hospitalisations for HF in the CRT-D group (CRT-D 19.5% vs. ICD 26.1%, HR 0.68, 95% CI 0.56 to 0.83, $p < 0.001$). The CONTAK-CD study[126] reported that 13.1% of the CRT-D group were hospitalised because of HF compared with 15.9% of the ICD group. Two people (13.3%) with an ICD and none of the CRT-D group were hospitalised because of HF in the small study by Piccirillo and colleagues.[138] When the studies were combined in a random-effects meta-analysis, CRT-D reduced the RR of HF hospitalisation by 25% compared with ICD therapy (RR 0.75, 95% CI 0.64 to 0.88, $p = 0.0005$) (*Figure 23*).

TABLE 63 Hospitalisation related to HF

Study	Outcome and follow-up	CRT-D, *n/N* (%)	ICD, *n/N* (%)	Effect	95% CI, *p*-value
CONTAK-CD[126]	At least one HF hospitalisation, 6 months	32/245 (13.1)	39/245 (15.9)	RR 0.82[a]	0.53 to 1.26, 0.37[a]
Piccirillo[138]	Hospitalisation because of worsening HF,	0/16 (0)	2/15 (13.3)	RR 0.19[a]	0.01 to 3.63, 0.27[a]
RAFT[140]	Hospitalisation for HF, mean 40 (SD 20) months	174/894 (19.5)	236/904 (26.1)	HR 0.68	0.56 to 0.83, < 0.001

a Calculated by reviewer.

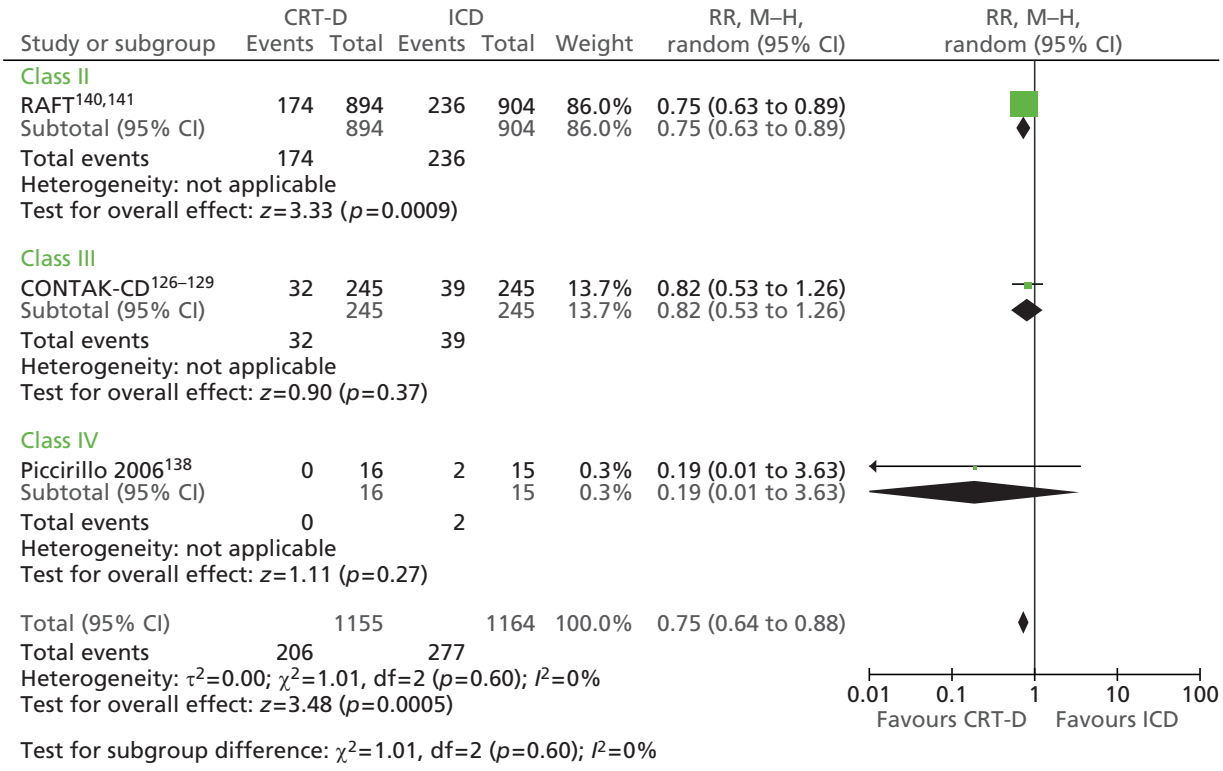

FIGURE 23 Heart failure hospitalisations.

Arrhythmias

The number of participants experiencing at least one episode of VT or VF can be seen in *Table 64*. The proportions appear similar between groups. Random-effects meta-analysis demonstrated no statistically significant difference between the groups 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 and follow-up	CRT-D, *n/N* (%)	ICD, *n/N* (%)	Effect	95% CI, *p*-value
CONTAK-CD[126]	At least one VT/VF event, 6 months	36/245 (14.7)	39/245 (15.9)	RR 0.92[a]	0.61 to 1.40, 0.71[a]
MIRACLE ICD[136]	At least one spontaneous episode of VT or VF, 6 months	42/187 (22)	47/182 (26)	RR 0.87[a]	0.61 to 1.25, 0.45,[a] 0.47[b]
MIRACLE ICD II[137]	At least one appropriately detected spontaneous episode of VT or VF, 6 months	19/85 (22)	26/101 (26)	RR 0.87[a]	0.52 to 1.46, 0.59,[a] 0.61[b]
Pinter[139]	VT event requiring therapy from the device, 6 months	7/36 (19.4)	6/36 (16.7)	RR 1.17[a]	0.43 to 3.13, 0.76,[a] NS[b]

NS, not significant.
a Calculated by reviewer.
b Statistical analysis reported in study report.

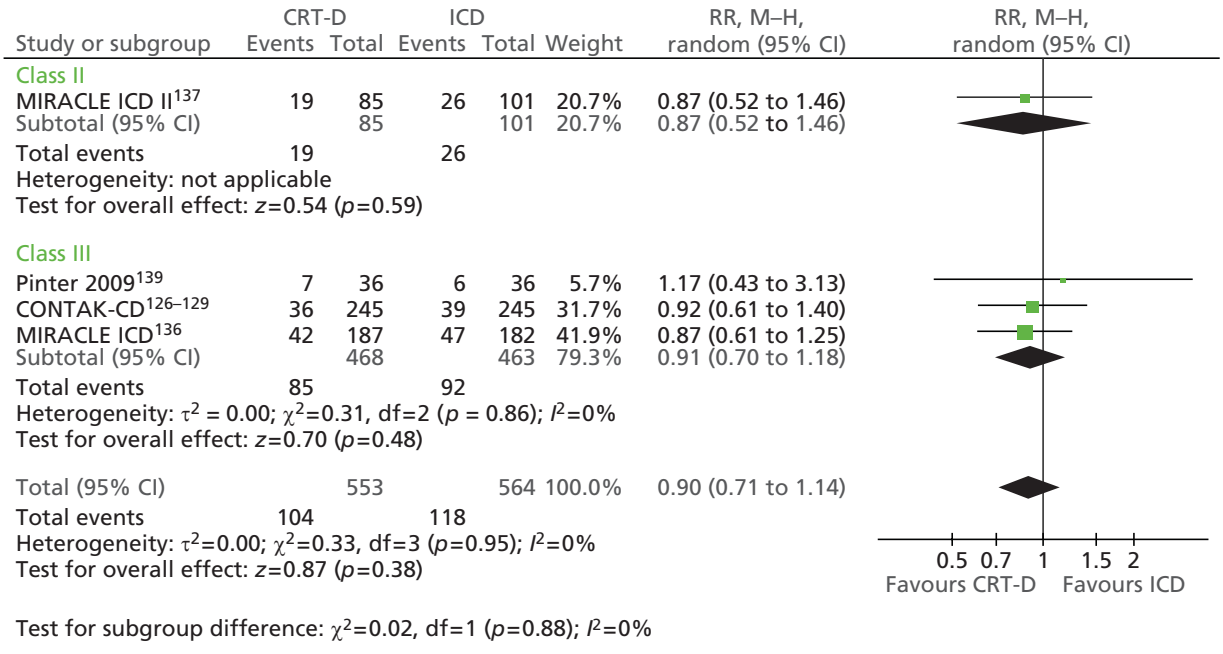

FIGURE 24 Arrhythmias.

New York Heart Association class

Six trials reported change in NYHA class; three reported mean or median change and three reported the number of participants who improved. The MIRACLE ICD,[136] MIRACLE ICD II[137] and RHYTHM ICD[144] trials reported a statistically significant improvement in mean or median NYHA class among people receiving CRT-D compared with people receiving and ICD (*Table 65*). Combining these studies in a random-effects meta-analysis gives a MD of –0.19 (95% CI –0.34 to –0.05, $p = 0.008$), although note that the MIRACLE ICD[136] trial is not estimable (*Figure 25*). A significantly greater proportion of the CRT-D group improved by one class or more in the RethinQ trial[142] (CRT-D 54% vs. ICD 29%, $p = 0.006$), and the majority (81%) of the participants in the CRT-D group in the study by Piccirillo and colleagues[138] showed an improvement in NYHA class, compared with only 7% of those in the ICD group (see *Table 65*); however, there is some uncertainty surrounding these data because of a discrepancy in reporting in the paper (see *Appendix 9*). In the CONTAK-CD trial[126] there was no statistically significant difference in the number of people who showed an 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, $p = 0.09$) (*Figure 26*).

TABLE 65 New York Heart Association class

Study	Outcome and follow-up	CRT-D, *n/N* (%)	ICD, *n/N* (%)	*p*-value
CONTAK-CD[126]	6 months			
	Improved by two classes	12[a]/109 (11)	2[a]/116 (2)	
	Improved by one 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[136]	Change in NYHA class, 6 months	($n = 165$) 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[137]	Change in NYHA class, 6 months	($n = 82$) mean –0.18 (SD 0.61)	($n = 98$) mean 0.01 (SD 0.63)	0.05
Piccirillo[138]	12 months			
	Improved by two classes[b]	5/16 (31.3)	0/15 (0)	
	Improved by one 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[142]	6 months			
	Improved by one or more class	41/76 (54)	23/80 (29)	0.006
	No change	31/76 (41)	51/80 (64)	
	Worsened	4/76 (5)	6/80 (8)	
RHYTHM ICD[144]	Change in NYHA class, 6 months	($n = 83$) mean –0.48 (SD 0.65)	($n = 43$) mean –0.28 (SD 0.63)	0.048

a Calculated by reviewer.
b Calculated by reviewer from information in text of paper; note that text does not correspond with table in paper.

Study or subgroup	CRT-D Mean	CRT-D SD	CRT-D Total	ICD Mean	ICD SD	ICD Total	Weight	MD, IV, random (95% CI)
Class II								
MIRACLE ICD II[137]	−0.18	0.61	82	0.01	0.63	98	62.5%	−0.19 (−0.37 to −0.01)
Subtotal (95% CI)			82			98	62.5%	−0.19 (−0.37 to −0.01)
Heterogeneity: not applicable								
Test for overall effect: $z=2.05$ ($p=0.04$)								
Class III								
MIRACLE ICD[136]	−1	0	165	0	3.2	162		Not estimable
RHYTHM ICD[144,145]	−0.48	0.65	83	−0.28	0.63	43	37.5%	−0.20 (−0.43 to 0.03)
Subtotal (95% CI)			248			205	37.5%	−0.20 (−0.43 to 0.03)
Heterogeneity: not applicable								
Test for overall effect: $z=1.67$ ($p=0.09$)								
Total (95% CI)			330			303	100.0%	−0.19 (−0.34 to −0.05)
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.00$, df=1 ($p=0.95$); $I^2=0\%$								
Test for overall effect: $z=2.64$ ($p=0.008$)								
Test for subgroup difference: $\chi^2=0.00$, df=1 ($p=0.95$); $I^2=0\%$								

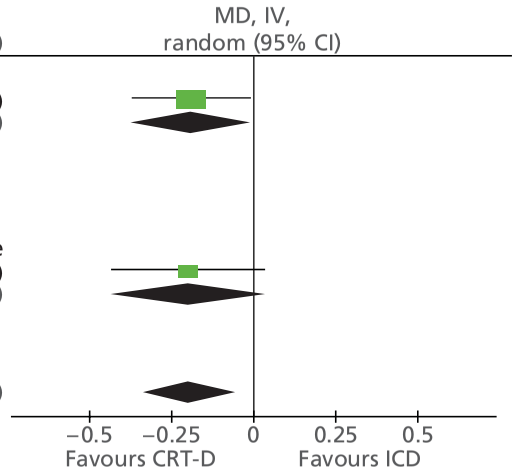

FIGURE 25 Change in NYHA class.

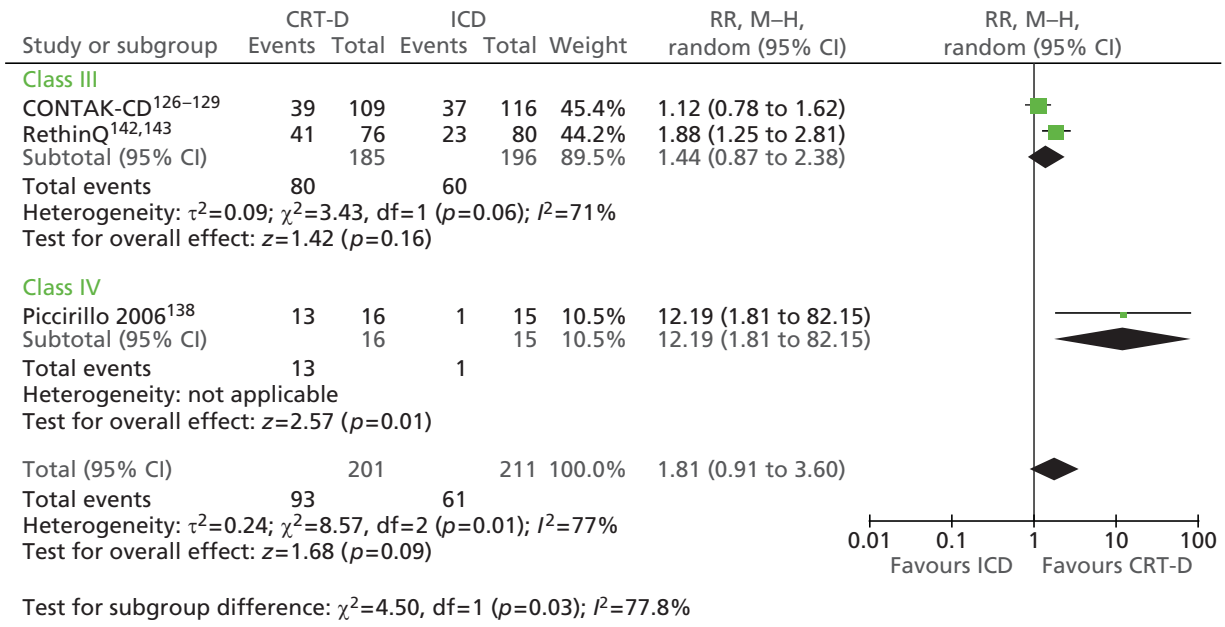

FIGURE 26 Proportion of people with improvement in NYHA class.

Worsening heart failure

The MADIT-CRT trial[130] reported a statistically significant reduction in the number of people experiencing a non-fatal HF event in the CRT-D group compared with the ICD group (CRT-D 13.9% vs. ICD 22.8%, HR 0.59, 95% CI 0.47 to 0.74, $p < 0.001$). Fewer HF events requiring intravenous therapy occurred in the CRT-D group (24 events in 16.1% of patients) than in the ICD group (41 events in 22.3% of patients) in the RethinQ trial.[142] Worsening HF (other than that defined by change in NYHA class; see previous section) was not reported by the other trials.

Left ventricular ejection fraction

Three[126,130,137] of the eight trials reporting LVEF described a statistically significant improvement in mean LVEF among people receiving CRT-D compared with those receiving an ICD, whereas three[136,139,142] trials reported no statistically significant difference between the groups in change from baseline (*Table 66*). The study by Piccirillo and colleagues[138] and the RHYTHM ICD study[144] did not provide a statistical comparison. Combining the trials in a meta-analysis showed a statistically significant improvement in LVEF in the CRT-D group compared with the ICD group (MD 2.15, 95% CI 0.45 to 3.86, $p = 0.01$) (*Figure 27*). There is substantial statistical heterogeneity ($\chi^2 = 21.12$, df = 7, $I^2 = 67\%$); however, the direction of the effect is fairly consistent between studies.

TABLE 66 Left ventricular ejection fraction

Study	Outcome and follow-up	CRT-D	ICD	Effect	95% CI, *p*-value
CONTAK-CD[126]	Change in LVEF (%), 6 months	(*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] 0.020[c]
MADIT-CRT[130]	Change in LVEF (%), average 2.4 years	(*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] < 0.001[c]
MIRACLE ICD[136]	Change in LVEF (%), 6 months	(*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] 0.12[c]
MIRACLE ICD II[137]	Change in LVEF (%), 6 months	(*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] 0.02[c]
Piccirillo[138]	LVEF (%) at 12 months	(*n* = 16) mean 28 (SD 4)	(*n* = 15) mean 22 (SD 8)	MD 6.00[b]	1.50 to 10.50, 0.009[b]
Pinter[139]	Change in LVEF (%), 6 months				
	Measured by MUGA	(*n* = 36) mean 1.7 (SD 5.4)	(*n* = 36) mean 0.6 (SD 6.8)		NS
	Measured by ECG	(*n* = 36) mean 3.9 (SD 8.9)	(*n* = 36) mean 1.9 (SD 6.8)	MD 2.00[b]	–1.66 to 5.66, 0.28,[b] NS[c]
RethinQ[142]	Change in LVEF (%), 6 months	(*n* = 68) median 1.2 (95% CI –0.4 to 4.4; SD 9.9[a])	(*n* = 74) median 2.0 (95% CI 0.3 to 4.2; SD 4.2[a])	MD 0.80[b]	3.83 to 2.23, 0.61,[b] 0.83[c]
RHYTHM ICD[144]	Change in LVEF (%), 6 months	(*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]

MUGA, multigated acquisition; NS, not significant.
a SD calculated by reviewer.
b Calculated by reviewer.
c Statistical analysis reported in trial.

Study or subgroup	CRT-D Mean	CRT-D SD	CRT-D Total	ICD Mean	ICD SD	ICD Total	Weight	MD, IV, random (95% CI)
Class II								
MADIT-CRT[130–135]	11	44.6	746	3	44.6	620	7.9%	8.00 (3.25 to 12.75)
MIRACLE ICD II[137]	3.8	8	68	0.8	6.2	85	14.8%	3.00 (0.69 to 5.31)
Subtotal (95% CI)			814			705	22.6%	5.05 (0.23 to 9.87)
Heterogeneity: $\tau^2 = 8.87$; $\chi^2 = 3.44$, df = 1 ($p = 0.06$); $I^2 = 71\%$								
Test for overall effect: $z = 2.05$ ($p = 0.04$)								
Class III								
Pinter 2009[139]	3.9	8.9	36	1.9	6.8	36	10.5%	2.00 (–1.66 to 5.66)
CONTAK-CD[126–129]	5.1	10.4	222	2.8	10.3	216	16.1%	2.30 (0.36 to 4.24)
RHYTHM ICD[144,145]	4.3	9.9	83	2.9	6.2	43	13.0%	1.40 (–1.42 to 4.22)
MIRACLE ICD[136]	1.2	8.4	132	1.7	5	133	17.0%	–0.50 (–2.17 to 1.17)
RethinQ[142,143]	1.2	9.9	68	2	8.4	74	12.4%	–0.80 (–3.83 to 2.23)
Subtotal (95% CI)			541			502	69.0%	0.79 (–0.58 to 2.16)
Heterogeneity: $\tau^2 = 0.86$; $\chi^2 = 6.27$, df = 4 ($p = 0.18$); $I^2 = 36\%$								
Test for overall effect: $z = 1.13$ ($p = 0.26$)								
Class IV (Final value)								
Piccirillo 2006[138]	28	4	16	22	8	15	8.4%	6.00 (1.50 to 10.50)
Subtotal (95% CI)			16			15	8.4%	6.00 (1.50 to 10.50)
Heterogeneity: not applicable								
Test for overall effect: $z = 2.61$ ($p = 0.009$)								
Total (95% CI)			1371			1222	100.0%	2.15 (0.45 to 3.86)
Heterogeneity: $\tau^2 = 3.71$; $\chi^2 = 21.12$, df = 7 ($p = 0.004$); $I^2 = 67\%$								
Test for overall effect: $z = 2.48$ ($p = 0.01$)								
Test for subgroup difference: χ^2=6.96, df=2 (p=0.03); I^2=71.3%								

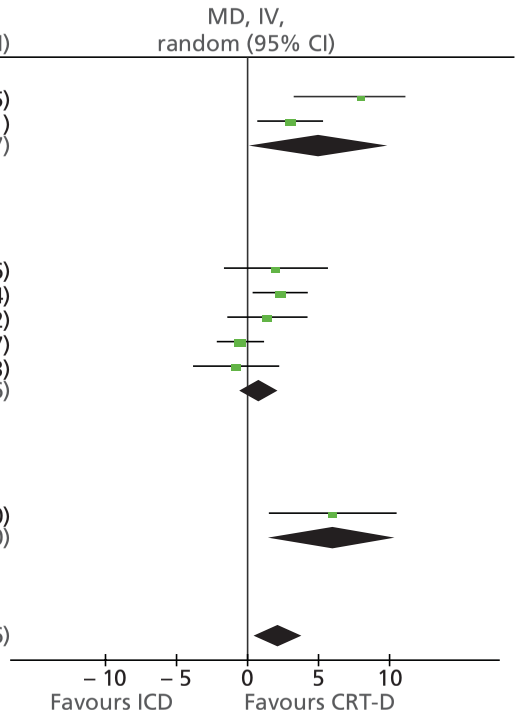

FIGURE 27 Change in LVEF.

Exercise capacity

Exercise capacity was reported by six of the eight trials, with six studies measuring distance walked in 6 minutes and two trials measuring exercise duration, five trials measuring peak VO_2 and one trial reporting the proportion of participants with an increase of at least 1.0 ml/kg body weight/minute in peak oxygen consumption (*Table 67*). The CONTAK-CD trial[126] found improvements in both peak VO_2 and distance walked in 6 minutes, which were statistically significantly greater in the CRT-D group than in the ICD group. The MIRACLE ICD[136] and RHYTHM ICD[144] trials found statistically significant improvements in peak VO_2 but not distance walked in 6 minutes; the MIRACLE ICD[136] trial also found significant improvements in exercise duration in favour of CRT-D. The MIRACLE ICD II trial[137] (mild HF) 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 compared with ICD. The RethinQ trial[142] found no statistically significant differences in distance walked in 6 minutes or the proportion of participants with

TABLE 67 Exercise capacity

Study	Outcome and follow-up	CRT-D	ICD	*p*-value
CONTAK-CD[126]	Change in peak VO_2 (ml/kg/minute), 3–6 months	(*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 distance (m), 3–6 months	(*n* = 224) mean 35 (SE 7; SD 104.8[a])	(*n* = 220) mean 15 (SE 7; SD 103.8[a])	0.043
MIRACLE ICD[136]	Change in 6-minute walk distance (m), 6 months	(*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/minute), 6 months	(*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 (seconds), 6 months	(*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[137]	Change in peak VO_2 (ml/kg/minute), 6 months	(*n* = 66) mean 0.5 (SD 3.2)	(*n* = 79) mean 0.2 (SD 3.2)	0.87
	Change in exercise duration (seconds), 6 months	(*n* = 66) mean 42 (SD 167)	(*n* = 79) mean 37 (SD 186)	0.56
	Change in VE/VCO_2 (ml/minute), 6 months	(*n* = 66) mean –1.8 (SD 6.2)	(*n* = 78) mean 0.5 (SD 5.2)	0.01
	Change in 6-minute walk distance (m), 6 months	(*n* = 78) mean 38 (SD 109)	(*n* = 93) mean 33 (SD 98)	0.59
Pinter[139]	Change in 6-minute walk distance (m), 6 months[b]	(*n* = 36) mean 53.3 (SD 113.3)	(*n* = 36) mean 27.3 (SD 71.1)	NS
RethinQ[142]	Change in peak VO_2 (ml/kg/minute), 6 months	(*n* = 76) median 0.4 (95% CI –0.6 to 1.2) (SD 3.9[a])	(*n* = 80) median 0.5 (95% CI –0.3 to 1.1) (SD 3.1[a])	
	Peak VO_2, increase ≥ 1.0 ml/kg/minute, *n*/*N* (%), 6 months	(*n* = 76) 35/76 (46)	(*n* = 80) 33/80 (41)	0.63
	Change in 6-minute walk distance (m), 6 months	(*n* = 75) median 26 (95% CI 0 to 46) (SD 100[a])	(*n* = 79) median 6 (95% CI –17 to 30) (SD 104.9[a])	0.23
RHYTHM ICD[144]	Change in peak VO_2 (ml/kg/minute), 6 months	(*n* = 83) mean 0.52 (SD 2.5)	(*n* = 43) mean –1.41 (SD 4.6)	0.001
	Change in 6-minute walk distance (m), 6 months	(*n* = 83) mean 13 (SD 74)	(*n* = 43) mean –15 (SD 142)	0.07

NS, not significant; VE/VCO_2, ventilatory response to exercise (minute ventilation/minute carbon dioxide production).
a SD calculated by reviewer.
b Assumed values are mean (SD) but this is not specified in the paper.

an increase of at least 1.0 ml/kg body weight/minute in peak VO_2. There was no statistically significant difference in the change in 6 minute-walk distance in the study by Pinter and colleagues.[139]

Meta-analysis of these trials demonstrated that the change from baseline in peak VO_2 (MD 0.75 ml/kg/minute, 95% CI 0.23 to 1.27 ml/kg/minute, $p = 0.005$) (*Figure 28*) and distance walked in 6 minutes (MD 14.5 m, 95% CI 2.9 to 26.1 m, $p = 0.01$) (*Figure 29*) were statistically significantly greater in the CRT-D group than in the ICD group. There was little statistical heterogeneity in these studies and, although the MIRACLE ICD[136] and RethinQ[142] trials report medians and not means, the difference remains statistically significant when these studies are omitted.

Quality of life

Six[126,136,137,139,142,144] of the eight trials reported change in QoL at 6 months, assessed using the MLWHFQ (*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 and colleagues[139] also reported the DASI, the one-item Global Visual Analogue Scale and the SF-36. Comparisons of baseline to 6-month changes were statistically significantly different for the general health component of the SF-36 only [CRT-D –5.8 (SD 14.9) vs. ICD –5.8 (SD 13.6), $p = 0.02$].

Adverse events

As described earlier, three[130,138,140] of the trials compared CRT-D and ICD devices whereas all participants in the six remaining trials[126,136,137,139,142,144] 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 be assessed only in the former three trials and, of these, only the MADIT-CRT[130] and RAFT[140] trials 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 who had implantation attempted, as in six of the trials only those with successful implantation were randomised. However, adverse event data were reported for all participants who underwent implantation or attempted implantation in the CONTAK-CD,[126] MADIT-CRT,[130] MIRACLE ICD,[136] MIRACLE ICD II,[137] RAFT[140] and RHYTHM ICD[144] studies. The MIRACLE ICD[136] and MIRACLE ICD II[137] studies also reported total complications for those with successful implants.

Five[125,136,137,142,144] of the trials using the same device in all participants, that is, CRT on compared with CRT off, reported adverse events for both interventions combined (*Table 70*). The MIRACLE ICD trial[136] also reported adverse events separately for the CRT on and CRT off groups, as did the MADIT-CRT[130] and RAFT[140] trials for the CRT-D and ICD groups (*Table 71*). Adverse events were not reported in the study by Pinter and colleagues,[139] and Piccirillo and colleagues[138] 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[136,137,139,144] clearly described the implantations as successful (83.3–91%).

Perioperative deaths occurred in between 0.1% (MADIT-CRT[130]) and 2.4% (RHYTHM ICD[144]) of participants (see *Tables 70* and *71*), although it is not clear whether or not 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,[140,142,144] and the overall lead-related adverse event rate was 14.5% in the CONTAK-CD trial.[126] The MIRACLE ICD[136] and MIRACLE ICD II[137] trials reported the proportion of complications that were related to the left ventricular lead before hospital discharge (23% of 159 complications and 34% of 56 complications respectively). In total, 4% of people receiving CRT-D in the MADIT-CRT trial[130] had the left ventricular lead repositioned during the first 30 days (see *Table 71*).

Study or subgroup	CRT-D Mean	CRT-D SD	CRT-D Total	ICD Mean	ICD SD	ICD Total	Weight	MD, IV, random (95% CI)
Class II								
MIRACLE ICD II[137]	0.5	3.2	66	0.2	3.2	79	17.6%	0.30 (–0.75 to 1.35)
Subtotal (95% CI)			66			79	17.6%	0.30 (–0.75 to 1.35)
Heterogeneity: not applicable								
Test for overall effect: z=0.56 (p=0.57)								
Class III								
CONTAK-CD[126–129]	0.8	4.4	216	0	4.3	201	23.7%	0.80 (–0.04 to 1.64)
RHYTHM ICD[144,145]	0.52	2.5	83	–1.41	4.6	43	10.4%	1.93 (0.45 to 3.41)
MIRACLE ICD[136]	1.1	2.5	120	0.1	2.5	121	32.1%	1.00 (0.37 to 1.63)
RethinQ[142,143]	0.4	3.9	76	0.5	3.1	80	16.2%	–0.10 (–1.21 to 1.01)
Subtotal (95% CI)			495			445	82.4%	0.84 (0.23 to 1.46)
Heterogeneity: τ^2=0.16; χ^2=5.10, df=3 (p=0.16); I^2=41%								
Test for overall effect: z = 2.69 (p=0.007)								
Total (95% CI)			561			524	100.0%	0.75 (0.23 to 1.27)
Heterogeneity: τ^2=0.12; χ^2=6.03, df=4 (p=0.20); I^2=34%								
Test for overall effect: z=2.80 (p=0.005)								
Test for subgroup difference: χ^2=0.77, df=1 (p=0.38); I^2=0%								

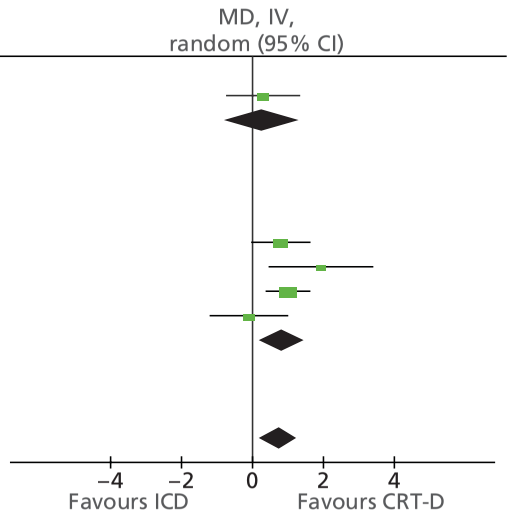

FIGURE 28 Change in peak VO_2.

Study or subgroup	CRT-D Mean	CRT-D SD	CRT-D Total	ICD Mean	ICD SD	ICD Total	Weight	MD, IV, random (95% CI)
Class II								
MIRACLE ICD II[137]	38	109	78	33	98	93	13.7%	5.00 (–26.33 to 36.33)
Subtotal (95% CI)			78			93	13.7%	5.00 (–26.33 to 36.33)
Heterogeneity: not applicable								
Test for overall effect: z=0.31 (p=0.75)								
Class III								
Pinter 2009[139]	53.3	113.3	36	27.3	71.1	36	7.0%	26.00 (–17.69 to 69.69)
CONTAK-CD[126–129]	35	104.8	224	15	103.8	220	35.7%	20.00 (0.60 to 39.40)
RHYTHM ICD[145,146]	13	74	83	–15	142	43	6.5%	28.00 (–17.33 to 73.33)
MIRACLE ICD[135]	55	109.2	152	53	100.2	153	24.3%	2.00 (–21.53 to 25.53)
RethinQ[142,143]	26	100	75	6	104.9	79	12.8%	20.00 (–12.36 to 52.36)
Subtotal (95% CI)			570			531	86.3%	16.04 (3.56 to 28.51)
Heterogeneity: τ^2=0.00; χ^2=2.05, df=4 (p=0.73); I^2=0%								
Test for overall effect: z=2.52 (p=0.01)								
Total (95% CI)			648			624	100.0%	14.53 (2.94 to 26.11)
Heterogeneity: τ^2=0.00; χ^2=2.46, df=5 (p=0.78); I^2=0%								
Test for overall effect: z=2.46 (p=0.01)								
Test for subgroup difference: χ^2=0.41, df=1 (p=0.52); I^2=0%								

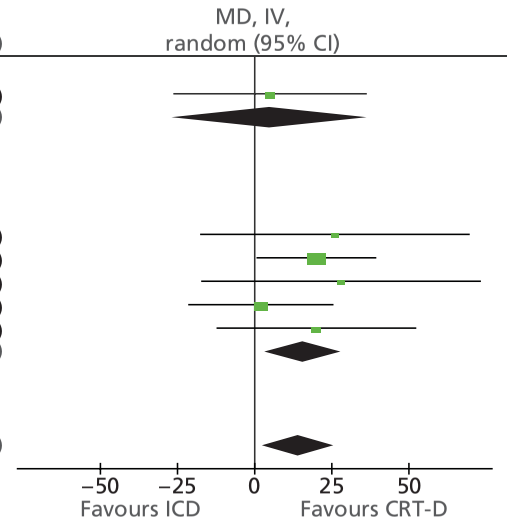

FIGURE 29 Change in 6-minute walk distance.

TABLE 68 Quality of life

Study	Outcome[a] and follow-up	CRT-D	ICD	*p*-value
CONTAK-CD[126]	Change in MLWHFQ score, 6 months	(*n* = 234) mean –7 (SE 2) (SD 30.6[b])	(*n* = 255) mean 5 (SE 2) (SD 31.9[b])	0.39[c]
MIRACLE ICD[136]	Change in MLWHFQ score, 6 months	(*n* = 162) median –17.5 (95% CI –21 to –14) (SD 22.6[b])	(*n* = 157) median –11 (95% CI –16 to –7) (SD 28.5[b])	0.02
MIRACLE ICD II[137]	Change in MLWHFQ score, 6 months	(*n* = 81) mean –13.3 (SD 25.1)	(*n* = 96) mean –10.7 (SD 21.7)	0.49
Pinter[139]	Change in score, 6 months[d]			
	DASI	(*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
	MLWHFQ, 6 months			
	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[d]			
	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
	PCS	(*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
	MCS	(*n* = 36) mean 5.1 (SD 10.1)	(*n* = 36) mean 0.5 (SD 12.4)	NS
RethinQ[142]	Change in MLWHFQ score, 6 months	(*n* = 76) median –8 (95% CI –10 to –1) (SD 19.7[b])	(*n* = 80) median –7 (95% CI –11 to 3) (SD 31.5[b])	0.91
RHYTHM ICD[144]	Change in MLWHFQ score, 6 months	(*n* = 83) mean –7.8 (SD 22)	(*n* = 43) mean 3.4 (SD 31)	0.009

NS, not significant.
a For the MLWHFQ, more negative change scores indicate greater improvement.
b SD calculated by reviewer.
c Reported as not statistically significant in the paper but statistically significant in meta-analysis ($p < 0.0001$).[126]
d Assumed values are mean (SD) but not always stated.

Study or subgroup	CRT-D Mean	CRT-D SD	CRT-D Total	ICD Mean	ICD SD	ICD Total	Weight	MD, IV, random (95% CI)
Class II								
MIRACLE ICD II[137]	–13.3	25.1	81	–10.7	21.7	96	17.3%	–2.60 (–9.58 to 4.38)
Subtotal (95% CI)			81			96	17.3%	–2.60 (–9.58 to 4.38)
Heterogeneity: not applicable								
Test for overall effect: $z = 0.73$ ($p = 0.47$)								
Class III								
Pinter 2009[139]	–7.8	20.1	36	–0.2	13.5	36	14.5%	–7.60 (–15.51 to 0.31)
CONTAK-CD[126–129]	–7	30.6	234	5	31.9	225	22.4%	–12.00 (–17.72 to –6.28)
RHYTHM ICD[144,145]	–7.8	22	83	3.4	31	43	9.4%	–11.20 (–21.60 to –0.80)
MIRACLE ICD[136]	–17.5	22.6	162	–11	28.5	157	22.7%	– 6.50 (–12.16 to –0.84)
RethinQ[142,143]	–8	19.7	76	–7	31.5	80	13.7%	–1.00 (–9.20 to 7.20)
Subtotal (95% CI)			591			541	82.7%	–7.83 (–11.53 to –4.12)
Heterogeneity: $\tau^2 = 4.42$; $\chi^2 = 5.32$, df = 4 ($p = 0.26$); $I^2 = 25\%$								
Test for overall effect: $z = 4.14$ ($p < 0.0001$)								
Total (95% CI)			672			637	100.0%	– 6.90 (–10.41 to – 3.40)
Heterogeneity: $\tau^2 = 5.78$; $\chi^2 = 7.19$, df = 5 ($p = 0.21$); $I^2 = 30\%$								
Test for overall effect: $z = 3.86$ ($p = 0.0001$)								
Test for subgroup difference: χ^2=1.68, df=1 (p=0.19); I^2=40.5%								

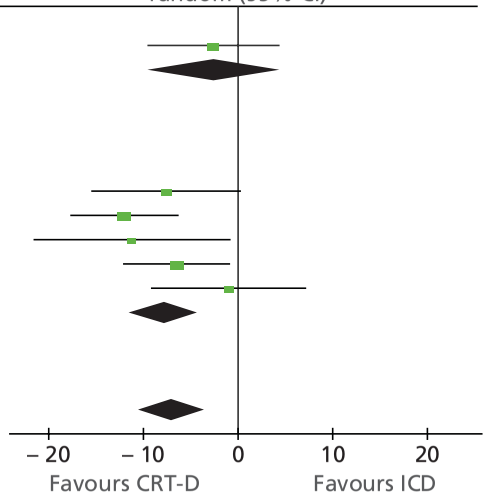

FIGURE 30 Change in MLWHFQ score.

TABLE 69 Flow of participants through the studies

	CONTAK CD[126]	MADIT-CRT[130]	MIRACLE ICD[136]	MIRACLE ICD II[137]	Piccirillo[138]	Pinter[139]	RAFT[140]	RethinQ[142]	RHYTHM ICD[144]
Enrolled, *n*	581	1820	429	222			1798	250	205
Attempted implantation, *n*	567	Unclear[a]	429	210		90	Unclear[b]	250[c]	205
Implanted, *n*/*N* (%)	501/567 (88.4)	1790/1820 (98.4)[d]	379/429 (88.3)[e]	191/210 (91.0)[e]		75/90 (83.3)[e]	1787/1798 (99.4)[f]	Unclear[c]	182/205 (88.8)[e]
Randomised, *n*	490	1820	369	186	31	72	1798	172	179
Only successful implants randomised?	Yes	No	Yes	Yes	Unclear	Yes	No	Yes	Yes
Efficacy analysis, *n*	490	1820	369	186	31	72	1798	156	126

a Paper states that 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 and lack of venous access; unclear whether the last two were before/during implantation attempt.
c Paper states that 4/250 (1.6%) did not undergo successful implantation but unclear whether successful implantation occurred in the remaining 246/250 patients (two died and three 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 841/888 (94.7%) attempted implants in CRT-D group.
Note: shaded squares show points at which adverse event data were reported.

TABLE 70 Adverse events reported for study population

Study	Adverse events	*n/N* (%) (95% CI)
CONTAK-CD[126,129]		
Attempted implantation (*n* = 567)	Operative mortality	12/567 (2.1) (0.9 to 3.3)
	Overall lead-related adverse event rate	75/517[a] (14.5) (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[136]		
Attempted implantation (*n* = 429)	Experienced complication from implant to hospital discharge	120/429 (28) (159 complications)
	Complication related to left ventricular lead	37/159 (23% of complications) (included 15 coronary sinus dissections and four cardiac perforations)
	HF decompensation	6/429 (received intravenous 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)
	Haemo/pneumothorax	3/429 (placement of chest tube)
	VT and VF	5/429 (three received external defibrillation, two received intravenous medication)
	Elevated pacing thresholds or loss of capture	7/429 (six received lead repositioning, one had set screw tightened in connector block)
	Died within 30 days of latest implant attempt	5/429 (1.2)
Successful implantation (*n* = 379)	From hospital discharge to the 6-month follow-up, total complications	175/379 (46) (398 complications)
MIRACLE ICD II[137]		
Attempted implantation (*n* = 210)	Died (before randomisation)	1/210
	From implant to hospital discharge	46/210 (22) (56 complications)
	Complications related to placement of left ventricular lead	19/56 (34% of complications) (including three coronary sinus dissections, three cardiac perforations and five lead dislodgements)
	Failed initial implant attempt[b]	23/210
Successful implantation (*n* = 191)[b]	From hospital discharge to 6 months	66/191 (35) (109 complications)
	Complications related to left ventricular lead	19/109 (17) (including 11 lead dislodgements, one cardiac perforation, three with diaphragmatic muscle stimulation and four elevated pacing thresholds)

TABLE 70 Adverse events reported for study population (*continued*)

Study	Adverse events	*n*/*N* (%) (95% CI)
RethinQ[142]		
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 haematoma	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[144]		
Enrolled patients ($n = 205$), average 12.1 (SD 3.4) patient-months' follow-up	Death (before randomisation or unsuccessful implant)	5/205 (2.4)
	Total complications (adverse events requiring invasive intervention)	21/205 (10.2) (29 events)
	Coronary sinus perforation/dissection	2 (1.0) (two events)
	Diaphragmatic/phrenic nerve stimulation	3 (1.5) (three events)
	Lead dislodgement or migration	8 (3.9) (nine events)
	Bleeding/haematoma	6 (2.9) (six events)
	Blood clot/thrombosis	1 (0.5) (one event)
	High defibrillation/ cardioversion requirements	2 (1.0) (two events)
	Infection	1 (0.5) (one event)
	Noise on EGM post shock (non-SJM right ventricular lead)	1 (0.5) (one event)
	Pneumothorax	2 (1.0) (two events)
	Retained foreign body (surgical sponge)	1 (0.5) (one event)
	Elevated pacing threshold – left ventricular lead	1 (0.5) (one event)
	Total observations (adverse events managed without invasive intervention)	57 (27.8) (68 events)
	Asystolic episode during left ventricular lead placement	1 (0.5) (one event)
	Bleeding/haematoma	10 (4.9) (10 events)
	Blood clot/thrombosis	2 (1.0) (two events)

continued

TABLE 70 Adverse events reported for study population (*continued*)

Study	Adverse events	*n*/*N* (%) (95% CI)
	Coronary sinus perforation/dissection	6 (2.9) (six events)
	Diaphragmatic/phrenic nerve stimulation – left ventricular lead	10 (4.9) (10 events)
	Diaphragmatic/phrenic nerve stimulation – right ventricular lead	2 (1.0) (two events)
	Elevated pacing thresholds – left ventricular lead	10 (4.9) (10 events)
	Elevated pacing thresholds – right ventricular lead	2 (1.0) (two events)
	Heart block at implant	2 (1.0) (two events)
	High defibrillation/ cardioversion requirements	1 (0.5) (one event)
	Hypotension requiring ventilator support	1 (0.5) (one event)
	Inappropriate therapy for SVT	10 (4.9) (13 events)
	Infection	3 (1.5) (three events)
	Possible pulmonary embolism	1 (0.5) (one event)
	T-wave sensing	2 (1.0) (three events)
	Pocket inflammation/seroma	1 (0.5) (one event)
	Left ventricular 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
Enrolled patients ($n = 205$), average 15.1 (SD 4.1) patient-months' follow-up	Total complications[c]	22/205 (10.7) (31events)
	Lead dislodgement or migration	9 (4.4) (10 events)
	Infection	2 (1.0) (two events)
	Total observations[c]	59 (28.8) (76 events)
	Diaphragmatic/phrenic nerve stimulation – left ventricular lead	14 (6.8) (14 events)
	Elevated pacing thresholds – left ventricular lead	12 (5.9) (12 events)
	Inappropriate therapy for SVT	11 (5.4) (14 events)
	Infection	4 (2.0) (four events)

EGM, electrogram; SJM, St Jude Medical; SVT, supraventricular tachycardia.
a 517 patients who had an attempted implant procedure with EASYTRAK leads, 448 with successful EASYTRAK lead implant.
b Paper states that 191/210 (91%) patients were successfully implanted, but also states that 23/210 failed the initial implant (210–23 = 187); there were also four patients with left ventricular lead dislodgements that were not corrected and were therefore not randomised.
c Only those observations with added data detailed here.[145]

TABLE 71 Adverse events reported by intervention

Study	Adverse event	CRT-D, *n*/*N* (%)	ICD, *n*/*N* (%)	Effect	95% CI, *p*-value
MADIT-CRT[130]					
Enrolled and randomised (*n* = 1820; CRT-D *n* = 1089, ICD *n* = 731)	Death in hospital after device implantation	1/1089 (pulmonary embolus)	0/731		
	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)	NA		
	Left ventricular coronary vein lead repositioned during first 30 days	44/1089 (4.0)	NA		
	Frequency of serious device-related adverse events during long-term follow-up after the first 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[136]					
		CRT on, *n*/*N* (%)	CRT off, *n*/*N* (%)		
Successful implantation and randomised (*n* = 369; CRT-D *n* = 187, CRT-off *n* = 182)	Complications after hospital discharge to 6 months				
	Left ventricular 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)		

continued

TABLE 71 Adverse events reported by intervention (*continued*)

Study	Adverse event	CRT-D, *n*/*N* (%)	ICD, *n*/*N* (%)	Effect	95% CI, *p*-value
RAFT[140]					
		CRT-D, *n*/*N* (%)	ICD, *n*/*N* (%)		
Implanted (*n* = 1787; CRT-D *n* = 888, ICD *n* = 899)	Death from worsening HF within 24 hours of implantation	0/888	1/899 (0.1)		
	Device-related hospitalisation	179/888 (20)	110/899 (12.2)	HR 1.68	1.32 to 2.13, < 0.001
	Adverse events within 30 days of implantation[a]	124/888 (14.0)	58/899 (6.5)		< 0.001
	Haemothorax or pneumothorax	11/888 (1.2)	8/899 (0.9)		0.47
	Device pocket haematoma 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 (0.2)	2/899 (0.2)		1

NA, not applicable.
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.

The RAFT trial[140] compared adverse events statistically between the CRT-D group and the ICD group (see *Table 71*). The rate of device- or implantation-related complications within 30 days of implantation was significantly higher in the CRT-D group than in the ICD group (CRT-D 13.3% vs. ICD 6.8%, $p < 0.001$), as were the rates of device-related hospitalisations (CRT-D 20% vs. ICD 12.2%, HR 1.68, 95% CI 1.32 to 2.13, $p < 0.001$), lead dislodgement requiring intervention (CRT-D 6.9% vs. ICD 2.2%) and coronary sinus dissection (CRT-D 1.2% vs. ICD 0%). After the first 30 days, the MADIT-CRT trial[130] reported 4.5 (CRT-D group) and 5.2 (ICD group) serious device-related adverse events per 100 device-months.

Subgroup analyses reported by included randomised control trials

Three trials reported prespecified subgroup analysis. The MADIT-CRT trial[130] presented prespecified stratified analysis according to ischaemic or non-ischaemic cardiomyopathy classification. A similar benefit from CRT-D was found in those with ischaemic or non-ischaemic cardiomyopathy (*Table 72*). Subgroup analysis of risk of death or HF according to selected clinical characteristics found that CRT-D was associated with a greater benefit in people with a QRS duration of ≥ 150 milliseconds than in those with a QRS duration of < 150 milliseconds ($p = 0.001$ 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, left ventricular end-diastolic volume and left ventricular end-systolic volume) (see *Table 72*). Additional analysis stratified by men and women reported in a secondary publication[135] is presented in *Table 73* and shows that women achieved significantly better results from CRT-D than men.

TABLE 72 Subgroup analysis: MADIT-CRT trial[130]

Subgroup	CRT-ICD	ICD only	Effect	95% CI, *p*-value
Patients with ischaemic cardiomyopathy (NYHA class I or II)				
	(*n* = 598)	(*n* = 401)		
Death from any cause or non-fatal HF event, *n*/*N* (%)	122/598 (20.4)	117/401 (29.2)	HR 0.67	0.52 to 0.88, 0.003
HF 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 non-ischaemic cardiomyopathy (NYHA class I or II)				
	(*n* = 491)	(*n* = 330)		
Death from any cause or non-fatal HF event, *n* (%)	65 (13.2)	68 (20.6)	HR 0.62	0.44 to 0.89, 0.01
HF 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 HF according to selected clinical characteristics				
	No. of events/ no. of patients		**Effect**	**95% CI, *p*-value for interaction**
Age (years)				
< 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]	
Non-ischaemic II	133/821		HR 0.60[a]	
QRS duration (milliseconds)				
< 150	147/645		HR 1.06	0.74 to 1.52
≥ 150	225/1175		HR 0.48	0.37 to 0.64, 0.001
LVEF (%)				
≤ 25	101/646		HR 0.70[a]	
> 25	271/1174		HR 0.60[a]	
LVEDV (ml)				
≤ 240	184/828		HR 0.70[a]	
> 240	184/969		HR 0.62[a]	
LVESV (ml)				
≤ 170	190/835		HR 0.66[a]	
> 170	178/962		HR 0.70[a]	
All patients	372/1820		HR 0.66	

LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume.
a HRs estimated from figure by reviewer.

TABLE 73 Outcomes by sex: MADIT-CRT trial[135]

Outcome	Women ($n = 453$)		Men ($n = 1367$)		p-value for interaction
	CRT-D	ICD	CRT-D	ICD	
HF or death (primary end point), n/N (%)	29/275 (11)	51/178 (29)	159/814 (20)	137/553 (25)	
	CRT-D vs. ICD HR 0.31, 95% CI 0.19 to 0.50, $p < 0.001$		CRT-D vs. ICD HR 0.72, 95% CI 0.57 to 0.92, $p < 0.01$		< 0.01
HF only	$n = 73$ events, CRT-D vs. ICD HR 0.30, 95% CI 0.18 to 0.50, $p < 0.001$		$n = 249$ events, CRT-D vs. 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 vs. ICD HR 0.28, 95% CI 0.10 to 0.79, $p = 0.02$		$n = 107$ events, CRT-D vs. ICD HR 1.05, 95% CI 0.70 to 1.57, $p = 0.83$		< 0.03

The RAFT trial[140] reported an analysis of 11 prespecified subgroups (*Table 74*) and presented outcomes separately for the NYHA class II and III subgroups (*Table 75*). CRT-D and ICD were associated with a similar reduction in the composite primary outcome of death or hospitalisation for HF ($p = 0.91$ for interaction), death from any cause and hospitalisation for HF for NYHA classes II and III. A statistically significant interaction was found between treatment and QRS duration ($p = 0.003$), with CRT-D more effective in people with an intrinsic QRS duration of ≥ 150 milliseconds (HR 0.59, 95% CI 0.48 to 0.73) than in those with an intrinsic QRS duration of < 150 milliseconds (HR 0.99, 95% CI 0.77 to 1.27, $p = 0.002$ for interaction) or those with a paced QRS duration of ≥200 milliseconds (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 morphological type was also found, with CRT-D more effective in people with LBBB than in those with non-specific intraventricular conduction delay.

The RethinQ trial[142] presented prespecified stratified analysis according to QRS interval (≥ 120 milliseconds or < 120 milliseconds) and cardiomyopathy classification (ischaemic or non-ischaemic) (*Table 76*). A statistically significant improvement in the proportion of people with an increase of at least 1 ml/kg body weight/minute in peak oxygen consumption was found with CRT-D for people with a QRS interval of ≥ 120 milliseconds (58.9% vs. 19.7%, $p = 0.02$), but not for those with a QRS interval of < 120 milliseconds (42.2% vs. 51.2%, $p = 0.45$). There was a statistically significant increase in the proportion with an improvement in NYHA class with CRT-D for both a QRS interval ≥ 120 milliseconds (70.7% vs. 28.0%, $p = 0.01$) and a QRS interval < 120 milliseconds (49.4 vs. 29.3%, $p = 0.04$). There was no statistically significant difference between CRT-D and ICD in QoL or distance walked in 6 minutes for either QRS interval subgroup. Analysis stratified by ischaemic or non-ischaemic 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-ischaemic cardiomyopathy (55.0 m vs. 2.5 m, $p = 0.01$), but not for those with ischaemic cardiomyopathy (4.2 m vs. 5.8 m, $p = 0.57$).

TABLE 74 Subgroup analysis: RAFT trial[140]

Subgroup	HR (95% CI)	*p*-value for interaction
Age: < 65 years vs. ≥ 65 years		0.75
Sex: male vs. female		0.09
NYHA class: II vs. III		0.91
Underlying heart disease: ischaemic vs. non-ischaemic		0.90
QRS duration		
Intrinsic QRS < 150 milliseconds vs.	0.99 (0.77 to 1.27)	0.003,[a] 0.002,[b] 0.003[c]
Intrinsic QRS ≥ 150 milliseconds vs.	0.59 (0.48 to 0.73)	
Paced QRS ≥ 200 milliseconds	1.07 (0.63 to 1.84)	
LVEF (%): < 20 vs. ≥ 20		0.05
QRS morphological 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/minute/1.73 m^2): < 60 vs. ≥ 60		0.70

GFR, glomerular filtration rate; NIVCD, non-specific intraventricular conduction delay.
a Interaction between treatment and QRS duration.
b More effective in those with an intrinsic QRS duration of ≥ 150 milliseconds (HR 0.59; 95% CI 0.48 to 0.73) than in those with an intrinsic QRS duration of < 150 milliseconds (HR 0.99, 95% CI 0.77 to 1.27, $p = 0.002$ for interaction).
c More effective in those with an intrinsic QRS duration of ≥ 150 milliseconds (HR 0.59, 95% CI 0.48 to 0.73) than in those with a paced QRS duration of ≥ 200 milliseconds (HR 1.07, 95% CI 0.63 to 1.84, $p = 0.03$ for interaction).

TABLE 75 New York Heart Association subgroup analysis: RAFT trial[140]

Subgroup	CRT-D, *n*/*N* (%)	ICD, *n*/*N* (%)	Effect	95% CI, *p*-value
NYHA class II				
	(*n* = 708)	(*n* = 730)		
Primary outcome: death or hospitalisation for HF	193/708 (27.3)	253/730 (34.7)	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 HF	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 HF	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 HF	59/186 (31.7)	77/174 (44.3)	HR 0.63	0.45 to 0.88, 0.006

TABLE 76 Subgroup analysis: RethinQ trial[142]

Subgroup	CRT-D on + OPT (QRS ≥ 120 milliseconds, *n* = 17; QRS < 120 milliseconds, *n* = 59)	ICD + OPT (QRS ≥ 120 milliseconds, *n* = 25; QRS < 120 milliseconds, *n* = 55)	*p*-value
QRS interval at 6 months[a]			
Peak oxygen consumption, increase of ≥ 1 ml/kg/minute			
QRS ≥ 120 milliseconds	58.9	19.7	0.02
QRS < 120 milliseconds	42.2	51.2	0.45
Proportion of patients improved by one or more NYHA class			
QRS ≥ 120 milliseconds	70.7	28.0	0.01
QRS < 120 milliseconds	49.4	29.3	0.04
QoL, median change (%)			
QRS ≥ 120 milliseconds	0	–3.7	0.24
QRS < 120 milliseconds	–8.9	–7.0	0.63
6-minute walk distance (m), median change			
QRS ≥ 120 milliseconds	0.0	–19.1	0.86
QRS < 120 milliseconds	33.7	10.3	0.31
	CRT-D on + OPT (ischaemic, *n* = 40; non-ischaemic, *n* = 36)	**ICD+OPT (ischaemic, *n* = 41; non-ischaemic, *n* = 39)**	***p*-value**
Cardiomyopathy classification at 6 months[a]			
Peak oxygen consumption, increase of ≥ 1 ml/kg/minute			
Ischaemic	40.0	44.2	0.82
Non-ischaemic	52.6	38.4	0.25
Proportion of patients improved by one or more NYHA class			
Ischaemic	55.3	29.5	0.02
Non-ischaemic	53.2	28.4	0.04
QoL, median change (%)			
Ischaemic	–5.9	–3.6	0.68

Summary of clinical effectiveness: people with both conditions

- Nine RCTs were included comparing CRT-D with ICD in people both at risk of SCD as a result of ventricular arrhythmias and with HF as a result of LVSD and cardiac dyssynchrony.
- No RCTs comparing CRT-D with OPT or CRT-D with CRT-P were identified for this population.
- The risk of bias was low in some of the trials but unclear in others because of inadequate reporting.
- Length of follow-up was 6 months in five trials, 1 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 HF; the majority of participants were in NYHA class II in three trials, in NYHA class III in four trials, described as 'mild to moderate' in one trial and in 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 milliseconds) and evidence of mechanical dyssynchrony on ECG. 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 (eight RCTs; RR 0.84, 95% CI 0.73 to 0.96, $p = 0.01$) and total cardiac deaths (six 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 HF despite OPT, a LVEF ≤ 30% from ischaemic or non-ischaemic causes, a wide QRS interval and planned ICD implantation for indicated primary or secondary prevention of SCD.
- Fewer trials reported HF deaths or SCDs separately, and there were no HF deaths or SCDs in some of these trials. Combining three RCTs in a meta-analysis found little difference in the rate of SCD between the CRT-D group and the ICD group (RR 1.45, 95% CI 0.43 to 4.92, $p = 0.55$).
- The RAFT trial found a statistically significant reduction in the rate of HF hospitalisations with CRT-D. Two small trials found no significant difference between the groups for this outcome. Combining these trials in a meta-analysis demonstrated that CRT-D reduced the RR 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 between the groups in the proportion of people experiencing at least one episode of VT or VF (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, $p = 0.008$). The results were more heterogeneous among the three trials reporting the proportion of people who improved by one or more NYHA class: two trials found a statistically significant improvement with CRT-D but one trial found no difference between the groups (meta-analysis RR 1.81, 95% CI 0.91 to 3.60, $p = 0.09$).
- There was substantial statistical heterogeneity in LVEF among the trials, although the direction of effect was fairly consistent. Meta-analysis found a significant improvement in LVEF with CRT-D compared with ICD (eight RCTs; MD 2.15%, 95% CI 0.45% to 3.86%, $p = 0.01$).
- There was a greater improvement in exercise capacity in the CRT-D group than in the ICD group, as demonstrated by change from baseline in peak VO_2 (five RCTs; MD 0.75, 95% CI 0.23 to 1.27, $p = 0.005$) and 6-minute walk distance (six RCTs, MD 14.5 m, 95% CI 2.9 to 26.1 m, $p = 0.01$).
- 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 reporting other measures of QoL (DASI, one-item Global Visual Analogue Scale and SF-36) found that differences between the groups in 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 the rate of device- or implantation-related complications within 30 days of implantation was significantly higher in the CRT-D group than in the ICD group (13.3% vs. 6.8%, $p < 0.001$), as was the rate of device-related hospitalisations (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 a QRS duration of ≥ 150 milliseconds than in those with a QRS duration of < 150 milliseconds, and the third trial found a significant increase in the proportion of people with an improvement in peak oxygen uptake among those with a QRS interval of ≥ 120 milliseconds but not among those with a QRS interval of < 120 milliseconds. CRT-D was associated with greater benefit in women than in men (one trial) and with greater benefit in people with LBBB than in those with non-specific intraventricular conduction delay (one trial). One trial found a statistically significant improvement with CRT-D for distance walked in 6 minutes for those with non-ischaemic cardiomyopathy (55.0 m vs. 2.5 m, $p = 0.01$) but not for those with ischaemic cardiomyopathy (4.2 m vs. 5.8 m, $p = 0.57$). Other evaluated subgroups showed no statistically significant effects.

Summary of Southampton Health Technology Assessments Centre's peer review of clinical effectiveness in the Association of British Healthcare Industries 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.[151] The clinical effectiveness evidence presented in this MS has been briefly appraised (see *Appendix 10*). The MS also presented individual patient data (IPD) network meta-analysis (NMA) (see following section) and an economic model (see *Chapter 5*, *Review of the manufacturers' submission*).

A systematic review of clinical effectiveness was undertaken in the MS.[151] 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 those in the NICE scope[61] and the results were not presented according to the population groups defined in the NICE scope. As a result of this, the MS and the Southampton Health Technology Assessments Centre's (SHTAC) systematic reviews differ in the evidence included (see *Appendix 10*).

The MS does not explicitly report the conclusions from the systematic review of clinical effectiveness in the main body of the submission. The executive summary states that 'there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF' (p. 4);[151] 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 in the following section.

Individual patient 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 in the different subgroups of people who have HF.[151] 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 HRQoL. In undertaking the IPD NMA, the MS recognises the heterogeneous nature of patients with HF 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 subgroups of patients as identified in the scope for the NICE appraisal, to trying to establish which subgroups 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 subgroups with HF, the availability of IPD from the manufacturers makes a NMA meta-regression possible and justified.

This section presents a critical appraisal of the IPD NMA using a structured approach (see *Appendix 10*). It provides an assessment of the appropriateness of the methods used and of the results and conclusions presented.

Methods

Network of evidence

The systematic review of clinical effectiveness reported in the MS included a comprehensive and transparent search strategy, the criteria and reasons for study selection, extraction of baseline data on patient characteristics and study outcomes, quality assessment of studies and the process followed to complete these stages. The studies identified in the systematic review provided the basis for developing the network of evidence for the IPD NMA. However, the IPD NMA included only a subset of those studies 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[71,75,81,84,89,95,97] identified by the SHTAC systematic review (see earlier in this chapter). 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 three trials ($n = 4432$) 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, NMAs were produced to compare outcomes using aggregate data from all trials in the network with outcomes using data from the trials included in the IPD only, finding no significant differences. Similar comparisons were not produced for the other outcomes.

Issues relating to differences in the 13 IPD trials were also considered. The effects of length of follow-up, trial crossover, missing data and data handling were discussed in the MS, particularly with relation to all-cause mortality. Length of follow-up was restricted to that specified in trial protocols (commercial-in-confidence information has been removed) to limit the effects of trial crossover at the longest follow-up time (commercial-in-confidence information has been removed). Missing data for the covariables appeared limited (commercial-in-confidence information has been removed), with data imputed through multiple imputations when necessary (details provided in appendix 6 of the MS[151]). 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 HF 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 of 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 subgroup-specific treatment effects to be estimated and provided 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, when direct and indirect evidence is available. This is important in the current assessment when direct evidence may be limited (e.g. CRT-D vs. CRT-P and CRT-D vs. 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 the effects of covariables to be considered and, when necessary, the approach to their inclusion to be 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 the trial follow-up, visual review of the extrapolations and of the shape of the instantaneous hazard over time, the Akaike information criterion (AIC), Cox–Snell residuals, tests of the 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 presents only 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 or not the approach was suitable. IPD NMAs using meta-regression were undertaken to estimate the relative treatment effects (i.e. HRs) 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 NMAs excluding the covariables were conducted at the aggregate level (i.e. trial). This allowed a comparison of the unadjusted efficacy estimates from the NMAs with those produced by pairwise meta-analyses from aggregate trial data and with the individual trial estimates. This enabled 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 analysis that should be undertaken (i.e. fixed vs. 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 a negative binomial regression model (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 criterion (BIC), AIC and two times log-likelihood score] and the covariates were 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 subgroups estimates were either not calculated or 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 when 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.

Health-related quality of life was assessed using the EQ-5D. UK age- and gender-specific utilities[152] were adjusted using disease- and treatment-specific decrements/increments estimated from the three IPD trials reporting EQ-5D data 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 they appeared skewed (commercial-in-confidence information has been removed). 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 using the MD from 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 counterintuitive results. Exploratory analysis using MLWHFQ data at 6 months, the MS systematic review of clinical effectiveness and a correction for a placebo effect was used to adjust the estimates for use in the MS cost-effectiveness model. Duration of benefit was estimated by 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.

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 to demonstrate the heterogeneity in the IPD population. Predicted survival rates were reported to (commercial-in-confidence information has been removed). The baseline risk model was used in the MS cost-effectiveness model for the baseline survival curve (see *Table 37*, p. 121, in the MS[151]). Covariables included in the model with a statistically significant effect were age, sex, ischaemic aetiology, LVEF, NYHA class (I/II, III/IV) and QRS duration (< 120 milliseconds, ≥ 120 milliseconds).

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 differences in the HRs for fixed- and random-effects models and for IPD compared with aggregate data for all trials in the network and for the pairwise meta-analyses. As such, it was considered appropriate to use the IPD for the NMA and to use fixed-effects models. The fixed-effects IPD NMA without the covariables estimated the HRs compared with (commercial-in-confidence information has been removed) for CRT-D, (commercial-in-confidence information has been removed) for CRT-P and (commercial-in-confidence information has been removed) for ICDs. HRs were presented for CRT-D compared with CRT-P (commercial-in-confidence information has been removed) and for CRT-D compared with ICD (commercial-in-confidence information has been removed). The MS states that proportional hazards tests showed that the benefits were maintained over time [global *p*-value for device terms (commercial-in-confidence information has been removed)].

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 table 39, p. 132, in the MS[151]). The final NMA model was used to show the predicted treatment effect for different subgroups, presented as HRs with CIs (assumed to be 95% CIs 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' (p. 130).[151] This is particularly important in relating the broad conclusions made to the results presented in the MS. The analyses highlighted that age, sex, 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 (see figure 19, pp. 133–4[151]) and from HRs presented in *Table 77* that for the majority of subgroups the devices provide some benefit for all-cause mortality compared with OPT (49 of 52 comparisons). However, the benefit provided by the devices is rarely statistically significant (14 of 52 comparisons show significant benefit; four of 52 comparisons are of 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 subgroups for which the benefit is statistically significant or on the margins of statistical significance. ICDs provided a statistically significant benefit compared with OPT for men aged < 60 years irrespective of QRS duration or LBBB status and were marginally insignificant for both men aged ≥ 60 years and women aged < 60 years with a QRS duration from ≥ 120 milliseconds to < 150 milliseconds and without LBBB. CRT-D benefited a wider group of patients compared with OPT. Benefits that were statistically significant or on the margins of statistical significance were reported for men and women of all ages with a QRS duration of ≥ 150 milliseconds and for women of all ages with a QRS duration from ≥ 120 milliseconds to < 150 milliseconds. In contrast, CRT-P had a statistically significant effect only for women aged ≥ 60 years with a QRS duration of ≥ 150 milliseconds and with LBBB.

TABLE 77 Hazard ratios (95% CIs) for all-cause mortality from the NMA with covariables for the comparisons between the different devices and OPT

QRS (milliseconds)	Device	Sex and age group			
		Male < 60 years	Male ≥ 60 years	Female < 60 years	Female ≥ 60 years
Non-LBBB					
< 120	ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
≥ 120 to < 150	ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
	CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
	CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
≥ 150	ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
	CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
	CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
LBBB					
≥ 120 to < 150	ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
	CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
	CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
≥ 150	ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
	CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

TABLE 77 Hazard ratios (95% CIs) for all-cause mortality from the NMA with covariables for the comparisons between the different devices and OPT (*continued*)

QRS (milliseconds)	Device	Sex and age group			
		Male < 60 years	Male ≥ 60 years	Female < 60 years	Female ≥ 60 years
	CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

Source: figure 19, pp. 133–4, in the MS.[151]

Post-submission note Following submission of this report we were informed of an error in the ABHI submission that had led to incomplete accounting of the covariance between the model parameters. Correcting the error resulted in a narrowing of the CIs around the HRs for the comparisons with OPT. As SHTAC did not have access to the IPD analyses, the error cannot be verified. Although this increased the number of comparisons for which there was a statistically significant benefit (28/52), the groups identified differed little from those that were shown to benefit significantly or that were on the margins of statistical significance in the previous SHTAC assessment. In the reanalysis ICDs were shown to provide a statistically significant benefit for all men irrespective of age, QRS duration or LBBB status and for women aged < 60 years with a QRS duration from ≥ 120 milliseconds to < 150 milliseconds and without LBBB. CRT-D benefited a wider group of patients. Benefits that were statistically significant or on the margins of statistical significance were reported for men and women of all ages with a QRS duration ≥ 120 milliseconds and with or without LBBB. In contrast, CRT-P had a statistically significant effect only for men and women aged ≥ 60 years with a QRS duration of ≥ 150 milliseconds and with LBBB.

All-cause hospitalisation

The baseline regression model (see table 40, p. 139, in the MS[151]) for patients randomised to OPT produced monthly probabilities of hospitalisation for the different subgroups (*Table 78*). These were used for the baseline assessment. When data allowed, treatment effects were estimated using a process similar

TABLE 78 Baseline monthly probabilities of hospitalisation by covariate pattern (patient receiving OPT)

	NYHA class I/II	NYHA class III	NYHA class IV
Non-ischaemic aetiology			
QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Ischaemic aetiology			
QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

Assumed starting age 66 years.
Source: table 41, p. 140, in the MS.[151]

to a fixed-effects NMA (see table 42, p. 142, in the MS[151]) and are presented in *Table 79*. Limited data meant that estimates could not be provided for some groups (i.e. ICD NYHA class IV and CRT-P NYHA class I/II) and are thought unreliable for others (i.e. CRT-D NYHA classes III and IV). Alternative values have been put forward in the MS with justifications (see *Table 79*), which appear reasonable. The effects of the devices on all-cause hospitalisations were translated into monthly transition probabilities (*Tables 80–82*), which were used in the economic model presented in the MS.

Health-related quality of life

The NBRM (see table 52, p. 152, in the MS[151]) for patients randomised to OPT was used to generate baseline results for the different subgroups (*Table 83*). Given the limitations of the data set 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 stated that they were felt to be within acceptable tolerance levels. Treatment effects on HRQoL were estimated as mean change from baseline using the IPD (*Table 84*). As several estimates appeared counterintuitive, reflecting the limited and skewed data available, the MS adjusted the values based on IPD analysis of MLWHFQ 6-month data and a systematic review (see *Table 84*). As a result, the MS suggests that caution should be used when interpreting the results.

TABLE 79 All-cause hospitalisation treatment effects derived from the NMA and used in the MS economic model (events per month)

	Derived value	Value used in model	Justification
ICD			
NYHA class I/II	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis clinically plausible
NYHA class III	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis clinically plausible
NYHA class IV	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Device not assessed in this patient group
CRT-P			
NYHA class I/II	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Device not assessed in this patient group
NYHA class III	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis clinically plausible
NYHA class IV	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis clinically plausible
CRT-D			
NYHA class I/II	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis clinically plausible
NYHA class III	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis not clinically plausible. Assumed same as CRT-P-value given common component (CRT)
NYHA class IV	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis not clinically plausible. Assumed same as CRT-P-value given common component (CRT)

Source: tables 43 and 44, pp. 142–3, in the MS.[151]

TABLE 80 Monthly all-cause hospitalisation transition probabilities (ICD, events per month)

	NYHA class I/II	NYHA class III	NYHA class IV
Non-ischaemic aetiology			
QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	NA
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	NA
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	NA
Ischaemic aetiology			
QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	NA
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	NA
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	NA

NA, not applicable.
Source: table 45, p. 144, in the MS.[151]

TABLE 81 Monthly all-cause hospitalisation transition probabilities (CRT-P, events per month)

	NYHA class I/II	NYHA class III	NYHA class IV
Non-ischaemic aetiology			
QRS < 120 milliseconds	NA	NA	NA
QRS 120–149 milliseconds	NA	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	NA	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Ischaemic aetiology			
QRS < 120 milliseconds	NA	NA	NA
QRS 120–149 milliseconds	NA	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	NA	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

NA, not applicable.
Source: table 46, p. 144, of the MS.[151]

TABLE 82 Monthly all-cause hospitalisation transition probabilities (CRT-D, events per month)

	NYHA class I/II	NYHA class III	NYHA class IV
Non-ischaemic aetiology			
QRS < 120 milliseconds	NA	NA	NA
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Ischaemic aetiology			
QRS < 120 milliseconds	NA	NA	NA
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

N/A, not applicable.
Source: table 47, p. 145, in the MS.[151]

TABLE 83 Comparison of indicative individuals with population equivalents

		Decrements from unity		
NYHA class	Sex	Population norm	Derived	Disease-specific component[a]
Non-ischaemic aetiology				
I/II	Male	0.2100	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
I/II	Female	0.2098	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
III	Male	0.2100	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
III	Female	0.2098	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
IV	Male	0.2100	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
IV	Female	0.2098	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Ischaemic aetiology				
I/II	Male	0.2100	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
I/II	Female	0.2098	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
III	Male	0.2100	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
III	Female	0.2098	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
IV	Male	0.2100	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
IV	Female	0.2098	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

a Corresponds to difference between population norm and derived value and is to be interpreted as the impact of the disease above and beyond what would naturally occur.
Assumed starting age 66 years.
Source: tables 53 and 54, p. 153, in the MS.[151]

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	
	n	Utility value (mean, SE)[a]	Utility value[b]	Justification for value used in economic model
NYHA class I/II				
OPT	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	No clinical reason why person already receiving OPT would have a change in utility
ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Value derived from IPD analysis (commercial-in-confidence information has been removed). Systematic review suggests ICDs have a positive impact
CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Cost-effectiveness results not generated for this treatment option
CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Value derived from IPD analysis (commercial-in-confidence information has been removed). Systematic review and MLWHFQ analysis suggest that CRT-D has a positive impact
NYHA class III				
OPT	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	No clinical reason why person already receiving OPT would have a change in utility
ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Results from IPD analysis not significantly different from zero. Literature review suggests that ICDs have no benefit in this group
CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Value derived from IPD analysis (commercial-in-confidence information has been removed). Literature review and MLWHFQ analysis suggest that CRT-P has a benefit in this group
CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Assumed same as CRT-P as not thought clinically different. IPD results derived from small patient numbers. Literature review and MLWHFQ analysis suggest that CRT-D has a benefit in this group
NYHA class IV				
OPT	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	No clinical reason why person already receiving OPT would have a change in utility
ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Cost-effectiveness results not generated for this treatment option
CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Not enough information available. Assumed same as for NYHA class III. Analysis of MLWHFQ data supports this assumption

continued

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 (*continued*)

	IPD analysis		Economic model	
	n	Utility value (mean, SE)[a]	Utility value[b]	Justification for value used in economic model
CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Not enough information available. Assumed same as for NYHA class III. Analysis of MLWHFQ data supports this assumption

a Mean changes from baseline in EQ-5D at 6 months.
b 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: tables 56 and 58, pp. 155 and 157, in the MS.[151]

Validation of the adjusted values provided in the MS is difficult because of the lack of published evidence; as such, the increments presented should be viewed with caution. (Commercial-in-confidence information has been removed) and so this was applied in the economic model presented in the MS.

Discussion

The MS presented an IPD NMA using meta-regression to assess the effectiveness of ICDs, CRT-P and CRT-D for different subgroups of people with HF. As part of the NMA, the MS used a systematic review to identify the network of evidence for which IPD were 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, although 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 in the MS did not take account of the subgroups identified by the scope for the NICE appraisal.[61] Instead, it looked for subgroups of HF 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 subgroups of HF 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 counterintuitive results, and the 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 with OPT for all-cause mortality. Comparison of CRT-D with both CRT-P and ICDs showed a statistically significant benefit for CRT-D. These results appeared appropriate when compared with the original trial results and the pairwise meta-analyses undertaken in the SHTAC systematic review (see earlier in this chapter) and the MS. When including covariates to identify subgroups that benefited from the different devices, the outcomes were less clear and the MS advises that the results should be interpreted with caution. It was evident that all of the devices appeared beneficial compared with OPT; however, rarely were differences statistically significant. CRT-D appeared to have a statistically significant benefit for people of all ages with a QRS duration of ≥ 150 milliseconds and for women of all ages with a QRS duration from ≥ 120 milliseconds to < 150 milliseconds. Although CRT-D showed benefit for men of all ages, its effects were marginally insignificant. ICDs appeared to have a statistically significant benefit for men aged < 60 years for all QRS durations and for men aged ≥ 60 years with a QRS duration from ≥ 120 milliseconds to < 150 milliseconds and without LBBB. CRT-P showed a statistically significant benefit only for women with a QRS duration of ≥ 150 milliseconds and with 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–III (commercial-in-confidence information has been removed) and CRD-P in NYHA groups III and IV (commercial-in-confidence information has been removed). Estimates for CRT-D suggested a constant effect for all NYHA groups (commercial-in-confidence information has been removed) and so were adjusted in the MS to reflect those of CRT-P.

Health-related quality of life

Baseline estimates of HRQoL from the IPD using the EQ-5D showed that patients in NYHA class I/II had similar values to population norms, whereas patients in NYHA classes III and IV had values that were progressively lower. Treatment estimates were counterintuitive, reflecting the limited IPD available. As a consequence, adjustments were made which assumed that CRT-P and CRT–D had the same effect on EQ-5D values and ICDs had an effect on NYHA class I/II only. Benefits were thought to last for a fixed period of (commercial-in-confidence information has been removed).

Chapter 5 Economic analysis

The aim of this section is to assess the 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
- 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 HF
- a systematic review of studies of the HRQoL of people at risk of SCD or with HF
- a review of the MS to NICE[151]
- an independent economic model and cost-effectiveness evaluation (the SHTAC model).

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 the treatment of arrhythmias and CRT for the treatment of HF. 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 generalisability of their results.

The methods and inclusion criteria considered for this review of economic evaluations are presented in *Chapter 3* and details of the search strategy are documented in *Appendix 2*. Given the volume of studies meeting the inclusion criteria, data extraction was undertaken as follows: for studies included in previous assessments, data extraction was derived from these reports and checked against original publications; for newly identified evidence, data were extracted directly from the original publications.

Quantity and quality of research available

The literature searches identified 1410 studies that potentially met the inclusion criteria set out in *Chapter 3* (see *Inclusion and exclusion criteria*). From screening titles and abstracts, 1334 publications were excluded and 76 were retrieved for full screening. Of these, 22 did not meet the inclusion criteria:

- six were found not to be full economic evaluations
- six were abstracts (five from 2010 and 2011 and one study treated as an abstract as it did not report sufficient details for inclusion)
- three references were unobtainable and thus did not provide sufficient details for inclusion
- three had a different comparator from that specified in the research protocol
- two had a different population from that specified in the research protocol
- one had a different intervention from that specified in the research protocol
- one was a non-English-language report.

A list of relevant excluded studies is provided in *Appendix 11*.

A total of 54 papers met the inclusion criteria.[63,64,149,153–203] Three studies were each reported in two publications; therefore, 51 separate economic evaluations were included in this review. A flow chart describing the identification of the included studies is provided in *Figure 31*.

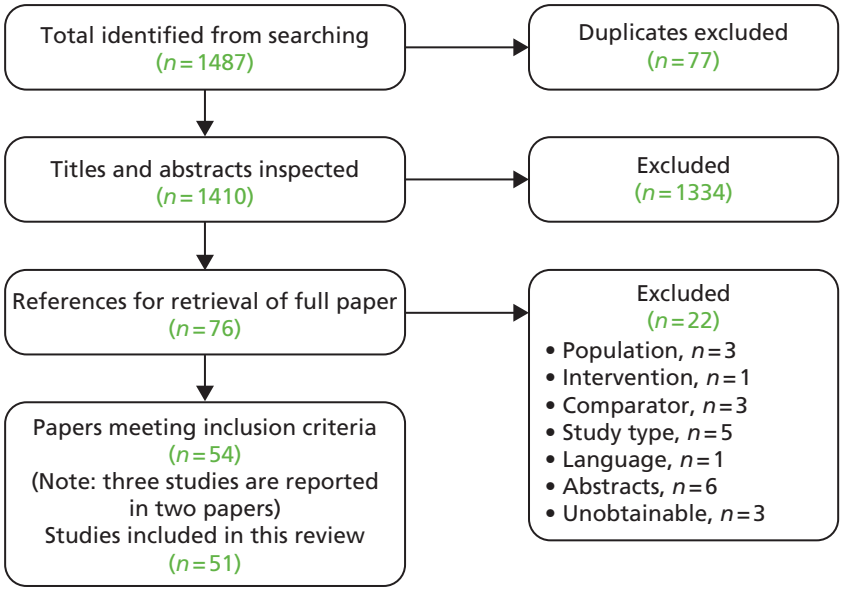

FIGURE 31 Flow chart of identification of studies for inclusion in the review of cost-effectiveness.

The included economic evaluations were categorised according to the type of the interventions that they assessed. Thirty-six[63,149,153–186] of the included studies assessed ICDs and 17[64,155,172,187–200] assessed CRT. Two[155,172] of these studies assessed both ICDs and CRT; details of these two studies have been included within both the ICD and the CRT sections.

Economic evaluations of implantable cardiac defibrillators

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* 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,[63,153,175] three elsewhere in Europe,[160,164,174] two in Brazil[155,178] and one each in Australia[172] and Japan.[149] Two studies were conducted in two countries (one in the UK and France[156] and one in Germany and the USA[173]). Study type was predominantly cost–utility analysis[149,153,155,157–160,162–165,170,174,176–182,185] and cost-effectiveness analysis[63,154,166–169,171–173,175,183,184,186] with two cost–benefit analyses.[156,161] Most studies used a Markov model[149,153,155,157–160,162–164,166–168,171,174,176–182,185] with five studies using a trial-based analysis[169,170,173,183,186] and the remaining studies using a variety of methods. Most studies used a long-term time horizon of > 20 years,[149,153–155,157–160,162,164–166,168,172,174–182,185] six studies had a short time horizon of < 7 years[63,156,161,167,169,173] and six studies had a medium time horizon of between 8 and 19 years.[163,170,171,183,184,186] Fourteen studies were based on a single trial[63,154,156,157,161,164,169–171,173,174,180,183,186] with the MADIT II trial[101] (six studies[154,157,164,171,180,186]) and the SCD-HeFT trial[105] (four studies[156,161,170,174]) the most commonly used. Ten studies used more than one trial, through meta-analysis, systematic review or different trial populations,[149,153,155,160,163,172,176,177,181,182] 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 the studies ($n = 15$) reported that ICDs were cost-effective,[149,154–156,160,161,166–170,172,175,180,185] with an additional six finding ICDs cost-effective for high-risk groups according to study definitions.[158,165,173,176,177,181] Nine studies did not find ICDs cost-effective[153,157,159,162,163,174,178,183,186] and six studies were unclear whether ICDs were cost effective or not.[63,164,171,179,182,184]

The judgements of the methodological quality assessment of the studies on ICDs are summarised in *Table 86*. The studies vary in their quality and relevance to the UK NHS. As already described, many studies were conducted in countries outside the UK and it is unclear how generalisable their results are to the UK

TABLE 85 Summary of the characteristics of the economic evaluations of ICD vs. OPT

Study	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 a LVEF ≤ 30%	Survival	MADIT II[101]	Cost-effective (US$50,500 per LYG)
Bertoldi *et al.* 2011[155]	Brazil	HF NYHA class II, III or IV; EF ≤ 35%	Markov	Meta-analysis of trials	Marginally cost-effective (INT$32,663 per QALY)
Buxton *et al.* 2006[153]	UK	Secondary prevention patients at risk of SCD with previous CA or VT	Markov	Observational data and CIDS[84]	Not cost-effective (£76,139 per QALY)
Caro *et al.* 2007[156]	UK and France	HF NYHA class II or III; LV dysfunction ≤ 35%	DES	SCD-HeFT[105]	Cost-effective (cost–benefit ratio 0.17 UK)
Chan *et al.* 2006[157]	USA	Ischaemic heart disease and LVEF ≤ 30%	Markov	MADIT II[101]	Not cost-effective in all MADIT II patients (US$55,800 per QALY); risk stratification with MTWA improves cost-effectiveness (US$48,800 per QALY)
Chan *et al.* 2009[158]	USA	Cardiomyopathy (EF ≤ 35%) and no previous VA	Markov	Prospective cohort	Cost-effective for high-risk groups (US$70,881 per QALY)
Chen and Hay 2004[159]	USA	Newly diagnosed HF NYHA class II or III	Markov	Not stated	Not cost-effective (US$97,863 per QALY)
Cowie *et al.* 2009[160]	Belgium	LVEF ≤ 35%; HF NYHA class II or III; or previous MI	Markov	AMIOVIRT,[69] CAT,[82] DEFINITE,[90] MADIT I,[99] MADIT II,[101] SCD-HeFT[105]	Cost-effective (€29,530 per QALY)
Deniz *et al.* 2009[161]	Canada	HF NYHA class II or II; LV dysfunction ≤ 35%	DES	SCD-HeFT[105]	Cost-effective (cost–benefit ratio of 0.05)
Feingold *et al.* 2010[162]	USA	Children (10–15 years) with dilated cardiomyopathy and HF	Markov	Paediatric cardiology prospective studies	Not cost-effective (US$281,622 per QALY)
Filion *et al.* 2009[163]	Canada	Severe LV dysfunction at risk of SCD	Markov	Meta-analysis of trials	Not cost-effective (CAD$108,900 per QALY)
Gandjour *et al.* 2011[164]	Germany	EF ≤ 30% or < 1 month after MI	Markov	MADIT II[101]	Unclear (€44,736 per QALY)
Goldenberg *et al.* 2005[165]	USA	Inherited cardiac disorders with high risk of SCD; patients aged 10–75 years	Survival	Several sources	Cost-effective in selected high-risk patients with inherited cardiac disorders because of gained productivity over lifetime (US$3328–600,000 per QALY)
Kupersmith *et al.* 1995[167]	USA	High-risk patients with VT/VF with ICD implant from 1980–7	Markov	Retrospective study with historical control subjects	Cost-effective (epicardial ICD US$31,100 per LYG; endocardial ICD US$25,700 per LYG)

continued

TABLE 85 Summary of the characteristics of the economic evaluations of ICD vs. OPT (*continued*)

Study	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
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 (US$15,600–29,600 per LYG)
Larsen *et al.* 1992[168]	USA	Patients with sustained VT/VF	Markov	Case series of ICD patients	Cost-effective (US$29,244 per LYG)
Larsen *et al.* 2002[169]	USA	EF ≤ 40%; sustained VT or resuscitated from CA	Trial	AVID[71]	Moderately cost-effective (US$66,677 per LYG)
Mark *et al.* 2006[170]	USA	HF NYHA class II or III; LV dysfunction ≤ 35%	Trial	SCD-HeFT[105]	Cost-effective (US$41,530 per QALY)
McGregor and Chen 2004[171]	Canada	Adults with a history of MI and a LVEF ≤ 30%	Markov	MADIT II[101]	Unclear (CAD$47,458 per LYG)
Medical Services Advisory Committee 2006[172]	Australia	Adults with a history of MI and a LVEF ≤ 30%; or HF NYHA class II or III and LV dysfunction ≤ 35%	Decision tree	SCD-HeFT,[105] COMPANION[116]	Cost-effective in patients with moderate to severe symptoms of CHF (AUS$39,885 per LYG)
Mushlin *et al.* 1998[173]	Germany and USA	Adults with a history of MI and a LVEF ≤ 30%	Trial	MADIT[99]	Cost-effective in selected high-risk patients (US$27,000 per LYG)
Neyt *et al.* 2008[174]	Belgium	HF NYHA class II or II; LV dysfunction ≤ 35%	Markov	SCD-HeFT[105]	Not cost-effective (€132,100 per QALY)
O'Brien *et al.* 1992[175]	UK	Patients at high risk of SCD	Simple calculation model	ICD case series	Cost-effective (£15,400 per LYG)
Owens *et al.* 1997[176]	USA	CA survivors at high risk of SCD	Markov	CASH,[81] MADIT[99]	Cost-effective for high-risk groups (US$74,400 per QALY)
Owens *et al.* 2002[177]	USA	Patients at risk of SCD (trial characteristics)	Markov	MADIT,[99] AVID,[71] CIDS, CASH,[81] MUSTT,[146] CABG Patch[75]	Cost-effective in high-risk groups (US$54,700 per QALY)
Parkes *et al.* 2000[63]	UK	Patients at risk of SCD from arrhythmias	Survival calculation	AVID[71]	Unclear (£40,500–87,000 per LYG)
Ribeiro *et al.* 2010[178,201]	Brazil	HF NYHA class II and III; LVEF ≤ 35%	Markov	Several sources; scenario with MADIT I[99]	Not cost-effective (R$68,318 per QALY)
Sanders *et al.* 2001[179]	USA	Patients with MI who did not have sustained VA	Markov	Range of ICD efficacies evaluated	Unclear (US$71,800 per QALY –US$557,900 per 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 a LVEF ≤ 30%	Markov	MADIT II[101]	Cost-effective (US$50,900 per QALY)

TABLE 85 Summary of the characteristics of the economic evaluations of ICD vs. OPT (*continued*)

Study	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
Sanders *et al.* 2005[181]	USA	Patients at risk of SCD (trial characteristics)	Markov	MADIT,[99] CABG Patch,[75] MUSTT,[146] MADIT II,[101] DEFINITE,[90] DINAMIT,[95] COMPANION,[116] SCD-HeFT[105]	Cost-effective in selected high-risk patients (US$34,000–70,200 per QALY)
Sanders *et al.* 2010[182]	USA	Patients with LV dysfunction	Markov	MADIT,[99] MADIT II,[101] DEFINITE,[90] MUSTT,[146] SCD-HeFT[105]	Unclear, varies widely among trials (US$37,031–138,458 per QALY)
Sheldon *et al.* 2001[183] and O'Brien *et al.* 2001[202]	Canada	Secondary prevention patients at risk of SCD with previous CA or VT	Trial	CIDS[84]	Not cost-effective (CAD$213,543 per LYG) but more attractive in patients with at least two risk factors for SCD (CAD$65,195 per LYG)
Wang *et al.* 2008[149]	Japan	Brugada syndrome with abnormal heart	Markov	Several trials including DEBUT[89]	Cost-effective (US$14,667 per QALY)
Weiss *et al.* 2002[184]	USA	VT or VF	Retrospective cohort study		Unclear (US$78,400 per LYG)
You *et al.* 2007[185]	Canada	Hypertrophic cardiomyopathy at risk of SCD (no previous CA)	Markov	ICD registries and cohort studies	Cost-effective (US$19,400 per QALY)
Zwanziger *et al.* 2006[186]	USA	Adults with a history of MI and a LVEF $\leq$ 30%	Trial	MADIT II[101]	Not cost-effective for trial, 3.5 years time horizon (US$235,000 per LYG)

CA, cardiac arrest; DES, discrete event simulation; EF, ejection fraction; ICER, incremental cost-effectiveness ratio; LV, Left ventricular; LYG, life-year gained; MTWA, microvolt T-wave alternants; VA, ventricular arrhythmia.

TABLE 86 Summary of the quality of the economic evaluations of ICDs

Study	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[153]	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

Study	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
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
Medical Services Advisory Committee 2006[172]	Y	N	Y	Y	Y	N	Y	N	Y	Y
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[63]	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

continued

TABLE 86 Summary of the quality of the economic evaluations of ICDs (*continued*)

Study	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
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] and O'Brien *et al.* 2001[202]	Y	N	Y	N	Y	N	?	Y	Y	Y
Wang *et al.* 2008[149]	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

?, not possible to answer question as the information was not reported clearly or there was missing information; N, no; Y, yes.

NHS. Generally, the later studies are of higher quality. Earlier studies were less likely to include QALYs, long-term life horizons or all relevant costs and consequences.

Five studies[153,155,160,178,182] were considered to be of high methodological quality by meeting all or all but one ('Setting comparable to the UK') of the recognised criteria.[38,66] Of these, only one study[153] was conducted for a UK setting and perspective and is considered of most relevance. 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.

Buxton and colleagues[153]

Buxton and colleagues[153] developed a Markov model to estimate the cost-effectiveness of ICDs compared with AAD treatment in the UK in secondary prevention patients at risk of SCD (see *Appendix 12* for data extraction). The economic evaluation was part of a wider study of the clinical characteristics, survival, QoL 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.[71,81,84] 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 and amiodarone problems; and 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[84] 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 the EQ-5D, from a sample of 229 patients. The levels of most of the HRQoL measures were lower in the cohort than in the 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 AADs and 0.83 for ICD patients with 0.80 for patients receiving AADs.

Buxton and colleagues[153] collected resource and cost data for 211 patients from Papworth NHS Trust and 167 patients from Liverpool NHS Trust. In addition to the costs of the implantation, post-discharge costs (tests, medications and follow-up consultation) and costs of additional hospitalisations were also calculated. The mean initial cost 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, implantation cost, associated tests and hospital stay).

Buxton and colleagues[153] concluded that the benefit from an ICD may not be sufficient to make the technology cost-effective in the UK. The mean incremental cost-effectiveness ratio (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 > 70 years with a LVEF of < 35%. Patients with a LVEF of < 35% had an ICER of £72,000 per QALY over 20 years. Extrapolating over the lifetime of the patients with a low LVEF gave an ICER of £48,372 per QALY. A reduction in the cost of the implant/replacement and improvements in the reliability of ICDs (repair/replacement of 3% per patient-year instead of 6% in the base case) would reduce the ICER to £35,500 per QALY.

As noted earlier, this study 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 this study was published and for slightly

different populations and different settings, present a range of conclusions about the cost-effectiveness of ICDs, from not cost-effective[178] to uncertain if cost-effective,[182] marginally cost-effective[155] and cost-effective.[160]

Economic evaluations of cardiac resynchronisation therapy

Seventeen economic evaluations of the use of CRT concern patients with HF.[64,155,172,187–200] *Table 87* provides an overview of these studies. Four studies were conducted in the UK[64,189,190,198] with six conducted elsewhere in Europe.[187,188,191,193,196,199] Two studies were carried out in Australia,[172,195] two in the 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 ($n = 11$),[64,155,187,188,193,194,196–200] with six studies using other methodology[172,190–192,195] and one using trial-based analysis.[189] Twelve studies used a long-term time horizon of > 20 years[64,155,172,188,189,191,194–198,200] and five studies had a short time horizon of < 8 years.[187,190,192,193,199] Eight studies were based on a single trial, with the CARE-HF[109] (five studies[188–191,198]) and COMPANION[116] (three studies[172,192,196]) trials the most commonly used. Five studies used more than one trial, through meta-analysis, systematic review or different trial populations[155,194,195,197,200] and four studies used other sources of evidence to model the intervention effect.[64,130,193,199] The majority of the studies ($n = 15$) reported that CRT was cost-effective.[64,155,172,187–193,195,196,198–200] Two studies (conducted in the USA[197] and Canada[194]) in patients in NYHA class III and with a prolonged QRS duration were uncertain whether or not CRT was cost-effective.

The judgements of the methodological quality assessment of the studies on CRT are summarised in *Table 88*. The studies vary in their quality and relevance to the UK NHS. As mentioned earlier, 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 10 years and generally are of 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 HF, which may limit relevance to the UK.

Six studies[64,155,188,194,196,197] were considered to be of high methodological quality by meeting all or all but one ('Setting comparable to the UK') of the recognised criteria.[38,66] Of these, one study,[64] conducted for a UK setting, is considered to be of most relevance. We describe this study in more detail in the following section.

Fox and colleagues[64]

Fox and colleagues[64] (also reported in Bond and colleagues[203]) developed a Markov model to compare CRT-P and CRT-D with OPT in patients with HF in the UK (see *Appendix 12* 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) because of LVSD (with LVEF ≤ 35%) and electrical dyssynchrony (QRS duration > 120 milliseconds) 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 or ICD related), hospitalised (HF, HF and heart transplant) and death (sudden cardiac cause, HF, non-cardiac related).

The baseline population mortality in the OPT arm was taken from the CARE-HF trial[109] 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 the CARE-HF trial 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;[210] class III 0.61 and class IV 0.44 from Calvert and colleagues[211]) 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 costs 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

TABLE 87 Summary of characteristics of economic evaluations of CRT vs. 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 per QALY)
Bertoldi *et al.* 2011[155]	Brazil	HF NYHA class II, III or IV; EF ≤ 35%	Markov	Meta-analyses	Cost-effective (INT$15,723 per QALY)
Blomstrom *et al.* 2008[191]	Denmark, Finland, Sweden	HF NYHA class III or IV; LVEF < 35%	Survival	CARE-HF[109]	Cost-effective (Denmark €4759 per QALY; Finland €3571 per QALY; Sweden €6493 per QALY)
Bond *et al.* 2009[203] and Fox *et al.* 2007[64]	UK	HF NYHA class III or IV; LVEF < 35%; QRS > 120 milliseconds	Markov	Systematic review and other published sources	Cost-effective (£16,738 per QALY)
Callejo *et al.* 2010[188]	Spain	HF NYHA class III or IV; LVEF < 35%	Markov	CARE-HF[109]	Cost-effective (€28,612 per QALY)
Calvert *et al.* 2005[189]	UK	HF NYHA class III or IV; LVEF < 35%	Trial-based	CARE-HF[109]	Cost-effective (€19,319 per QALY)
Caro *et al.* 2006[190]	UK	HF NYHA class III or IV; LVEF < 35%	DES	CARE-HF[109]	Cost-effective (£15,247 per QALY)
Feldman *et al.* 2005[192]	USA	HF NYHA class III or IV; LVEF ≤ 35%; QRS > 120 milliseconds	Survival	COMPANION[116]	Cost-effective (US$19,600 per QALY)
Heerey *et al.* 2006[193]	Ireland	HF NYHA class III or IV; QRS interval > 130 milliseconds	Markov	Retrospective cohort study	Cost-effective (dominant)
McAlister *et al.* 2004[194]	Canada	HF NYHA class III and prolonged QRS duration	Markov	Systematic review (nine RCTs: MIRACLE,[121] MIRACLE ICD,[136] PATH-CHF,[204] COMPANION,[116] MUSTIC-SR,[125] MUSTIC-AF,[205] Garrigue *et al.*,[206] CONTAK-CD,[126] RD-CHF[207])	Uncertain (US$90,700 per QALY)
Medical Services Advisory Committee 2006[195]	Australia	HF NYHA class III or IV; LVEF < 35%	Decision tree	CARE-HF,[109] MIRACLE[121]	Cost-effective for patients with moderate to severe chronic HF (NYHA classes III and IV) (Aus$12,257 per QALY for a public hospital)
Neyt *et al.* 2011[196]	Belgium	HF NYHA class III or IV; LVEF ≤ 35%; QRS interval > 120 milliseconds	Markov	COMPANION[116]	Cost-effective (€11,200 per QALY)

continued

TABLE 87 Summary of characteristics of economic evaluations of CRT vs. OPT (*continued*)

Study	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
Nichol *et al.* 2004[197]	USA	HF NYHA class III and prolonged QRS duration	Markov	MUSTIC-SR,[125] MUSTIC-AF,[205] Path-CHF,[204] CONTAK-CD,[126] MIRACLE,[121] MIRACLE ICD,[136] COMPANION,[116] Garrigue *et al.*,[206] RD-CHF[207]	Uncertain (US$107,800 per QALY)
Poggia *et al.* 2012[200]	Argentina	HF NYHA class I or II; LVEF ≤ 40%; QRS interval ≥ 120 milliseconds	Markov	Meta-analysis of REVERSE,[208] MADIT-CRT,[209] RAFT[140]	Cost-effective (INT$34,185 per QALY)
Yao *et al.* 2007[198]	UK	HF NYHA class III or IV; LVEF < 35%	Markov	CARE-HF[109]	Cost-effective (€7538 per QALY)
CRT-D vs. OPT					
Aidelsburger *et al.* 2008[199]	Germany	HF NYHA class III or IV	Markov	COMPANION[116] and Banz[187]	May be cost-effective for NYHA classes III and IV depending on device longevity (€88,143 per QALY)
Feldman *et al.* 2005[192]	USA	HF NYHA class III or IV; LVEF ≤ 35%; QRS > 120 milliseconds	Survival	COMPANION[116]	Cost-effective (US$43,000 per QALY)
Medical Services Advisory Committee 2006[172]	Australia	HF NYHA class III or IV; LVEF ≤ 35%; QRS > 120 milliseconds	Decision tree	COMPANION[116]	Cost-effective for patients with CHF NYHA III or IV, sinus rhythm, LVEF ≤ 35% and a QRS duration ≥ 120 milliseconds despite OPT (Aus$22,944/LYG for a public hospital)
Yao *et al.* 2007[198]	UK	HF NYHA class III or IV; LVEF < 35%	Markov	CARE-HF[109]	Cost-effective at WTP of €44,100 per QALY
CRT-D vs. CRT-P					
Bertoldi *et al.* 2011[155]	Brazil	HF NYHA class II, III or IV; EF ≤ 35%	Markov	Meta-analyses	Not cost-effective (INT$84,345 per QALY)
Bond *et al.* 2009[203] and Fox *et al.* 2007[64]	UK	HF NYHA class III or IV; LVEF < 35%; QRS interval > 120 milliseconds	Markov	Systematic review and other published sources	Not cost-effective (£40,160 per QALY)
Callejo *et al.* 2010[188]	Spain	HF NYHA class III or IV; LVEF < 35%	Markov	CARE-HF[109]	Not cost-effective (€53,547 per QALY)
Neyt *et al.* 2011[196]	Belgium	HF NYHA class III or IV; LVEF ≤ 35%; QRS interval > 120 milliseconds	Markov	COMPANION[116]	Not cost-effective (€57,000 per QALY)

TABLE 87 Summary of characteristics of economic evaluations of CRT vs. OPT (*continued*)

Study	Country	Population	Study type	Main source of effectiveness data	Authors' conclusion (ICER)
Yao *et al.* 2007[198]	UK	HF NYHA class III or IV; LVEF < 35%	Markov	CARE-HF[109]	Cost-effective (€18,017 per QALY)
CRT-D vs. ICD					
Bertoldi *et al.* 2011[155]	Brazil	HF NYHA class II, III or IV; EF ≤ 35%	Markov	Meta-analyses	Marginally cost-effective (INT$36,940 per QALY)

EF, ejection fraction; Int$, international dollars; LV, left ventricular; LYG, life-year gained; REVERSE, REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction; WTP willingness to pay.

currency for the analysis were 2005 and UK pounds, except for drug costs, which were 2006 and UK pounds.

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).[64,203] CRT-D compared with 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[64] also found that CRT-P was cost-effective when compared with OPT, whereas the other two studies were uncertain about cost-effectiveness.[194,197] Three of these high-quality studies[155,188,196] also compared CRT-D with CRT-P and found it not to be cost-effective.

Summary of published economic evaluations

- A systematic review of the cost-effectiveness of ICDs for the treatment of arrhythmias and CRT for the treatment of HF identified 51 studies (36 studies of ICDs[63,149,153–186] and 17 of CRT[64,155,172,187–200]). Two studies[55,172] analysed 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 and lifetime.
- Many of the studies were based on a single trial, with the MADIT II and SCD-HeFT trials the most common ICD trials and the CARE-HF and COMPANION trials 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 of the studies reported that ICDs were cost-effective, with the others either finding that ICDs were cost-effective only in high-risk groups or were not cost-effective or being uncertain about cost-effectiveness. Five studies[153,155,160,178,182] were considered to be of high methodological quality; these studies report different conclusions about cost-effectiveness. Of these, only one study was conducted for a UK setting and perspective and is considered to be of most relevance.[153] This study reported a mean ICER of £76,139 per QALY gained for an average UK secondary prevention patient over a 20-year time horizon and therefore concluded that the benefit from ICDs may not be sufficient to make the technology cost-effective as used in the UK (in 2006). 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.

TABLE 88 Summary of the quality of economic evaluations of CRT

Study	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] and Fox *et al.* 2007[64]	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
Medical Services Advisory Committee 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

Study	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. 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
Medical Services Advisory Committee 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
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] and Fox *et al.* 2007[64]	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

?, not possible to answer question as the information was not reported clearly or there was missing information; N, no; Y, yes.

- Almost all studies reported that CRT was cost-effective, with only two studies[194,197] being uncertain whether CRT was cost-effective. Six studies[64,155,188,194,196,197] were considered to be of high methodological quality, two of which were the studies reporting uncertainty about cost-effectiveness.[194,197] One of the high-quality studies[64] was conducted for a UK setting and is considered to be 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-P. The authors concluded that CRT-D is not cost-effective for left ventricular dysfunction and that CRT alone is the most cost-effective option in the population of patients evaluated (NYHA class III and IV with LVEF $\leq$ 35% and QRS duration > 120 milliseconds). CRT-D is more likely to be cost-effective in subgroups of younger patients or those with a 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 that ICD was cost-effective compared with OPT, one[172] found that CRT-D was cost-effective compared with OPT and the other[155] found that CRT-D was marginally cost-effective compared with ICD.

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 HRQoL by NYHA class for those with HF.

For adults, the NICE preferred measure of HRQoL is the EQ-5D[212] and this was used in the previous ICD[153] and CRT[64] TARs. 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 include studies using the EQ-5D (index not visual analogue scale). The search strategies used are described in *Appendix 2*. The inclusion and exclusion criteria for the review are shown in *Chapter 3* (see *Inclusion and exclusion criteria*).

The search strategy identified 6696 references, which after filtering for the EQ-5D resulted in 218 potentially relevant papers. Titles and abstracts were screened and the full texts of 22 papers were retrieved for further inspection. After examining the retrieved papers, six studies met the inclusion criteria.[27,153,211,213–215] 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 EQ-5D or did not report it in the required format. A list of the excluded studies is provided in *Appendix 13*.

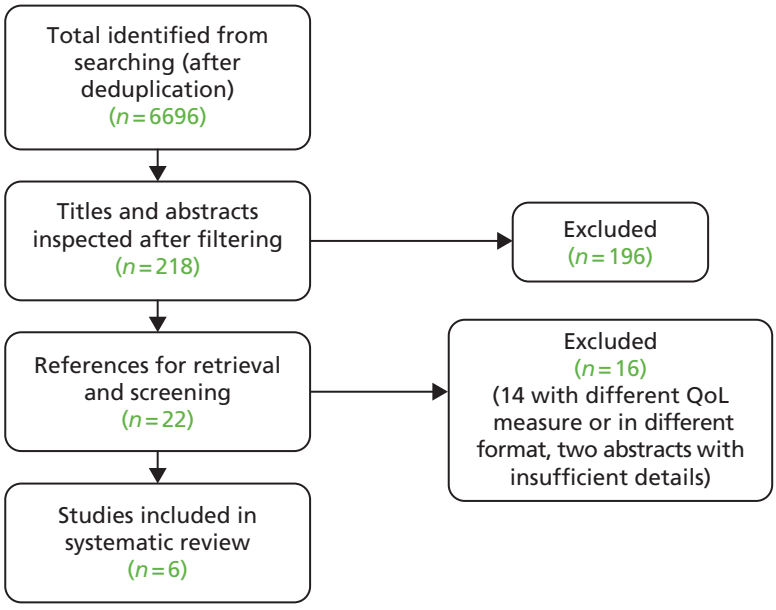

FIGURE 32 Flow chart of identification of studies for inclusion in the review of HRQoL.

Health-related quality of life was assessed using the EQ-5D in four studies of patients with HF[27,211,213,214] and two studies[153,215] of patients who had received an ICD (*Table 89*). Three studies were cohort studies[153,213,215] and three studies were observational analyses based on RCTs.[27,211,214]

TABLE 89 Characteristics of included QoL studies

Study	Country	Study type	Study population	Patient characteristics	QoL instrument and methodology	Results
Buxton *et al.* 2006[153]	UK	Retrospective cohort study	229 patients who had received an ICD	Mean age 60 years, 81% male; NYHA class ≥ III 26%	EQ-5D using UK population preferences	Mean EQ-5D was reported by time since ICD implantation (up to ≥ 6 years) and ranged from 0.69 to 0.78
Calvert *et al.* 2005[211]	UK	CARE-HF RCT[109]	813 patients with chronic HF because of LVSD and dyssynchrony	Mean age 65 years; 74% male; NYHA class III 94%, class IV 6%	EQ-5D using UK population preferences	Mean EQ-5D: 0.60 (95% CI 0.58 to 0.62). NYHA class III 0.61, class IV 0.44
Eurich *et al.* 2006[213]	USA/ Canada	Cohort study	298 patients with HF with LVSD	Mean age 60 years; male 75%; NYHA class I 11%, class II 43%, class III 41%, class IV 4%	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[214]	USA	EPHESUS RCT[214]	1395 patients with chronic HF after acute MI	Mean age 64 years; male 71%; patient origin: US 31%, Europe 52%, Latin America 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 to 0.864), II 0.771 (95% CI 0.761 to 0.781), III 0.673 (95% CI 0.727 to 0.765), IV 0.532 (0.480 to 0.584)
Groeneveld *et al.* 2007[215]	USA	Cohort study	Patients who had previously received ICD therapy for primary ($n = 45$) and secondary ($n = 75$) prevention	Mean age 60 years; male 73%; years since ICD implantation 2	EQ-5D (country of population preferences not reported)	Median EQ-5D score: primary prevention: 0.84 (IQR 0.77, 1), secondary prevention: 0.84 (IQR 0.78–1)
Holland *et al.* 2010[27]	UK	Cohort analysis within HeartMed RCT[216]	293 patients with HF following emergency hospital admission	Mean age 77 years; male 64%; SA NYHA class I/II 33%, class III 34%, class IV 33%	EQ-5D using UK population preferences at baseline and 6 months' follow-up	Mean baseline EQ-5D for SA NYHA class: 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)

EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; IQR, interquartile range; SA NYHA, self-assigned New York Heart Association.

Buxton and colleagues[153] conducted a retrospective postal survey of patients in the UK who had received an ICD between 1991 and 2002 as part of a wider review of ICD therapy. Based on 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 implantation affects HRQoL substantially over time, with values similar at 1 year (0.78) and at > 6 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[215] measured and compared HRQoL among primary and secondary prevention ICD recipients in the USA. They recruited 120 patients undergoing clinical evaluation at cardiac electrophysiology clinics who had previously received an ICD. The average duration since ICD implantation was 2 years. The authors found no difference between the EQ-5D values of primary and secondary patients, with health state utility values of 0.84 for both groups. They concluded that the QoL 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 because of the convenience sampling technique used.

Calvert and colleagues[211] investigated the HRQoL of 813 patients with chronic HF because of LVSD and dyssynchrony (NYHA class III or IV) in the CARE-HF RCT[109] in the UK. CARE-HF was a trial to investigate the effects of CRT-P on the mortality and morbidity of patients already receiving OPT. Baseline EQ-5D data were collected for 740 patients primarily (94%) in NYHA class III. The authors found that the mean baseline health state utility value was 0.6 and that HF had an important impact on all aspects of QoL, which was independent of age. A limitation of the study was that patients were not a random sample of patients with HF but were patients enrolled in a study who were already receiving OPT.

Eurich and colleagues[213] compared several HRQoL measures in 298 people with HF. Patients were recruited across 14 medical centre outpatient departments in the USA and Canada. HRQoL was assessed at baseline and at 6 weeks. EQ-5D health state valuations were completed for both UK and US population valuations. Mean EQ-5D (UK valuation) was 0.66 at baseline and 0.71 at 6 weeks for those with no change in NYHA status (70% of patients). This was a cohort study that evaluated the random changes observed in HF patients in the outpatient setting with no specific intervention during the follow-up period.

Gohler and colleagues[214] estimated utilities for NYHA classification and number of cardiovascular rehospitalisations for patients with chronic HF after acute MI in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) RCT. The EPHESUS trial was a multicentre RCT that investigated the effect of the 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 a 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 cardiovascular 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.

Holland and colleagues[27] conducted a cohort analysis within the HeartMed RCT. A total of 293 adults with HF were included from three large district general hospitals in the UK after an emergency admission and were followed up for 6 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 scores were 0.72, 0.53 and 0.47 for self-assigned NYHA classes I/II, III and IV, respectively, and mean 6-month EQ-5D scores were 0.6, 0.38 and 0.34 respectively. The authors concluded that HF patients' own assessment of their NYHA class is a predictor of outcomes in HF, in the same way as clinician-assigned NYHA classes are a predictor of outcomes; 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[215] and survey respondents at two centres in the UK.[153] This may have biased the results by not including patients who were representative of elsewhere with different experiences. However, in the absence of more rigorous information these studies supply some information of relevance. One of the studies suggests that there is no difference between the EQ-5D scores of primary and secondary prevention patients and that QoL for ICD patients was similar to that of the general population of similar age,[215] and the other shows no evidence that QoL changes over time since implant.[153]

Four cohort studies reported utility estimates for HF patients, with two conducted in the UK[27,153] and two in the USA.[213,214] Patient characteristics were generally similar across studies in terms of sex and age, except for one study[27] in which the mean age was greater (77 years compared with 60–65 years). The severity of HF as measured by NYHA class differed between the studies, with the percentage of NYHA class III participants ranging from 34%[27] to 94%.[211] Mean baseline EQ-5D scores were similar in the two studies that reported this (0.60[211] and 0.66[213]). Three studies reported mean baseline EQ-5D score by NYHA class. Mean baseline EQ-5D scores for NYHA class III were 0.61,[211] 0.63[214] and 0.53 in the study in which patients self-assigned NYHA class.[27] For NYHA class IV, mean baseline EQ-5D scores were 0.44,[211] 0.53[214] and 0.47.[27] Overall, the results suggest that HF has a significant effect on HRQoL. One study reports random changes in utility after 6 weeks in patients with no change in NYHA class[213] and another, which used a self-assigned NYHA classification, showed decreased EQ-5D scores in each NYHA class after 6 months.[27]

Summary of the health-related quality-of-life review

- The systematic review found six relevant HRQoL studies that measured EQ-5D in HF,[27,153,211,213–215] stratified by NYHA class, or that reported on patients who had previously received an ICD.
- Two studies[153,215] were conducted in patients who had received an ICD, one in the UK[153] of patients at two hospitals who were implanted between 1991 and 2002 and who responded to a postal questionnaire and one[215] of volunteers attending a defibrillator clinic in the USA.
- The UK ICD study reported that the mean EQ-5D score did not change with time after implantation (mean EQ-5D score ranged from 0.69 to 0.78 for the years up to ≥ 6 years since implantation). The US study reported no difference between the EQ-5D scores of primary and secondary prevention patients (median EQ-5D score 0.84) and that QoL for ICD patients was similar to that of the general population.
- Four cohort studies reported EQ-5D scores in HF, two[127,153] in the UK (one of which was based on the CARE-HF trial) and two[213,214] in the USA (one based on the EPHESUS trial).
- Two studies reported similar mean baseline EQ-5D scores of 0.60 (UK RCT-based study[211]) and 0.66 (US cohort study[213]).
- Three studies[27,211,214] reported mean baseline EQ-5D score by NYHA class. Mean baseline EQ-5D scores for NYHA class III were 0.61[211] and 0.53[214] (UK studies) and 0.63 (US study).[214] The lowest value was reported in the study[27] in which patients self-assigned NYHA class. Mean baseline EQ-5D scores for NYHA class IV were 0.44[211] and 0.47[27] (UK studies) and 0.53[214] (US study).
- One US study[213] reported random changes in utility after 6 weeks in patients with no change in NYHA class and one UK study[27] (which used a self-assigned NYHA classification) showed decreased EQ-5D scores in each NYHA class after 6 months.
- Overall, the results show decreased EQ-5D scores in HF compared with those of the general population, particularly in NYHA classes III and IV.

Review of the manufacturers' submission

As described in *Chapter 4* (see *Summary of Southampton Health Technology Assessments Centre's peer review of clinical effectiveness in the Association of British Healthcare Industries joint submission*), one MS consisting of a written report and an electronic model supporting the reported cost-effectiveness analyses

was submitted to NICE.[151] Further details on the submission and a discussion of the clinical data reviewed and presented can be found in *Chapter 4* and *Appendix 10*.

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.

Review of the cost-effectiveness analysis in the manufacturers' submission

A structured data extraction form was used to guide the review of the MS (see *Appendix 10*),[151] 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 HF, a NMA of IPD and a report of an economic evaluation undertaken for the NICE multiple technology appraisal process.

The cost-effectiveness analysis 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. IPD from 12,638 patients from 13 RCTs were used to inform the economic model. All individuals are adults with HF, with a LVEF $\leq 35\%$ and/or at risk of SCD. This heterogeneous group of patients was split into 48 subgroups according to their NYHA class, QRS duration, LBBB status and aetiology of heart disease, and cost-effectiveness results are reported for each subgroup.

The perspective adopted for the 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 HRQoL was incorporated as an intervention-specific increment. These estimates were derived from published sources and IPD from the trials included in the systematic review of clinical effectiveness studies in the MS.

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 included in the NICE scope.[61] However, not all of them were included as comparators for all patient subgroups in the MS, as no patients were identified for the following combinations:

- ICD excluded for NYHA class IV
- CRT-P excluded for NYHA class I/II and QRS duration < 120 milliseconds
- CRT-D excluded for QRS duration < 120 milliseconds.

Clinical advice indicated that these exclusions are reasonable.

Modelling approach

A cohort survival model was developed in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) with two states for alive and dead. Death is modelled using a series of covariate-based regression equations for baseline risk and treatment effect using long-term IPD. Based on 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 NMAs. For the model baseline survival curve, a Weibull distribution was used with the parameters of the risk model shown in *Appendix 10*. A similar approach is taken to estimate the probability of all-cause hospitalisation. HRQoL utilities are 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 those of 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 for all 4992 patient profiles [four NYHA classes, two aetiology status groups (ischaemic/non-ischaemic), three QRS categories, four LVEF categories, LBBB status (yes/no), two gender groups, 13 age categories]. In the second stage, results were aggregated over LVEF and age and gender categories, reducing the subgroups to 48, defined by NYHA class, QRS duration, LBBB status and aetiology.

Assumptions

The following additional assumptions are made in the model:

- The effects of treatment on HRQoL diminish over time. The model assumes that the benefit observed at 6 months is maintained for up to 5 years and thereafter begins to recede in a linear manner over the time period from 5 to 10 years. After 10 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 NYHA class of the patient.

Estimation of effectiveness

The clinical effectiveness estimates were based on a NMA of IPD from 13 clinical trials (12,638 patients, followed up for up to 7.5 years). The clinical trials were CARE-HF,[109] COMPANION,[116] CONTAK-CD,[126] DEFINITE,[90] MADIT,[99] MADIT II,[103] MADIT-CRT,[130] MIRACLE,[121] MIRACLE ICD,[136] RAFT,[140] RethinQ,[142] REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE)[208] and SCD-HeFT.[105] These trials were identified through a systematic review of the clinical effectiveness of all of the interventions. A further nine trials[69,82,125,138,139,144,241,244] were also identified in the review but IPD were not available for these trials (see *Chapter 4* and *Appendix 10* 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 also allowed the available direct and indirect evidence to be used to inform comparisons 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 later in this chapter.

The IPD NMA showed that ICDs, CRT-D and CRT-P were significantly more effective than OPT for people with HF when assessed for all-cause mortality, with CRT-D also providing statistically significant benefit compared with ICDs and CRT-P. The results of the analysis of those subgroups that benefited from the different interventions compared with OPT were less clear. CRT-D had a statistically significant benefit for all people with a QRS $\geq$ duration of $\geq$ 150 milliseconds and all women with a QRS $\geq$ duration from $\geq$ 120 milliseconds to $<$ 150 milliseconds and a marginally insignificant effect for all men with a QRS duration from $\geq$ 120 milliseconds to $<$ 150 milliseconds. ICDs had a significant benefit for men aged $<$ 60 years and for men aged $\geq$ 60 years with a QRS duration from $\geq$ 120 milliseconds to $<$ 150 milliseconds and without LBBB. CRT-P had a significant benefit for women with a QRS duration $\geq$ 150 milliseconds and LBBB. The NMA found that CRT-D had the strongest effect on all-cause mortality (commercial-in-confidence information has been removed). Treatment effects for the individual devices were also statistically significant (commercial-in-confidence information has been removed).

All devices reduced the rate of all-cause hospitalisations compared with OPT, with rates decreasing for NYHA classes I–III with ICDs (commercial-in-confidence information has been removed), for NYHA classes III (commercial-in-confidence information has been removed) and IV (commercial-in-confidence information has been removed) with CRT-P and for all NYHA classes with CRT-D (commercial-in-confidence information has been removed). HRQoL was assessed using the EQ-5D, showing counterintuitive results for the effects

of treatment. Adjustments were made assuming that CRT-P and CRT-D would have the same effects and that ICDs would have an effect only on NYHA classes I and II. Benefits were thought to last for (commercial-in-confidence information has been removed) years.

UK device longevity estimates were derived from NHS data from the Central Cardiac Audit Database (CCAD)[217] on all implants with verified life status from 2000 to 2011 (~ 40,000 implants). The MS considers that these device longevity estimates represent the best currently available estimates as CCAD contains data on a large number of implants and it 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 as it is commonly used to model such data and it was considered a good fit (in terms of both within-data accuracy and long-term predictive plausibility). Median time to device failure in the model was 7.1 years for ICDs, 10.4 years for CRT-P and 5.8 years for CRT-D. The methodology used by the manufacturers to estimate device longevity is commonly used; however, clinical advice indicated that these figures seem to be overestimated.

Critical appraisal of the cost-effectiveness analysis in the manufacturers' submission

The MS was appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements[67] and the Philips and colleagues' checklist.[68] Overall, the submission meets all of 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 critical appraisal of the MS.

TABLE 90 Critical appraisal of the economic evaluation[a]

No.	Item	MS	Comments
1	Is there a clear statement of the decision problem?	Yes	
2	Is the comparator routinely used in the UK NHS?	Yes	
3	Is the patient group in the study similar to those of interest in the UK NHS?	Yes	
4	Is the health-care system comparable to that in the UK?	Yes	
5	Is the setting comparable to that in 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 the 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

?, unclear.
a Questions in this checklist based on checklist in Philips *et al.*[67]

The model structure is consistent with the currently accepted theory of HF 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 the choice of evidence (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 systematic review of clinical effectiveness studies in the MS. 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, a comparison has been made between the results of the MS and results generated in previous appraisals and reasons have been given for any differences.

Estimation of quality-adjusted life-years

The approach taken for HRQoL was (1) to estimate UK-specific age and gender population utilities, (2) derive disease-specific decrements using IPD EQ-5D data and (3) 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[152] of 3395 individuals resident in the UK. Disease-specific decrements were taken from the CARE-HF,[109] MADIT-CRT[209] and RAFT[140] trials. For the impact of treatment, the utility increments were 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 10*.

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 counterintuitive given the nature of the underlying disease and the interventions, for example the results for CRT-D for NYHA class 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 CRT-P for NYHA class III/IV, ICDs are assumed to have (commercial-in-confidence information has been removed) for NYHA class III. ICDs are associated with a utility increment of (commercial-in-confidence information has been removed) for NYHA class I/II. CRT-D has a utility increment of (commercial-in-confidence information has been removed) for NYHA class I/II and (commercial-in-confidence information has been removed) for NYHA class III/IV. These values for ICDs and CRT-P were derived from the IPD analysis after subtracting the OPT NYHA class III value (commercial-in-confidence information has been removed). The values used for CRT-P were of a similar magnitude to those reported in the CARE-HF study, which gave a utility increment of 0.1 at 18 months after implantation compared with OPT patients.

In the model, the HRQoL benefit observed at 6 months is maintained up to 5 years and thereafter begins to recede in a linear manner over a time period of 5–10 years. After 10 years the model assumed that the individual with a CRT or an 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 those of Buxton and colleagues[153] and Fox and colleagues[64]), in which no benefit from the interventions was assumed. However, the device-specific increments used in the MS are similar to those used in some of the previous models.[177,192,196] The impact on HRQoL of treatment-related adverse events (such as infection and perioperative complications), considered in previous models, was not included in the MS.

Estimation of costs

The resource use accounted for in the MS included device-related resources, 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 hospitalised per month. Hospital costs were derived from the NHS reference costs[218] and combined with the average mean length of stay. The HF hospitalisation event cost was £2295 and the non-HF hospitalisation event cost was £2448.

Device costs were sourced from the average selling prices obtained 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 (HRG) tariff values.[218] Device-related infection costs were derived by inflating values in the previous TAR on CRT[64] to £3139. Device costs, with implantation costs, were £15,248, £8281 and £17,849 for ICDs, CRT-P and CRT-D respectively. Further device costs are shown in *Appendix 10*.

The manufacturers assumed that an OPT regimen is taken by all patients for HF treatment, regardless of whether or not they receive a device in addition, and the drug cost allocated in any given month to each patient alive is based on his or her baseline NYHA class. The proportions of patients using a range of HF medications, by NYHA class, were 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).[219] 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 classes II–IV.

Overall, the derivation of costs and assumptions presented in the MS seems 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.

Cost-effectiveness results

The base-case deterministic results are presented for 48 subgroups defined by NYHA class, QRS duration, LBBB status and aetiology, but not 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 base-case results can be found in the data extraction form (see *Appendix 10*) 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, fully aggregated results with reporting of total costs and QALYs are presented only for subgroups of NYHA III class patients comparing CRT-D with OPT. Overall, the results show that for most subgroups there is at least one device with an ICER of < £30,000 per QALY and that, in some cases, a different device might be cost-effective if a £20,000 per QALY threshold is considered.

The manufacturers conclude that, in many cases in which 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, with most deterministic sensitivity analyses reported in the MS consisting of scenario analyses. Not all forms of uncertainty were explored, only uncertainty associated with a few methodological assumptions. The MS does not report the ranges used for the sensitivity analyses, only the different scenarios tested, and does not identify the model parameters with the 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.

TABLE 91 Summary of the base-case deterministic results

HF severity	QRS duration (milliseconds)	Results summary
NYHA class I/II	< 120	The ICERs for ICD vs. OPT are < £25,200 per QALY gained
	120–149	ICD is a cost-effective treatment option[a] (ICER < £17,000 per QALY) for patients with no LBBB. For CRT-D, all ICERs are < £25,000 per QALY gained in LBBB patients (£20,608–24,343)
	≥ 150	CRT-D is cost-effective treatment[a] with an ICER of < £28,000 per QALY gained for all options
NYHA class III	< 120	ICD vs. OPT generates ICERs of < £30,000 per QALY
	120–149	CRT-P is cost-effective.[a] CRT-D generates ICERs between £23,900 and £27,400 per QALY gained relative to CRT-P
	≥ 150	CRT-P is cost-effective vs. OPT (ICER < £20,000 per QALY). Compared with CRT-P, CRT-D generates ICERs of < £30,000 per QALY gained. ICD is either dominated or extendedly dominated
NYHA class IV	< 120	No comparative analysis was possible in this patient group as no patients were identified for this combination
	≥ 120	For CRT-P compared with OPT, all ICERs are close to or < £20,000 per QALY gained. For the comparison between CRT-D and CRT-P, all ICERs are > £30,000 per QALY gained

a According to willingness-to-pay threshold of £20,000–30,000 per QALY gained.

The following scenarios were tested in sensitivity analyses: removal of treatment effect tapering (mortality and HRQoL), use of alternative NYHA-based IPD results and 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 HRQoL 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 in NYHA class IV than in patients in 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 compared with NYHA class I–III patients. This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups 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 were conducted for a few subgroups, selected to reflect the baseline characteristics of participants in the MADIT-CRT trial, but no overall population analysis was performed. Because of the complexity of patient-level heterogeneity, the MS reported that a full probabilistic sensitivity analysis would take several months to execute. Results were presented graphically for four subgroups, men and women with and without LBBB, for patients of 65 years, NYHA class II, ischaemic, QRS duration > 150 milliseconds and LVEF between 20% and 25% patients. For these subgroups, CRT-D and OPT showed a similar probability of being cost-effective at a willingness-to-pay (WTP) threshold of £20,000 per QALY. The manufacturers concluded that the 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 probabilistic sensitivity analysis, such as mean values, distributions and variability of those variables. Credible intervals for the 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 the probabilistic sensitivity analysis are appropriate to reflect uncertainty in parameter estimates.

The MS compares the cost-effectiveness estimates with those produced in the previous appraisals of CRT in patients with NYHA class III/IV HF developed by Fox and colleagues[64] and the review of ICDs in primary prevention.[153] The estimates from the MS model are markedly lower than those that were generated in the models developed for TA95[42] and TA120.[43] The following reasons are given for the differences: real-time reduction in production costs, increases in device longevity compared with values used in previous models, better estimates of the impact of treatment on mortality and better understanding of the impact of treatment on HRQoL.

Summary of the Association of British Healthcare Industries 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 on IPD data according to patient clinical characteristics.
- The model compared ICDs, CRT-P and CRT-D with OPT.
- The model met all but two of the criteria for methodological quality.
- The cost-effectiveness results are presented in the submission for subgroups according to NYHA class, QRS duration, LBBB status and aetiology.
- The cost-effectiveness results do not directly address questions posed in the scope from NICE 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 one device with an ICER of < £30,000 per QALY gained and in some cases a different device might have an ICER of < £20,000 per QALY gained.

Critique of the Association of British Healthcare Industries submission

The ABHI economic model is a cohort survival model with survival based on a series of covariate-based regression equations. The model includes the costs and HRQoL 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 HF 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 the model structure, the assumptions used in the model have not been fully reported and explained and there is no evidence given in the MS for internal validation of the model.

The manufacturers' joint submission presented an IPD NMA to assess the effectiveness of the different interventions for people with HF. It used meta-regression, allowing the effects of various patient characteristics on treatment outcomes to be assessed and any subgroups 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 *Chapter 4* (see *Individual patient data network meta-analysis: a critical appraisal*), 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 on IPD data from over 12,000 patients and 13 RCTs and are of high quality; as stated by the MS[151] this 'represent[s] the first analysis of its kind and magnitude' (p. 2). 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 that 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 covariables included (i.e. number of variables and subcategories) and the lack of data for specific outcomes assessed. As a consequence, the MS suggests that the analyses for all-cause mortality which include treatment effect modifiers (i.e. subgroups) should be interpreted cautiously, and it makes adjustments to counterintuitive 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 determine 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.[61] 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 made over costing and resource use are similar to the approach used by Fox and colleagues[64] 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 on all available implant data from CCAD and, as stated by the manufacturer, represent the best device longevity estimates 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 those of Buxton and colleagues[153] and Fox and colleagues[64]), in which no benefit from the interventions 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[177,192,196] and are of a similar magnitude to those reported in the CARE-HF study.[109]

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 with those from previously developed economic models. Uncertainty is not comprehensively assessed in the MS as the sensitivity analyses presented are limited to a few scenarios. The methodology used in the MS for the probabilistic sensitivity analysis is not described in sufficient detail to determine whether or not joint parameter uncertainty was properly assessed.

Independent economic evaluation

Statement of the decision problem and perspective for the cost-effectiveness analysis

In accordance with the NICE scope,[61] we developed an economic model to estimate the cost-effectiveness of:

- ICDs for people at risk of SCD as a result of ventricular arrhythmias compared with standard care without an ICD
- CRT-P or CRT-D for people with HF 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, ICDs and OPT.

The perspective of the analysis was that of the NHS and PSS. A 3.5% rate was used to discount future health gains and costs.

Strategies and comparators

The scope for the appraisal as defined by NICE[61] stated that the interventions to be considered are ICDs for patients at risk of SCD and CRT for patients with HF as a result of LVSD and cardiac dyssynchrony, alongside standard care (also referred to as OPT).

The scoped population groups are eligible for different interventions and comparators; hence, the cost-effectiveness analyses were performed specifically for each population group. *Table 92* presents the relevant comparisons for each group, as per the scope[61] developed by NICE for this assessment.

1. For people at increased risk of SCD as a result of ventricular arrhythmias despite OPT, an ICD with OPT will be compared with standard care (OPT without an ICD).
2. For people with HF as a result of LVSD 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).
3. For people with both conditions described above, CRT-D with OPT will be compared with an ICD with OPT, CRT-P with OPT or standard care (OPT alone).

Methods for the economic analysis

Model type and rationale for the model structure

All-cause mortality, SCD, HF mortality and death from other causes were key outcomes in the clinical trials reviewed in *Chapter 4*. Secondary outcomes included hospitalisation from HF, NYHA class and QoL. 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 HF (see *Appendix 2*). References identified by these searches, along with previous economic evaluations reviewed earlier (see *Systematic review of existing cost-effectiveness evidence*), informed the development of a Markov state transition model.

A Markov model developed in Microsoft Excel (2010) 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 4-weekly cycles. Disease progression varies according to the characteristics of the population group and the care pathway that 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 QALYs.

The adaptation of the model developed by Fox and colleagues[64] for TA120[43] was found appropriate for the analysis of the cost-effectiveness of ICDs for the treatment of arrhythmias and the cost-effectiveness of CRT devices for the treatment of HF. For patients with HF as a result of LVSD and cardiac dyssynchrony considered as candidates for CRT, we based the pathways on those included in the model developed

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

Note: in OPT strategies patients are treated initially with OPT and subsequently receive devices as clinically necessary.

for TA120.[64] 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. Further details on the development of the model can be found in *Appendix 14*.

Our model structure is similar to that of the model developed by Fox and colleagues.[64] The key events modelled were hospitalisation because of HF or arrhythmias, transplantation, surgical failure, death, perioperative complications of the implant procedure, routine device replacement, lead displacement, infections and device upgrades.

Figure 33 provides a general schematic of the health states that 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 submodel, whereas patients undergoing management with a device enter in the implant surgery state and will typically transition to stable in the device submodel.

Patients in a stable health state (either receiving OPT or with a device) can remain stable, be hospitalised because of HF or arrhythmia or 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 because of HF may be referred for heart transplantation. Patients in any of the live health states (stable, hospitalised and transplanted) can die from arrhythmia (SCD), HF or any other cause (cardiac or non-cardiac). Transitions between health states vary according to the population group and the treatment received.

The model structure was developed to reflect the management of patients under current clinical practice, consisting of a simplistic approximation of the clinically plausible care pathways. Therefore, the model allows patients initially managed with OPT or CRT-P to have a device implanted or upgrade to a different device according to disease progression.

The model output obtained with this approach is intended to capture the impact of all treatments received by the patient over a lifetime, instead of only those of the treatment initially allocated, providing a more realistic estimation of the consequences of the adoption of a particular technology as initial treatment.

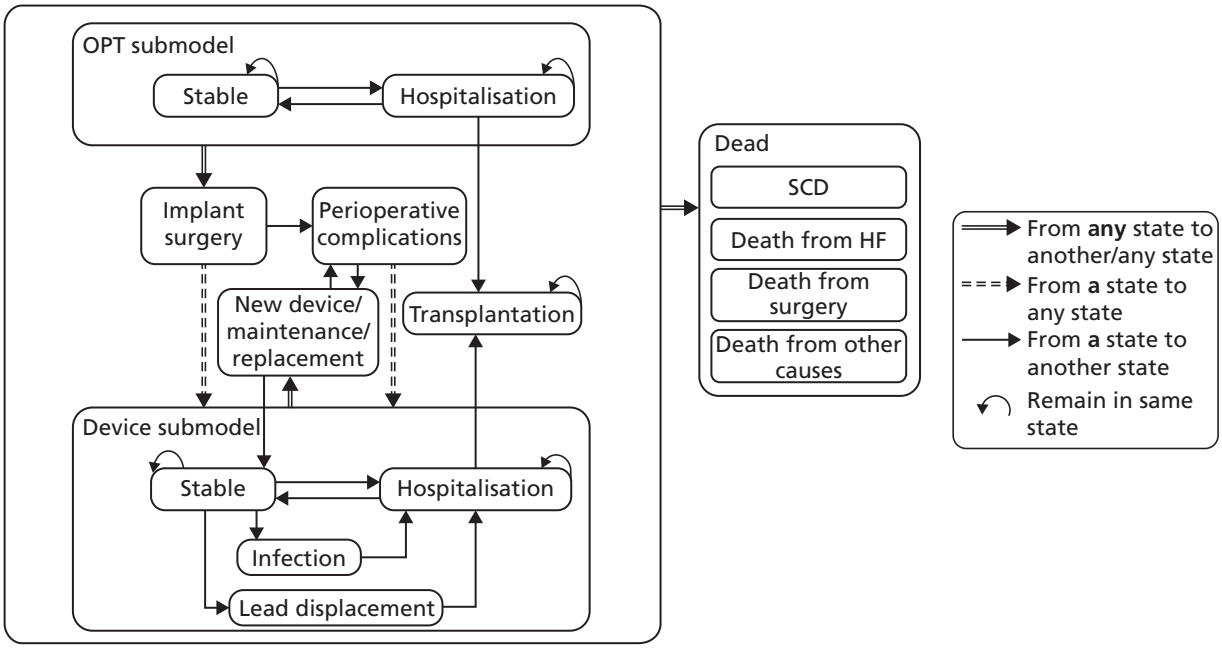

FIGURE 33 General schematic of the model.

Relevant patient populations

The baseline cohorts modelled for the economic analysis consist of the three population groups who were identified in the scope developed by NICE[61] for this assessment:

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

Baseline characteristics (age, sex and, when relevant, proportion in each NYHA class) for the modelled cohorts were based on values reported in relevant clinical trials providing data to populate the model.

Treatment pathways

Population 1: patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite receiving optimum pharmacological therapy

The treatment pathways modelled for each cohort of population 1 patients are shown in *Table 93*.

Receiving an implantable cardiac defibrillator and optimum pharmacological therapy 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 because of HF, 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 implantation are referred for reimplantation 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 because of HF, severe arrhythmias, 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 be referred for heart transplantation (if hospitalised for HF). Stable ICD patients are also subject to periodic battery replacement. As with initial implant surgery and reimplantation, these routine replacement procedures expose the patient to a risk of procedure-related death, perioperative complications and unsuccessful implantation.

Receiving optimum pharmacological therapy In this arm, patients enter the model in a stable health state in which they are treated with OPT to prevent major ventricular arrhythmia. Stable OPT patients can remain stable, be hospitalised because of HF or be hospitalised because of major arrhythmia and therefore referred for ICD implantation. Hospitalised patients can return to the stable health state after treatment, be referred for ICD implantation (if hospitalised for major arrhythmia) or be referred for transplantation (if hospitalised for HF). Patients referred for ICD implantation are assumed to follow the same pathway described above for the cohort who enter the model receiving an ICD + OPT and to be subject to the same risk of events.

TABLE 93 Treatment pathways for population 1

	Treatment	
Cohort	First	Second
OPT	OPT	ICD + OPT
ICD + OPT	ICD + OPT	–

Model assumptions for population 1 Being an adaptation of the economic model developed by Fox and colleagues[64] for TA120,[43] our model relies on some of the assumptions underlying Fox and colleagues' model that were validated by clinical advice:

- patients being managed with OPT alone who experience hospitalisation because of non-fatal arrhythmia are assumed to be referred to and undergo ICD implantation
- patients receiving OPT and hospitalised because of HF who experience a serious arrhythmic event are assumed to be implanted with an ICD and to become stable with the device or be hospitalised because of 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
- patients with an unsuccessful implantation are assumed to have reimplantation attempted in the following cycle
- patients undergoing reimplantation 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 because of unsuccessful ICD implantation.

Population 2: patients with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite receiving optimum pharmacological therapy

Table 94 summarises the treatment pathways modelled for each cohort of population 2 patients.

Receiving optimum pharmacological therapy Patients enter the model in a stable health state being treated with OPT to prevent HF. Stable OPT patients may remain stable or be hospitalised because of HF or severe arrhythmia. OPT patients who are hospitalised may return to the stable health state with OPT after treatment or 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.

TABLE 94 Treatment pathways for population 2

	Treatment			
Cohort	First	Second	Third	Fourth
OPT	OPT	CRT-P + OPT	CRT-D + OPT	ICD + OPT
	OPT	CRT-D + OPT	ICD + OPT	OPT
CRT-P	CRT-P + OPT	CRT-D + OPT	ICD + OPT	OPT
	CRT-P + OPT	OPT	CRT-P + OPT	CRT-D + OPT
	CRT-P + OPT	OPT	CRT-D + OPT	ICD + OPT
CRT-D	CRT-D + OPT	ICD + OPT	OPT	CRT-P + OPT
	CRT-D + OPT	ICD + OPT	OPT	CRT-D + OPT

Receiving CRT-P and optimum pharmacological therapy Patients with HF 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 because of HF 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 an unsuccessful CRT-P implantation may return to the OPT stable health state or be hospitalised because of HF or 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 HF, lead displacement, infection or battery failure. CRT-P patients who are hospitalised may return to the stable with CRT-P after treatment state, remain hospitalised, be referred for an upgrade to CRT-D if they experience serious arrhythmias or be referred for a heart transplant if they experience worsening HF.

Receiving CRT-D and optimum pharmacological therapy Patients with HF enter the model undergoing CRT-D implantation surgery. Similar to patients who enter the model undergoing CRT-P implantation surgery, those who receive 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 because of HF 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 an unsuccessful CRT-D implantation are assumed to undergo an ICD implantation. 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 because of HF or severe arrhythmia, perioperative complications, lead displacement, infection or battery failure. Those with an unsuccessful ICD implantation are assumed to be managed with OPT alone and follow the pathway described earlier for population 2 receiving OPT.

Patients who are stable with CRT-D alongside OPT can be hospitalised if they experience HF or severe arrhythmia, lead displacement, infection or battery failure. CRT-D patients who are hospitalised may return to the stable with CRT-D after treatment state, remain hospitalised or be referred for a heart transplant if they experience worsening HF.

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[64] for TA120[43] following clinical validation:

- patients with CRT-P who experience a serious arrhythmic event are assumed to be referred for CRT-D implantation
- patients who survive an unsuccessful CRT-P implantation are assumed to return to being managed with OPT alone
- patients who are hospitalised because of HF and who are referred for a device upgrade are assumed to be implanted and become stable with the device or to be hospitalised because of HF, perioperative complications, lead displacement or infection in the following cycle.

Other assumptions were incorporated according to clinical advice:

- patients who survive an unsuccessful CRT-D implantation are assumed to undergo an ICD implantation
- for consistency with an unsuccessful CRT-P implantation, patients who survive an 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 of these strategies allow for subsequent device implants and upgrades. The treatment pathways modelled for each cohort of population 3 patients are presented in *Table 95*.

Receiving CRT-D and optimum pharmacological therapy Patients with both conditions who enter the model undergoing CRT-D implantation surgery follow a pathway which is similar to that described earlier for population 2 receiving CRT-D + OPT. Patients who survive an unsuccessful CRT-D implantation are also assumed to undergo an ICD implantation. However, patients with an ICD who become hospitalised because of HF are referred for CRT-D reimplantation.

Receiving CRT-P and optimum pharmacological therapy Patients with both conditions who enter the model undergoing CRT-P implantation surgery follow a similar pathway to that of population 2 receiving CRT-P + OPT described earlier.

Receiving implantable cardiac defibrillator and optimum pharmacological therapy Patients enter this arm of the model undergoing ICD implantation surgery. Those who survive with a successful ICD implantation can become stable with the device or be hospitalised because of HF, a serious arrhythmic event, perioperative complications, lead displacement, infection or battery failure. Those hospitalised for HF are upgraded to a CRT-D implant. Those with an unsuccessful ICD implantation are assumed to be managed with OPT alone and follow the pathway described below for those receiving OPT.

Receiving optimum pharmacological therapy Patients with both conditions who enter the model being managed with OPT alone may remain stable with OPT or be hospitalised because of HF or severe arrhythmia. Patients hospitalised for HF may return to the stable health state with OPT after treatment or be referred for CRT-P implantation, CRT-D implantation or transplantation. OPT patients who are hospitalised because of serious arrhythmias are referred for CRT-D implantation. 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.

TABLE 95 Treatment pathways for population 3

	Treatment			
Cohort	First	Second	Third	Fourth
OPT	OPT	CRT-D + OPT	ICD + OPT	OPT
	OPT	CRT-P + OPT	CRT-D + OPT	ICD + OPT
ICD + OPT	ICD + OPT	CRT-D + OPT	ICD + OPT	OPT
	ICD + OPT	OPT	CRT-D + OPT	ICD + OPT
	ICD + OPT	OPT	CRT-P + OPT	CRT-D + OPT
CRT-P + OPT	CRT-P + OPT	CRT-D + OPT	ICD + OPT	OPT
	CRT-P + OPT	OPT	CRT-D + OPT	ICD + OPT
	CRT-P + OPT	OPT	CRT-P + OPT	CRT-D + OPT
CRT-D + OPT	CRT-D + OPT	ICD + OPT	OPT	CRT-P + OPT
	CRT-D + OPT	ICD + OPT	OPT	CRT-D + OPT

Model assumptions for population 3 Some of the assumptions underlying the model of Fox and colleagues,[64] which were 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 because of HF are assumed to be referred for a CRT-D
- patients who are hospitalised because of HF and who are referred for a device upgrade are assumed to be implanted and to become stable with the device or be hospitalised because of HF, perioperative complications, lead displacement or infection in the following cycle.

Clinical experts confirmed the reasonability of other assumptions used in our model:

- patients who survive an unsuccessful CRT-D implantation are assumed to undergo an ICD implantation
- for consistency with an unsuccessful CRT-P implantation, patients who survive an 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 a device can be in hospital because of perioperative complications, lead displacement, routine device replacement or infection. The pathways subsequent to each of these events are common to all populations:

- *Perioperative complications*: patients with perioperative complications can become stable with the device or continue to be hospitalised because of HF, lead displacement, battery failure or infection.
- *Heart failure*: patients hospitalised because of HF can return to the stable state with the device, continue to be hospitalised because of HF, experience a device-related infection or a lead displacement or be referred for a heart transplant. Concerning populations 2 and 3 exclusively, patients receiving CRT-P who are hospitalised because of HF can be referred for an upgrade to CRT-D if they experience a major arrhythmia or need a routine device replacement.
- *Lead displacement*: patients experiencing lead displacement will undergo 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 for an initial implantation.
- *Routine device replacement*: patients will undergo re-surgery to replace the device because of 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.
- *Infection*: to treat a device-related infection, patients will undergo explantation of the device, treatment for the infection and reimplantation of a new device. These patients are assumed to have the same risks of surgical death, surgical failure and any complications as for 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 can die from any health state in the model
- 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 the probability of death for non-transplanted patients, except in the first cycle
- only patients who are hospitalised because of HF are assumed to be at risk of a heart transplant
- patients referred for transplantation are assumed to remain in this health state until they die
- patients hospitalised because of HF while being managed with OPT are assumed to have a null probability of remaining hospitalised because of HF in the following cycle
- patients hospitalised because of perioperative complications are assumed to have no risk of surgical death or surgical failure
- all patients undergoing surgery (as a result of the initial implantation, a reattempt at implantation, routine device replacement or infection) are assumed to have the same risk of surgical failure.

Discounting

In accordance with current NICE guidance,[67] future costs and benefits were discounted at a rate of 3.5%. The impact of discounting using rates of 0% and 6% were explored in sensitivity analysis.

Presentation of the 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 HF 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.

The 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.

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 a disproportionate impact on the 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 probabilistic sensitivity analysis.[220] 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 is described in the following section. *Appendix 15* reports the variables included in the probabilistic sensitivity analysis, the form of distribution used for sampling and the parameters of the distribution.

Data sources and parameter estimates

Population 1: patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimum pharmacological therapy

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,[71] MADIT II[101] and SCD-HeFT[105]) were included in this analysis. According to the evidence found in *Chapter 4* (see *People at risk of sudden cardiac death as a result of ventricular arrhythmias*), patients who survived cardiac arrest or sustained VT are likely to be those for whom ICDs have consistently shown benefit. As the AVID trial[71] was the largest trial found for this population, the results of this trial were used for our base-case analysis of patients at increased risk of SCD as a result of ventricular arrhythmia. MADIT II[101] was the trial with largest number of patients with remote MI and was considered representative of a relevant group who might benefit from ICDs for primary prevention of SCD. Similarly, the results from the SCD-HeFT trial[105] were used to inform a subgroup analysis of patients with mild to moderate HF with an indication for an ICD. An additional subgroup analysis was conducted for patients with cardiomyopathy using as a baseline the all-cause mortality reported for the SCD-HeFT[105] subgroup of patients with non-ischaemic CHF in the placebo arm.

Kaplan–Meier curves for overall survival for the OPT arms (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 were assessed visually. Those showing better goodness of fit were used to estimate survival beyond trial follow-up. Hence, baseline time-dependent transition probabilities for transition to the all-cause mortality health state for the model OPT arm were calculated from the estimated hazard functions.[220] 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 (see *Chapter 4*, *People at risk of sudden cardiac death as a result of ventricular arrhythmias*, *All-cause mortality*) 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,[71] the MADIT II trial[101] and the SCD-HeFT trial.[105] Details of the regression analyses and comparison between the regression results and the observed survival in these trials are shown in *Appendix 15*. 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 15* for further details). To do this, scanned images of the Kaplan–Meier curves were imported in Engauge software (Engauge Digitizer – Digitizing software version 4.1; see http://digitizer.sourceforge.net/) and the extracted data points were then exported to Microsoft Excel for further analysis. *Table 96* shows the parameters of the Weibull functions used in the model to estimate time-dependent mortality for the OPT arm of the population 1 model.

TABLE 96 Weibull model parameters for all-cause mortality: population 1

Parameter	Mean (SE)			
	AVID[71] ($R^2 = 0.994$)	MADIT II[101] ($R^2 = 0.9903$)	SCD-HeFT[105] ($R^2 = 0.993$)	SCD-HeFT[105] non-ischaemic CHF subgroup ($R^2 = 0.985$)
$\ln(\lambda)$	–3.380 (0.026)	–4.628 (0.047)	–5.288 (0.039)	–4.821 (0.037)
γ	0.696 (0.009)	1.007 (0.017)	1.083 (0.011)	0.883 (0.011)

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

The effect of an 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 *Chapter 4* (see *People at risk of sudden cardiac death as a result of ventricular arrhythmias*, *All-cause mortality*). For the base-case analysis (secondary prevention of cardiac arrest), the pooled RR of 0.75 (95% CI 0.61 to 0.93) was used. For the subgroup analysis of patients with remote MI, a pooled RR from the MADIT I[99] and MADIT II[103] trials of 0.57 (95% CI 0.33 to 0.97) was used. The SCD-HeFT[105] RR of 0.77 (95% CI 0.66 to 0.89) was used for the subgroup of patients with mild to moderate HF, and a pooled RR of 0.74 (95% CI 0.58 to 0.93) was used for patients with cardiomyopathy (derived from the SCD-HeFT[105] non-ischaemic CHF subgroup and the three cardiomyopathy trials[69,82,90]).

Hospitalisation

Hospitalisation because of heart failure MADIT II is the only RCT included in our systematic review (see *Chapter 4*, *People at risk of sudden cardiac death as a result of ventricular arrhythmias*, *Assessment of effectiveness*) reporting HF hospitalisations for patients at increased risk of SCD. The number of admissions per total number of trial participants (221 out of 1232 patients in the OPT and ICD arms) is reported for a 20-month follow-up period. The model accounts therefore for a risk of hospitalisation for HF of 0.0082 (95% CI 0 to 0.0202) per cycle for patients at risk of SCD being managed with OPT or ICD therapy, assuming that ICD therapy has no effect on HF hospitalisations.

Hospitalisation because of non-fatal arrhythmia The number of hospitalisations because of non-fatal arrhythmia is not reported by the trials included in our systematic review for population 1 (see *Chapter 4*, *People at risk of sudden cardiac death as a result of ventricular arrhythmias*, *Assessment of effectiveness*) 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 that a patient at increased risk of SCD managed with OPT will be hospitalised for a non-fatal arrhythmia is assumed to be the same as that for patients with HF (0.0075, 95% CI 0.0002 to 0.0148), derived from the number of events in both arms (OPT and CRT-P) of the MIRACLE trial.[121] The sensitivity of the cost-effectiveness results to this assumption is explored later in this chapter (see *Results of the independent economic analysis*, *Population 1: patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological therapy*) 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 because of non-fatal arrhythmias are assumed to be referred for ICD implantation (estimation described earlier). Patients hospitalised because of 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[109] OPT arm who were referred for CRT-D implantation (see *Data sources and parameter estimates*, *Population 2: patients with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite receiving optimum pharmacological therapy*).

Adverse events

Adverse events in patients being managed with ICDs were categorised into those occurring at the time of implantation (or during the initial inpatient stay) and a set of longer-term adverse events that could occur around the time of implantation and during all subsequent cycles. The former set of adverse events includes procedure-related mortality, surgical complications and implant failure whereas the latter set includes lead displacements, infections and device malfunctions and dislodgements. As noted in the systematic review (see sections on adverse events in *Chapter 4*), reporting of individual adverse events in the included trials is limited.

Procedure-related death Most trials of patients at increased risk of SCD in which surgical death was included explicitly as an outcome (MADIT II,[103] DEFINITE,[90] DINAMIT,[95] DEBUT[89]) report no deaths related to the implantation procedure, with only the CASH trial reporting 5/99 perioperative deaths. A pooled

probability of procedure-related death of 0.003 (95% CI 0 to 0.055) was used in the base-case analysis, based on five 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[71] 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 to 0.0962). The SCD-HeFT trial[108] reports a lower proportion of patients with unsuccessful implantation (1/829 patients). However, it is not clear whether this was failure of the initial implantation or followed revision of the initial implant procedure. The systematic review of RCTs and observational studies by Ezekowitz and colleagues[221] reports a probability of implant failure of 0.011 (95% CI 0.009 to 0.013), which was used in the model.

Complications Given the inconsistent reporting of perioperative and postoperative complications related to use of ICDs among the trials included in our systematic review, estimates from the systematic review of RCTs and observational studies by Ezekowitz and colleagues[221] were used in the model. *Table 97* presents the probabilities used for each type of event.

Epidemiological data

Distribution of patients by New York Heart Association 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: the AVID trial[71] for the secondary prevention of SCD and the MADIT II[101] and SCD-HeFT[105] trials for the primary prevention of SCD (*Table 98*).

A summary of the clinical variables in the model for population 1 is provided in *Table 99*.

TABLE 97 Peri- and postoperative complications with ICDs

Event	Risk[a]	95% CI
Perioperative complication		
Mechanical complication	0.053	0.046 to 0.062
Postoperative complications		
Lead problems	0.0012	0.0010 to 0.0014
Infections	0.0005	0.0004 to 0.0006

a Risk estimates for postoperative complications per 100 patient-years reported by Ezekowitz *et al.*[221] were converted to risk per 4-week cycle.

TABLE 98 Distribution of the participants of the AVID, MADIT II and SCD-HeFT trials by NYHA class at baseline

	AVID[71]		MADIT II[101]		SCD-HeFT[105]	
NYHA class	AAD	ICD	OPT	ICD	OPT	ICD
No HF, %	45	40	0	0	0	0
I, %	48	48	39	35	0	0
II, %	48	48	34	35	70	70
III, %	7	12	23	25	30	30
IV, %	7	12	4	5	0	0

TABLE 99 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	Log-normal
All-cause mortality by age	HR 18–59	0.62	0.0459	0.54	0.72	Log-normal
	HR 75+	1.41	0.0051	1.40	1.42	Log-normal
Death as a result of surgery	DFS_ICD	0.0034	0.0262	0	0.0548	Normal
Probability of surgical death from transplantation	DFS_TRP	0.122	0.007	0.109	0.136	Normal
Event probabilities (per cycle)						
Hospitalisation for 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 to	0.0059	Beta

LL, lower limit; UL, upper limit.

Population 2: patients with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite receiving optimum pharmacological therapy

Effectiveness data

Mortality and relative risks Following the approach of Fox and colleagues,[64] the population 2 model accounts for cardiac mortality (SCD and morality from worsening HF) and non-cardiac mortality.

Cardiac mortality The CARE-HF trial[111] is the trial with the longest follow-up period (mean 37.4 months) of those included in the clinical effectiveness review for people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT. The CARE-HF trial reports survival curves for SCD and death from worsening HF; hence, baseline time-dependent probabilities of SCD and death from HF were derived from CARE-HF survival curves in the control group. The methodology used to derive baseline mortality is described in the previous section and further details can be found in *Appendix 15*.

Weibull approximations were fitted to the Kaplan–Meier curves for SCD and death from worsening HF in patients from the CARE-HF trial. The scale (λ) and the shape (γ) parameters that define the Weibull models used for the estimation of SCD and HF deaths for the OPT arm are shown in *Table 100*. Time-dependent death probabilities for population 2 patients receiving devices (CRT-P, CRT-D or ICD) were then derived by applying device-specific HRs or RRs to the baseline probabilities (OPT arm).

TABLE 100 Weibull model parameters for SCD and HF mortality: population 2

Parameter	Mean	95% CI
SCD		
ln(λ)	–6.069	–6.173 to –5.964
γ	1.140	1.107 to 1.173
HF		
ln(λ)	–6.115	–6.256 to –5.974
γ	1.223	1.179 to 1.266

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

The relative effect of CRT-P on HF deaths was obtained from the meta-analysis in *Chapter 4* (see *People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony*, *Assessment of effectiveness*, *Heart failure deaths*) (encompassing the CARE-HF[109] and COMPANION[116] trials; RR 0.67; 95% CI 0.51 to 0.88). That for CRT-D patients was sourced from the COMPANION trial[116] (HR 0.73, 95% CI 0.47 to 1.11). The estimate for the RR of SCD for CRT-P patients obtained in the meta-analysis in *Chapter 4* (see *People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony*, *Assessment of effectiveness*, *Sudden cardiac death*) (pooled from the CARE-HF,[109] COMPANION[116] and MUSTIC[125] trials) is 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[109] and 1.13 from the COMPANION[116]). The RR of SCD for CRT-D patients was sourced from the COMPANION trial[116] (HR 0.44, 95% CI 0.23 to 0.86).

For population 2 patients who were using an ICD because of CRT-D implant failure, the RRs for SCD and death from worsening HF were sourced from the SCD-HeFT trial.[108] 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 HF. A RR 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 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 from HF and lower risk of SCD than the SCD-HeFT participants (population 1), these parameters were subject to sensitivity analysis (see *Results of the independent economic analysis*, *Population 2*).

Non-cardiac mortality Non-cardiac-related death rates were derived from the 2010 mortality statistics for England and Wales from the Office for National Statistics.[4] All deaths not allocated an *International Classification of Diseases*, 10th edition,[5] code I00–I52 (for heart disease) were included. *Table 101* shows the non-cardiac death rates by age used in the model for population 2. Proportions of UK patients with HF were estimated based on the 2011 statistics for incidence of HF by gender reported by the British Heart Foundation.[222]

Hospitalisation

Hospitalisation because of heart failure The hospitalisation baseline risk estimate (0.037, 95% CI 0.025 to 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[109] (252/404 events in 29.4 months), MIRACLE[121] (50/225 patients in 6 months), MUSTIC[125] (9/29 events in 3 months) and COMPANION[116] (235/308 events in 11.9 months).

The RR of hospitalisation because of HF for patients receiving CRT-P compared with those receiving OPT was estimated to be 0.58 (95% CI 0.35 to 0.96), pooling risks from the CARE-HF,[109] COMPANION,[116] MIRACLE[121] and MUSTIC[125] trials as described in *Chapter 4* (see *People with heart failure as a result of left*

TABLE 101 Non-cardiac mortality by age

Age group (years)	Probability of non-cardiac death per cycle
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	0.008566

ventricular systolic dysfunction and cardiac dyssynchrony, *Assessment of effectiveness*). The COMPANION trial[116] reports a RR of 0.77 (95% CI 0.63 to 0.93; $p = 0.008$) for patients receiving CRT-D compared with those receiving OPT. As per Fox and colleagues,[64] the risk of hospitalisation because of HF for patients with an ICD was assumed to be the same as for patients receiving OPT (RR = 1).

Hospitalisation because of non-fatal arrhythmia Fox and colleagues[64] report using the number of severe arrhythmic events reported in the MIRACLE trial[121] (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 to 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 receiving CRT-P. Given the lack of evidence on hospitalisation for arrhythmia for population 2 patients receiving 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 way to those occurring with ICDs, that is, into those occurring at the time of implantation or initial inpatient stay (procedure-related deaths, implant failures and perioperative complications) and longer-term adverse events (lead displacements, infections and device malfunctions).

Procedure-related death The probability of death related to the surgical procedure for CRT implantation was derived from the number of events reported in patients randomised to the CRT-arm in the trials included in our systematic review of clinical effectiveness. The CARE-HF trial[109] reported one death in 409 patients, the MIRACLE trial[121] one death in 571 patients, the MUSTIC tial[125] one death in 64 patients and the COMPANION trial[116] five deaths in 617 patients. A probability of procedure-related death of 0.048 (95% CI 0.0015 to 0.0081) per cycle is therefore considered in the model for CRT-P. The COMPANION trial[116] also reports three procedure-related deaths out of 595 patients in the CRT-D arm, which corresponds to a probability of procedure-related death 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 of implant failure of 0.084 (95% CI 0.070 to 0.097) per cycle was estimated for patients undergoing CRT-P implantation from four trials: CARE-HF[109] (19/409), MIRACLE[121] (43/571), MUSTIC[125] (5/64) and COMPANION[116] (78/617). The COMPANION trial[116] reports 54 implant failures in 595 patients undergoing CRT-D implantation; 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.

Perioperative complications Given the limited and heterogeneous reporting of surgical complications related to CRT implantation among the trials included in our systematic review, the probability of patients having an operative complication from a CRT implant was sourced from Fox and colleagues,[64] who report

a pooled risk of complications from the CARE-HF,[109] MIRACLE,[121] MUSTIC[125] and CONTAK-CD[126] trials and both CRT arms of the COMPANION trial.[116] A probability of perioperative complications 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 the follow-up periods: CARE-HF[109] (24/409), MIRACLE[121] (30/571) and MUSTIC[125] (8/58). These were used to estimate a pooled risk of lead displacement of 0.0037 (95% CI 0.0004 to 0.0071) for use in the model for patients being managed with CRT-P or CRT-D.

Infection A probability of 0.0006 (95% CI 0 to 0.002) for device-related infections in patients being managed with CRT-P was derived from the relevant trials included in the systematic review of clinical effectiveness that explicitly reported this outcome: CARE-HF[109] (3/409 in 29.4 months) and MIRACLE[121] (7/528 in 6 months). For CRT-D, a probability of infection of 0.0006 (95% CI 0 to 0.0015) was derived similarly, using the events reported in the CONTAK-CD[126] (7/517 in 6 months), RethinQ[142] (6/172 in 6 months), RHYTHM ICD[144] (4/205 in 15.1 months), MADIT-CRT[130] (12/1089 in 28.8 months) and RAFT[140] (21/888 in 40 months) trials.

Device upgrade after hospitalisation Following hospitalisation, patients being managed with OPT can be referred for CRT-P or CRT-D implantation, whereas patients being managed with CRT-P can be referred for CRT-D implantation. The probabilities of device upgrade after hospitalisation were derived from the CARE-HF trial,[111] assuming that the upgrades reported occurred after hospitalisation due to HF. For the OPT arm ($n = 404$), the CARE-HF trial[111] reports 43 upgrades to CRT-P and 23 upgrades to CRT-D in 29.4 months of follow-up, whereas in the CRT-P arm ($n = 409$) eight patients upgraded to CRT-D. This corresponds to a probability of 0.0033 (95% CI 0 to 0.009) for upgrading from OPT to CRT-P, 0.0018 (95% CI 0 to 0.0059) for upgrading from OPT to CRT-D and 0.0006 (95% CI 0 to 0.003) for upgrading from CRT-P to CRT-D.

Clinical advice indicated that patients with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT would upgrade to an ICD only in case of failure of CRT-D implantation, which can be estimated by multiplying the probability of upgrading from OPT to CRT-D (0.001, 95% CI 0 to 0.003) by the probability of CRT-D implant failure (0.087, 95% CI 0.064 to 0.109).

For population 2 patients who end up receiving an ICD, our model considers the same data for ICD-related adverse events reported earlier for population 1.

Epidemiological data

Distribution of patients per New York Heart Association class The distribution of HF patients by NYHA class used (*Table 102*) is the same as that used in the previous model by Fox and colleagues,[64] who derived the distribution of patients per NYHA class at baseline and 90 days from the CARE-HF trial[109] and the conference proceedings of the Brescia study by Curnis and colleagues.[223]

A summary of the clinical variables in the model for population 2 is shown in *Table 103*.

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 periods and comparing events between groups statistically (MADIT-CRT[130] and RAFT[140]) were included in this analysis. As reported in *Chapter 4*, length of follow-up was an average of 28.8 months in

TABLE 102 Distribution of patients by NYHA class

NYHA class	Mean (%)	LL (%)	UL (%)
OPT			
Proportion at baseline			
III[a]	93.8	75.42	100.00
IV[b]	6.2	4.98	7.42
Proportion at 90 days			
I[a]	10.1	8.12	12.08
II[a]	29.9	24.04	35.76
III	54.8	44.06	65.54
IV	5.2	4.18	6.22
Proportion at 18 months			
I[c]	12.7	10.21	15.19
II[a]	37.3	29.99	44.61
III	45.7	36.74	54.66
IV	4.3	3.46	5.14
CRT/ICD[d]			
Proportion at baseline[e]			
III	93.8	75.42	100.00
IV	6.2	4.98	7.42
Proportion at 90 days			
I[a]	29.5	23.72	35.28
II[a]	41.5	33.37	49.63
III	27.2	21.87	32.53
IV	1.8	1.45	2.15
Proportion at 18 months			
I[c]	31.5	25.33	37.67
II	44.4	35.70	53.10
III	22.5	18.09	26.91
IV	1.5	1.21	1.79

a 95% CIs were derived assuming SE = mean/10.
b Assumed to be equal to 1 minus the proportion of patients in NYHA class III.
c From Curnis *et al.*[223] conference proceeding.
d Assumed to be the same for any device type: CRT-P, CRT-D and ICD.
e Assumed to be the same as for OPT.
Source: CARE-HF trial.[109]

TABLE 103 Key clinical parameters used in the model for population 2

Parameter type	Parameter	Source estimate				Distribution
		Mean	SE	LL	UL	
Death from HF, age 65–74 years, OPT	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	Log-normal
	HR CRT-D	0.73	0.163	0.47	1.11	Log-normal
	HR ICD	1.14	0.153	0.88	1.48	Log-normal
Post-transplant mortality	RR TRP	0.35	0.035	0.281	0.419	Log-normal
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	Log-normal
	HR CRT-D	0.44	0.1607	0.23	0.86	Log-normal
	HR ICD	0.44	0.0765	0.31	0.61	Log-normal
All-cause mortality RR by age (years)	18–64	0.62	0.05	0.54	0.72	Log-normal
	75+	1.41	0.01	1.40	1.42	Log-normal
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	Beta
	CRT-D	0.005	0.003	0.000	0.011	Beta
	TRP	0.122	0.007	0.109	0.136	Beta
Hospitalisation for HF	OPT	0.037	0.006	0.025	0.049	Beta
	RR ICD	1	0.1	0.804	1.196	Beta
	RR CRT-P	0.58	0.1556	0.35	0.96	Beta
	RR CRT-D	0.77	0.0765	0.63	0.93	Beta
Transplant following HF hospitalisation	TRP	0.001	0.002	0.000	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	Beta
	CRT-P	0.007	0.004	0.000	0.015	Beta
	CRT-D	0.007	0.004	0.000	0.015	Beta
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	Beta
	OPT to CRT-D	0.002	0.002	0.000	0.006	Beta
	CRT-P to CRT-D	0.001	0.001	0.000	0.003	Beta
Surgical failure	ICD	0.011	0.001	0.009	0.013	Beta
	CRT-P	0.084	0.007	0.070	0.097	Beta
	CRT-D	0.087	0.012	0.064	0.109	Beta

TRP, transplant.

the MADIT-CRT trial[130] and 40 months in the RAFT trial.[140] Survival estimates from the trial with the 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,[61] we used its mortality estimates as the baseline for this population and used HRs and RRs to derive all-cause mortality for patients receiving OPT alone, ICD + OPT and CRT-P + OPT.

The methodology used to derive baseline mortality is similar to that described earlier for populations 1 and 2; further details can be found in *Appendix 15*. *Table 104* presents the parameters of the Weibull models obtained using data from the RAFT[140] and MADIT-CRT trials.[130]

Relative risk for implantable cardiac defibrillators The risk of all-cause mortality for patients with an ICD relative to those receiving CRT-D was derived from the pooled RR of 0.84 (95% CI 0.73 to 0.96) estimated in *Chapter 4* (see *People with both conditions*, *Assessment of effectiveness*, *All-cause mortality*) for CRT-D compared with ICD therapy. A RR of 1.19 (95% CI 1.04 to 1.37) for ICD therapy compared with CRT-D was used to estimate all-cause mortality in the ICD arm.

Relative risk for optimum pharmacological therapy In the systematic review of clinical effectiveness studies of people with both conditions, only RCTs comparing CRT-D with ICD therapy were found. However, the COMPANION trial[116] reports the HR for all-cause mortality for patients with HF as a result of LVSD and cardiac dyssynchrony, from which we derived the HR of 1.56 (95% CI 1.16 to 2.08) for OPT compared with CRT-D, assuming that the same relative effect would be expected in population 3.

Relative risk for CRT-Ps 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 ICDs, we used the evidence available on the clinical effectiveness of CRT-P and CRT-D in patients with HF as a result of LVSD and cardiac dyssynchrony. The only trial comparing CRT-P with CRT-D was the COMPANION trial.[116] A non-statistically significant RR of 1.20 (95% CI 0.96 to 1.52) for all-cause mortality was reported for CRT-P compared with CRT-D. However, the COMPANION trial[116] was not powered for this comparison. Considering the lack of robust evidence for 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 by varying the parameter between the assigned upper and lower limits of the 95% CI (0.80 to 1.20).

Hospitalisation because of heart failure The trials included in the systematic review of clinical effectiveness (see *Chapter 4*, *People with both conditions*, *Assessment of effectiveness*, *Hospitalisations related to heart failure*) do not report the number of hospitalisations because of HF. Instead, the

TABLE 104 Weibull model parameters for all-cause mortality: population 3

Parameter	Mean	95% CI
RAFT[140]		
ICD-CRT arm ($R^2 = 0.9894$)		
ln(λ)	–6.334	–6.467 to –6.202
γ	1.243	1.20 to 1.27
MADIT–CRT[130]		
Men, CRT-D arm ($R^2 = 0.989$)		
ln(λ)	–6.935	–7.005 to –6.865
γ	1.287	1.266 to 1.308

CONTAK-CD,[126] Piccirillo and colleagues[138] and RAFT[140] trials report the number of patients receiving CRT-D hospitalised for HF (at least once during the trial). In 6 months of follow-up, the CONTAK-CD trial[126] reported that 32 of 245 patients in the CRT-D arm were hospitalised; Piccirillo and colleagues[138] reported that none of 16 patients in the CRT-D arm, who were followed for 12 months, were hospitalised; and the RAFT trial[140] reported that 174 of 894 patients in the CRT-D arm were hospitalised during the 40 months of follow-up. 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 because of HF (probability of event occurring 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 because of HF was subject to sensitivity analysis (see *Results of the independent economic analysis*).

The RR of hospitalisation because of HF for patients with an ICD compared with those receiving CRT-D was estimated to be 1.33 (95% CI 1.14 to 1.56), the reverse of the RR of 0.75 (95% CI 0.64 to 0.88) obtained in *Chapter 4* (see *People with both conditions*, *Assessment of effectiveness*, *Hospitalisations related to heart failure*) by pooling risks from the CONTAK-CD,[126] Piccirillo and colleagues[138] and RAFT[140] trials.

The COMPANION trial[116] reports no significant differences in hospitalisations because of HF between CRT-P and CRT-D for patients with HF (see *Chapter 4*, *People with heart failure*, *Assessment of effectiveness*, *Hospitalisations because of heart failure*). Hence, assuming that no significant differences would be expected either in patients with both conditions (at risk of SCD as a result of ventricular arrhythmias and with HF as a result of LVSD and cardiac dyssynchrony), the risk of hospitalisation because of HF estimated for CRT-D (0.0077) was used for CRT-P (RR = 1).

Evidence on the RR of hospitalisation for HF in patients receiving OPT compared with CRT-D was found only for patients with HF (population 2). The COMPANION trial[116] reported a statistically significant difference in HF hospital admissions per patient between the CRT-D arm and the OPT arm (0.43 vs. 0.73 admissions per patient-year respectively). The RR estimated for hospitalisations because of HF for OPT compared with CRT-D was 1.67 (95% CI 1.51 to 1.86, $p < 0.00001$).

Hospitalisation because of non-fatal arrhythmia The baseline risk of hospitalisation for arrhythmia used in the model (probability of event occurring 0.029, 95% CI 0.015 to 0.042) was derived from trials included in the systematic review of clinical effectiveness (see *Chapter 4*, *People with both conditions*, *Assessment of effectiveness*) reporting the number of patients receiving CRT-D who experienced at least one episode of VF: MIRACLE ICD[136] (42/187), MICACLE ICD II[137] (19/85), CONTAK-CD[126] (36/245) and the trial by Pinter and colleagues[139] (7/36). Similar to the estimation of hospitalisations for HF, our model is likely to be underestimating the total number of hospitalisations for arrhythmic events and the value used was therefore subject to sensitivity analysis (see *Results of the independent economic evaluation*).

The meta-analysis (see *Chapter 4*, *People with both conditions*, *Assessment of effectiveness*) 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 RR 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 hospitalisations for arrhythmia comparing CRT-P or OPT with CRT-D. The COMPANION trial[116] states that hospitalisations because of other cardiac causes were not significantly different between the OPT group and the CRT group. Therefore, our model assumes that the risk of hospitalisation because of arrhythmia for patients managed with OPT alone or CRT-P is the same as that for patients managed 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 for population 2 (people with HF).

Epidemiological data

Distribution of patients per New York Heart Association class The RAFT trial[140] reported the number of patients by NYHA class at baseline (*Table 105*). No evidence on the effect of the devices on HF progression was found; hence, the model assumes no effect on patient 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 by one NYHA class at 6 months of treatment (see *Results of the independent economic analysis*).

A summary of the clinical variables in the model for population 3 is provided in *Table 106*.

Parameters common to all populations

Age-related mortality

The variation of risk of death according to age was incorporated in our model using the same estimates as those used by Fox and colleagues,[64] who derived the RR of death from the publication by Shahar and colleagues.[224] The RR of death for patients aged < 65 years compared with those aged 65–74 years is 0.62 (95% CI 0.54 to 0.72). For those aged ≥ 75 years compared with those aged 65–74 years the RR is 1.41 (95% CI 1.40 to 1.42).

Distribution of patients eligible for implantable cardiac defibrillator and cardiac resynchronisation therapy 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 access to cardiac care in the UK.[225] *Table 107* shows the estimated distribution of implanted devices by age.

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 HF. For population 3 with both conditions, the distribution of both ICD and CRT devices was used in the model.

TABLE 105 Distribution of patients by NYHA class

	Proportion at baseline, *n* (%)	
NYHA class	ICD (*n* = 904)	CRT-D (*n* = 894)
II	730 (80.8)	708 (79.2)
III	174 (19.2)	186 (20.8)

Source: RAFT trial.[140]

TABLE 106 Key clinical parameters used in the model for population 3

Parameter type	Parameter	Source estimate				Distribution
		Mean	SE	LL	UL	
All-cause mortality, baseline – CRT-D	ln(λ)	–6.334	0.068	–6.467	–6.202	Normal
	γ	1.234	0.018	1.199	1.270	Normal
	HR CRT-P	1	0.100	0.804	1.196	Log-normal
	HR ICD	1.190	0.084	1.042	1.370	Log-normal
	HR OPT	1.563	0.235	1.163	2.083	Log-normal
All-cause mortality RR by age (years)	18–64	0.621	0.046	0.54	0.72	Log-normal
	75+	1.410	0.005	1.4	1.42	Log-normal
Event probabilities (per cycle)						
Hospitalisation for HF	CRT-D	0.008	0.003	0.003	0.013	Beta
	RR ICD	1.333	0.133	1.136	1.563	Log-normal
	RR CRT-P	1	0.1000	0.804	1.196	Log-normal
	RR OPT	1.67	0.0893	1.51	1.86	Log-normal
Non-fatal arrhythmia requiring hospitalisation	CRT- D	0.029	0.007	0.015	0.042	Log-normal
	RR ICD	1.111	0.111	0.880	1.410	Log-normal
	RR CRT-P	1	0.1	0.804	1.196	Log-normal
	RR OPT	1	0.1	0.804	1.196	Log-normal
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	Beta
	OPT to CRT-D	0.002	0.002	0	0.006	Beta
	CRT-P to CRT-D	0.001	0.001	0	0.003	Beta
	ICD to CRT-D	0.007	0.003	0.001	0.013	Beta
Surgical mortality	ICD	0.003	0.026	0	0.055	Beta
	CRT-P	0.005	0.002	0.001	0.008	Beta
	CRT-D	0.005	0.003	0	0.011	Beta
Surgical failure	ICD	0.011	0.001	0.009	0.013	Beta
	CRT-P	0.084	0.007	0.070	0.097	Beta
	CRT-D	0.087	0.012	0.064	0.109	Beta
Device lifetime	ICD ln(λ)	–15.784	0.203	–16.182	–15.385	Normal
	ICD γ	1.943	0.027	1.889	1.996	Normal
	CRT-P ln(λ)	–14.222	0.242	–14.697	–13.747	Normal
	CRT-P γ	1.677	0.032	1.613	1.740	Normal
	CRT-D ln(λ)	–15.465	0.273	–16	–14.931	Normal
	CRT-D γ	1.935	0.036	1.863	2.006	Normal

LL, lower limit; UL, upper limit.

TABLE 107 Heart device implantation by age in the UK population

Age group (years)	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

Heart transplantation

Procedure-related mortality The model takes into account that patients subject to heart transplantation 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[226] from data for 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.[64] The RR 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[227] for UK patients receiving a heart transplant (10.6 years) and those on OPT (3.7 years).

Transplant following hospitalisation for heart failure Abraham and colleagues[121] report two heart transplants in 532 participants in the MIRACLE trial. As in Fox and colleagues,[64] for population 2 we assumed that these patients were referred for transplantation after hospitalisation for HF, estimating a 0.0014 (95% CI 0 to 0.0062) probability of transplantation per cycle for patients hospitalised for HF.

Given the paucity of data regarding the number of transplants after hospitalisation for HF in the trials for populations 1 and 3, our model assumes the same risk as that for patients with HF (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 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 for initial device implantation, device-related complications and device replacement) or infection.

Utilities by New York Heart Association class The utility values by NYHA class used in the model (*Table 108*) were from one study[214] (described earlier in the systematic review of HRQoL studies) that reported utility values for all NYHA classes.

Hospitalisation and heart transplant One observational analysis within the UK[27] was also included in the systematic review. Holland and colleagues[27] reported utility estimates per NYHA class at baseline in patients with HF following emergency hospital admission, estimating an average score of 0.57 (see *Table 108*). This utility value is similar to that estimated by McAlister and colleagues[194] and used in Fox and colleagues' model.[64] Our model also assumed that the proportion of time hospitalised was on average one-quarter of the month.

TABLE 108 Utilities for patients with HF

Health state	NYHA class	Utility value (95% CI)	Source
Stable	I	0.855 (0.845 to 0.864)	Gohler *et al.*[214]
	II	0.771 (0.761 to 0.781)	
	III	0.673 (0.727 to 0.765)	
	IV	0.532 (0.48 to 0.584)	
Hospitalisation and heart transplantation		0.57	Holland *et al.*[27]
Decrement due to surgery		0.05	Assumption[64]
Decrement due to infection		0.1	Assumption[64]

As in Fox and colleagues' model,[64] utility estimates for transplantation were assumed to be similar to those for hospitalised patients and post-transplanted patients were assumed to have a similar HRQoL to 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 QoL of patients eligible for ICD or CRT. As per Fox and colleagues,[64] decrements of 0.05 for the impact of surgery and of 0.1 for infection were assumed.

Health-related quality of life associated with implantable cardiac defibrillators

One study[153] reporting utilities for UK patients at increased risk of SCD as a result of ventricular arrhythmias was included in the systematic review of HRQoL studies described earlier. Buxton and colleagues[153] concluded that there was no evidence that self-reported HRQoL changes substantially over time. Therefore, we assumed that 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 was used in our model in combination with utility values by NYHA class from Gohler and colleagues[214] (see *Table 108*) to estimate a NYHA class-weighted average utility value.

Buxton and colleagues[153] also found that patients who had suffered inappropriate ICD shocks had significantly lower HRQoL, reporting mean utility values of 0.7 and 0.8 for patients with at least one inappropriate shock and with no shocks respectively. Patients who experience inappropriate shocks are expected to be hospitalised and have their HRQoL affected. The impact of inappropriate shocks on HRQoL and costs was implicitly accounted for in our economic model through the hospitalisation rates used. Following clinical advice, we incorporated the probability of hospitalisation for severe arrhythmia in patients with an ICD. Although there is limited evidence on hospitalisations for severe arrhythmia in the trials included in our systematic review for population 1, we assumed that patients with an ICD are as likely to be hospitalised for non-fatal arrhythmia as patients being managed with OPT alone (see *Data sources and parameter estimates*, *Population 1*).

Health-related quality of life associated with cardiac resynchronisation therapy

For population 2, the impact of CRT on the HRQoL of patients with HF over time was captured in the model by changes in the distribution of patients with HF by NYHA class derived from the relevant trials (see *Data sources and parameter estimates*, *Population 2*, *Distribution of patients per New York Heart Association class*). Given that evidence of the impact on the distribution of patients by NYHA class was available only for population 2 patients receiving 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 the devices on HF 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 *Data sources and parameter estimates*, *Population 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% for NYHA classes II and III respectively), the model assumes similar utility values for patients receiving CRT, an 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 for HRQoL in 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 in the scenario analysis (see *Results of the independent economic analysis*), assuming that 50% of patients with a CRT device improve by one NYHA class at 6 months of treatment.

Utility values by NYHA class from Gohler and colleagues[214] were then used to estimate NYHA class-weighted average utility values for patients for all populations. *Table 108* summarises the utility values used in our model and their sources.

Resource use and costs

Resource use and cost estimation aimed to cost all relevant resources consumed in the care of patients in the three populations being studied. Similar to the previous model for the assessment of CRT devices,[64] the resources considered in the current model include medication and resources involved in device implantation, device-related complications and maintenance, hospitalisation for HF 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 the total cost per intervention.

Device costs The device-related costs used in the economic model (*Table 109*) correspond to the estimates provided in the MS. 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 109 Device costs

Device component	Mean cost (£)	Lower value (£)[a]	Upper value (£)[a]
Whole system			
CRT-P	3411	2742	4080
CRT-D	12,293	9884	14,702
ICD	9692	7792	11,592
Leads[b]			
CRT-P	811	652	970
CRT-D	541	435	647
ICD	543	437	649
Battery			
CRT-P	2600	2090	3110
CRT-D	11,752	9449	14,055
ICD	9149	7356	10,942

a Lower and upper values were estimated assuming SE = mean/10.
b Lead cost was estimated from the difference between the whole system cost and the generator unit cost.
Source: MS.[151]

Estimates of device longevity were also sourced from the ABHI joint submission, which reports the Kaplan–Meier plots of time to device replacement derived from data submitted to CCAD. Estimates of mean time to replacement were derived from the reported survival functions for use in the model. *Table 110* presents the parameters of the Weibull approximations obtained for each device type and the respective mean lifetimes. Clinical advice indicated that the longevity of the devices might be overestimated; hence, these parameters were subject to sensitivity analysis and a scenario of shorter device longevity was explored (see *Results of the independent economic analysis*).

Procedure-related costs Costs associated with device implantation, complications or maintenance were sourced from the 2012–13 UK NHS tariff,[229] whereas the costs of hospitalisations and transplantation were derived from the 2010–11 NHS Reference Costs (NHS trusts and primary care trusts combined HRG data).[218]

Table 111 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 reference costs[218] as a weighted average of the lower and upper quartile unit costs reported for elective and long-stay non-elective care.

Hospitalisation The economic model developed for the current assessment accounts for hospitalisation for HF and hospitalisation for severe arrhythmia. According to Fox and colleagues,[64] fewer resources are expected to be used to manage hospitalised patients with a device than hospitalised patients receiving OPT. Thus, the conservative approach of assuming the same resource use for all groups was taken. The costs associated with the management of hospitalisation for HF and arrhythmia were derived from the 2010–11 NHS Reference Costs[218] and are presented in *Table 111*.

The HRG codes EB03H and EB03I refer to HF 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

TABLE 110 Mean device lifetime

Parameter	Mean	95% CI
ICDs		
ln(λ)	–15.784	–16.182 to –15.385
γ	1.943	1.889 to 1.996
Device longevity (years)	8.20	12.76 to 5.40
CRT-P		
ln(λ)	–14.222	–13.747 to –14.697
γ	1.677	1.613 to 1.74
Device longevity (years)	11.81	22.22 to 6.58
CRT-D		
ln(λ)	–15.465	–16.000 to –14.931
γ	1.935	1.863 to 2.006
Device longevity (years)	7.19	13.05 to 4.14

Mean replacement frequency calculated as $(1/\lambda)^{\wedge}((1/\gamma)) \times \Gamma(1+(1/\gamma))$ where Γ is the mathematical gamma function (see Tappenden *et al.*[228]).
Source: MS.[151]

TABLE 111 Procedure costs

Procedure	Mean cost (£)	Lower value (£)	Upper value (£)	Source
Device-related procedures				
Implantation, reimplantation and lead displacement/replacement				
CRT-P	4870	3356	7816	UK tariff 2012–13[229] elective EA07Z and MS[151a]
CRT-D	5556	5363	18,267	UK tariff 2012–13[229] elective EA12Z
ICD	5556	5363	18,267	UK tariff 2012–13[229] elective EA12Z
Explant				
CRT-P	2748	2153	4542	UK tariff 2012–13[229] elective EA39Z
CRT-D	2748	2153	4542	UK tariff 2012–13[229] elective EA39Z
ICD	2748	2153	4542	UK tariff 2012–13[229] elective EA39Z
Battery failure/device replacement				
CRT-P	2748	2153	4542	UK tariff 2012–13[229] elective EA39Z
CRT-D	5556	5363	18,267	UK tariff 2012–13[229] elective EA12Z[b]
ICD	5556	5363	18,267	UK tariff 2012–13[229] elective EA12Z[c]
Hospitalisation				
HF	2308	1669	2578	NHS Reference Costs 2010–11[218] EB03H/EB03I
Arrhythmia	1372	922	1601	NHS Reference Costs 2010–11[218] EB07H/EB07I
Heart transplant	35,606	21,449	43,315	NHS Reference Costs 2010–11[218] EA02Z

a Difference between the UK tariff for EA07Z and the CRT-P whole-system cost in the MS.[151]
b Clinical advice indicated that the battery replacement cost for CRT-D should be the same as that for an ICD.
c As in Fox *et al.*,[64] the cost of ICD battery replacement was assumed to be the same as the cost of initial implantation.

conduction disorders with or without complications. The cost of hospitalisation for arrhythmia was estimated in the same way as the cost of hospitalisation for HF.

Transplantation The cost of a heart transplant was estimated as a weighted average of the national average unit costs reported for elective and long-stay non-elective care (HRG code EA02Z).

Device implantation Device implantation involves a surgical procedure and device-related resources; hence, the costs of a whole system and of the implantation procedure (see *Tables 109* and *111*) were included. The HRG code specific for 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 implantation (a conservative approach was taken given the higher cost of EA12Z than EA07Z).

Upgrades and routine replacements Device upgrades and routine/maintenance replacements were assumed to be similar in terms of resource use and costs to 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 rates of operative complications were sourced from the RAFT trial,[140] a large RCT of patients who are at risk of SCD as a result of ventricular arrhythmia and with HF as a result of LVSD 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 112* for each device type.

The unit cost estimation for lead displacements, infections and device malfunctions is described in the following section. 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[64] 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, which is expected to use similar resources to those used for initial implantation. For cost estimation, the cost of the leads and of 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. The resource use and costs involved in the treatment of infections are provided in *Table 113*.

The HRG code 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).

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 the approach of Fox and

TABLE 112 Proportions of operative complications in the RAFT trial

Complications	CRT, *n* (%)	ICD, *n* (%)
Device-related problems requiring replacement[a]	4 (4)	1 (2)
Complications requiring intervention[b]	75 (75)	31 (65)
Infections	21 (21)	16 (33)
Total	100	48

a Reported as device pocket problems requiring revision.
b Includes lead-displacement and device pocket haematoma requiring intervention.
Source: RAFT trial.[140]

TABLE 113 Resource use and costs associated with the treatment of infection

Item	Mean (£)	Lower limit (£)	Upper limit (£)	Source
Explant cost	2748	2153	4542	UK tariff 2012–13[229] elective EA39Z
Extra bed-day cost	316	190	370	NHS Reference Costs 2010–11[218] EA39Z
Length of stay (days)	4.43	2.65	7.12	NHS Reference Costs 2010–11[218] EA39Z
Outpatient visit cost	123	94	148	NHS Reference Costs 2010–11[218] – Service 320 – Cardiology
Total cost of infection[a]				
CRT-P	12,553	7285	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 *Tables 109* and *111*.

colleagues,[64] the cost of the procedure for battery replacement for an ICD was assumed to be the same as the cost of initial implantation (HRG code EA12Z), whereas that for CRT-P was assumed to the same as the cost of device explant (HRG code EA39Z). Clinical advice indicated that the cost of the procedure for battery replacement for CRT-D should be the same as that for an ICD.

Device-related total costs

Table 114 summarises the device-related total costs used in the economic model. These include the costs of device components and procedure by event.

Drug costs

Patients with HF 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 of costs is similar to that taken by Fox and colleagues[64] and the MS,[151] in which 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 reported in the MS,[151] based on the systematic review and expert opinion. These are presented in *Table 115*.

Unit costs for the selected drugs were derived from BNF 61.[219] The 4-week cycle cost was assumed to be that of the 28-tablet pack (assuming one tablet per day) for all drugs except furosemide, for which the cost of three packs of 28 tablets (20 mg) was used. The drug cost by NYHA class is presented in *Table 116*. The cost of OPT for population 1 patients without HF was assumed to be the same as that for NYHA class I patients.

Results of the independent economic analysis

Population 1: patients at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological therapy

Base-case analysis: implantable cardiac defibrillators for secondary prevention of sudden cardiac death

The AVID trial[71] provided the estimates for all-cause mortality and the distribution of patients by NYHA class used for our base-case analysis of patients at increased risk of SCD as a result of ventricular arrhythmias, as it was the largest trial of 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

TABLE 114 Device-related total costs used in the model

Event	Mean cost (£)	Lower value (£)	Upper value (£)	Components
Initial implant and reimplantation				
CRT-P	8281	6098	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	5681	4008	8786	Lead and initial implantation costs
CRT-D	6097	5798	18,914	
ICD	6099	5799	18,916	
Battery failure/replacement				
CRT-P	5348	3884	6974	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	7285	15,265	Includes explant, reimplantation, 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	4884	2442	9768	Includes device-related problems requiring replacement (initial implantation cost), complications requiring intervention (lead replacement cost) and infections (infection cost)
CRT-D	6634	3317	13,268	
ICD	3432	1716	6864	

a Arbitrary range used for lower and upper values assuming half and double the mean cost.

TABLE 115 Drug use (OPT) by NYHA class

	Proportion of patients by NYHA class, %			
Drug (mg/day)	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.

TABLE 116 Drug costs (OPT) by NYHA class

	Cost (£) per 4 weeks by NYHA class			
Drug (mg/day)	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.

base-case analysis. The estimated base-case results for a mixed-gender cohort of 65-year-old patients are reported in *Table 117* 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 compared with 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.

The costs and QALYs estimated for each intervention are plotted in *Figure 34*.

Model outputs and validation

Overall survival estimated in the model was compared with that reported in the relevant trials (see *Appendix 16* for details).

Events The number of major events estimated in the economic model for the base-case analysis is presented in *Table 118* 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 for a serious arrhythmic event and patients who are referred for an ICD following hospitalisation for HF. As the number of implanted patients in the OPT alone arm is much smaller than the number in the ICD + OPT arm, less replacements and complications requiring a new device are estimated for this arm. The risks of hospitalisation because of HF and arrhythmia are similar for patients being managed with OPT alone and

TABLE 117 Base-case results for a cohort of 65-year-old patients from the AVID trial:[71] population 1

Intervention	Cost (£)	Life-years	QALYs	Incremental cost (£)	Incremental life-years	Incremental QALYs	ICER (£/QALY gained)
OPT	15,890	7.32	5.95	–	–	–	–
ICD + OPT	31,382	8.25	6.75	15,492	0.93	0.80	19,479

Discounted costs and benefits.

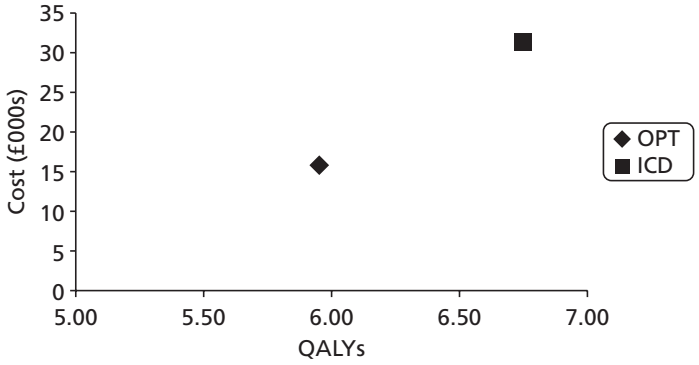

FIGURE 34 Cost-effectiveness plane: population 1.

TABLE 118 Number of events[a] for cohorts of 1000 patients: population 1

Event	Strategy	
	OPT	ICD + OPT
Initial implant	0	1000
Upgrade[b]	454	0
Implant reattempt[c]	10	22
Hospitalisation	1966	2244
Routine replacement	541	921
Postoperative complications	58	114
Lead displacement	77	171
Infection	32	71
Total no. of devices[d]	1037	2014

a Undiscounted number of events.
b ICD implants in patients initially managed with OPT alone.
c Following surgical failure.
d Sum of initial implants, upgrades, reattempts from surgical failures, routine replacements and infections (required new device).

patients being managed with ICD + OPT; thus, the numbers of these events are similar between arms as well.

The percentage of time spent in the main health state categories by an average patient for each strategy is presented in *Table 119*. Patients in both arms spend most of their time in the stable with therapy health state, and the proportions were similar between arms. A reduced proportion of time was then spent in the device-related intervention and hospitalisation health states.

Deterministic sensitivity analysis

Deterministic sensitivity analyses was 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.

TABLE 119 Overall distribution of an average patient's lifetime by health state category: population 1

Health state category	% of remaining life	
	OPT	ICD + OPT
Stable with therapy	97.61	96.50
OPT	47.78	0.00
ICD	49.83	96.50
Hospitalisation	1.19	1.55
Implant surgery	0.37	0.71
Routine replacement	0.43	0.63
Postoperative complications	0.06	0.12
Lead displacement	0.05	0.08
Infection	0.03	0.05
Device-related interventions[a]	0.93	1.59

a Sum of occupancy in implant surgery, postoperative complications, routine replacement, lead displacement and infection.

Mixed-age cohort Cost-effectiveness results were estimated for a scenario of a mixed-age and mixed-gender cohort of patients eligible for ICD for the 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 and Vascular Coalition[225] was used as a proxy for the distribution of patients at increased risk of SCD as a result of ventricular arrhythmia. Age-dependent variables in the population 1 model were those that determined all-cause mortality (baseline risk and RR of death by age group). *Table 120* shows the results for the mixed-age cohort and per age group.

Overall, the ICER increases with age as the QALY gain with ICD + OPT decreases compared with OPT alone as the decrement in incremental benefits from treatment over time is steeper than that for incremental costs. The ICER of £24,967 per QALY gained for the mixed-age cohort shows that ICD + OPT is within the WTP range of £20,000–30,000 per QALY gained.

TABLE 120 Base-case results by age and for a mixed-age cohort: population 1

Starting age (years)	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	9681	24,129	3.85	4.36	28,211
90	5382	18,232	2.40	2.45	288,611
Mixed	16,559	31,838	6.17	6.91	24,967

Implantable cardiac defibrillator for the primary prevention of sudden cardiac death

The MADIT II trial The MADIT II trial[101] was the trial with the largest number of patients with a remote MI and was considered representative of a relevant group who might benefit from ICD therapy for the primary prevention of SCD. Cost-effectiveness results for the subgroup analysis of patients with a remote MI, using MADIT II all-cause mortality for a cohort of 64-year-old patients and a pooled RR of 0.57 (effect of ICD + OPT on all-cause mortality relative to OPT), are presented in *Table 121*.

An increment of 1.18 QALYs per patient is estimated using ICD + OPT for the primary prevention of SCD at an additional cost of £16,800. The health benefit estimated from using ICD + OPT for the 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 a remote MI than that used in the base-case analysis (RR = 0.75). The estimated ICER for this patient group is £14,231 per QALY gained.

The SCD-HeFT trial The all-cause mortality rate in the placebo arm, the RR for ICDs of 0.77 (95% CI 0.66 to 0.89) and the distribution of patients by NYHA class from the SCD-HeFT trial[105] were used to inform an analysis of 60-year-old patients with mild to moderate HF with an indication for an ICD. *Table 122* 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 ICD + OPT for the primary prevention of SCD in patients with mild to moderate HF at an additional cost of £14,655 compared with OPT alone. The estimated ICER for this subgroup of patients (£29,756 per QALY gained) is just below the WTP threshold of £30,000 per QALY gained.

The two cohorts initially managed with OPT alone or ICD + OPT for the primary prevention of SCD showed higher costs and slightly longer life expectancy than in the base-case analysis (secondary prevention of SCD). However, given the greater severity of HF in these patients (see distribution by NYHA class in *Data sources and parameter estimates*, *Population 1*), both cohorts gained fewer QALYs than secondary prevention patients (base-case analysis).

Patients with cardiomyopathy The all-cause mortality rate reported for the SCD-HeFT[105] subgroup of patients with non-ischaemic CHF in the placebo arm was used as the baseline mortality rate for a subgroup analysis of 60-year-old patients with cardiomyopathy. The mortality preventative effect of ICDs was incorporated using a pooled RR of 0.74 (95% CI 0.58 to 0.93) from the non-ischaemic subgroup of the SCD-HeFT,[105] AMIOVIRT,[69] CAT[82] and DEFINITE[90] trials. The SCD-HeFT[105] distribution of patients by NYHA class was also used. *Table 123* reports the estimated cost-effectiveness results for this subgroup.

TABLE 121 The MADIT II trial[101] 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

TABLE 122 The SCD-HeFT trial[105] 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

TABLE 123 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

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 with the base case (secondary prevention of SCD), both treatment strategies for patients with cardiomyopathy have a higher cost and provide a greater benefit (about £9000 more for 1.67 or 1.88 QALYs more with ICD + OPT or OPT alone respectively) over a lifetime. The ICER estimated for the cardiomyopathy subgroup is £26,028 per QALY.

Univariate sensitivity analysis *Table 124* shows the results of the univariate sensitivity analyses conducted on key inputs in the model, allowing the estimation of their impact on the cost-effectiveness results. The range used for most parameters was their 95% CI.

The univariate sensitivity analyses for the structural parameters did not result in large changes to the ICER, apart from that for the model time horizon. The only analysis that increased the ICER to > £30,000 per QALY gained was that in which the time horizon was shortened to the survival follow-up period reported in the AVID trial[71] (as very few health benefits are accrued over that time period compared with the incremental cost of ICD implantation).

Among the mortality-related estimates, the model results showed particular sensitivity to the HR for all-cause mortality associated with the ICD + OPT arm, more than tripling to £78,268 per QALY gained when the upper limit of the HR (0.93) was used.

The event-related estimates that had the 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 95% CI the ICER ranged from £18,950 to £32,605 per QALY gained, and when the device lifetime was changed from 8 years to 13 years or 5 years the ICER ranged from £16,456 to £24,706 per QALY gained respectively.

Hospitalisation for arrhythmia There is limited reporting of the number of hospitalisations for non-fatal arrhythmia in the trials included in our systematic review for population 1 (patients at increased risk of SCD). Following clinical advice, our base-case analysis assumes the same risk as that for patients with HF (probability of event occurring 0.0075, 95% CI 0.0002 to 0.0148), derived from the MIRACLE trial.[121] As this is likely to be an underestimate of the risk for population 1 patients, a scenario analysis was conducted using the risk of hospitalisation for ventricular arrhythmia for population 3 patients with an ICD (also at increased risk of SCD as a result of ventricular arrhythmia).

In the population 3 model, the risk of hospitalisation because of arrhythmia for patients with an ICD is 0.032 (probability of event occurring; 95% CI 0.017 to 0.046), obtained by applying the pooled RR of 1.11 to the baseline risk of patients managed with CRT-D (0.029) derived in *Chapter 4* (see *People with both conditions*, *Assessment of effectiveness*, *Arrhythmias*). For the population 1 scenario, the risk of hospitalisation because of arrhythmia was assumed to be 0.032 for patients with an ICD and for patients being managed with OPT alone. *Table 125* summarises the cost-effectiveness results for this scenario. Compared with the base-case analysis, a slightly lower ICER (£18,185 per QALY gained) is estimated using a higher risk of hospitalisation for arrhythmia, as the OPT arm shows a substantial gain in QALYs compared with the ICD + OPT arm, despite the greater increase in cost.

TABLE 124 Univariate sensitivity analysis: population 1

Parameter	Base-case value	DSA value	Incremental cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	–	–	15,492	0.80	19,479
Structural parameters					
Time horizon	Lifetime	AVID trial follow-up (3 years)[71]	13,330	0.09	141,235
Discount rates of costs and benefits (%)	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 (ICDs)	0.75	0.61	17,126	1.37	12,480
		0.93	13,772	0.18	78,268
Age-related RR 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 for HF (OPT)	0.008	0	15,251	0.79	19,197
		0.020	15,869	0.80	19,920
RR of hospitalisation for HF (ICDs)	1	0.804	15,262	0.80	19,184
		1.196	15,723	0.80	19,773
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 (ICDs)	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), γ	–15.78, 1.94 (~ 8 years)	–16.182, 1.889 (~13 years)	13,158	0.80	16,456
		–15.385, 1.996 (~5 years)	19,467	0.79	24,706

TABLE 125 Hospitalisation because of 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

Utilities In the base-case analysis, NYHA class-weighted average utility estimates of 0.81 and 0.82 were used for the OPT arm and the ICD arm, respectively, using the distribution of patients per NYHA class in the AVID trial.[71] 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.[153] This lower average utility value led to an estimated 0.69 QALY gain (instead of the 0.80 QALY gain estimated for the base case). Therefore, the ICER of ICD + OPT compared with OPT alone for the secondary prevention of SCD increased to £22,372 per QALY gained.

Device-related costs All device-related costs (i.e. costs associated with implantation, perioperative complications, treatment of lead displacement, infection and device replacement) were varied to the lower and upper limits of their 95% CI, for example the ICD implantation cost was reduced by 14% to £13,155. For this scenario the ICER ranged from £16,888 to £37,832 per QALY gained.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis 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 CIs) included in the probabilistic sensitivity analysis, the form of distribution used for sampling and the parameters of the distribution. Probabilistic sensitivity analysis 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 [interquartile range (IQR) £9857 to £61,685 per QALY gained].

Figure 36 shows the variation in the probability of cost-effectiveness for both interventions as the WTP threshold 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 WTP threshold of £20,000 per QALY gained and a 82% probability of being cost-effective at a WTP threshold of £30,000 per QALY gained.

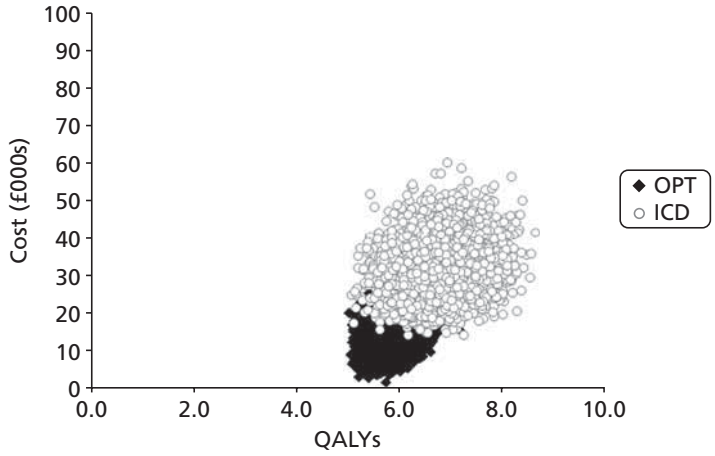

FIGURE 35 Cost-effectiveness scatterplot: population 1.

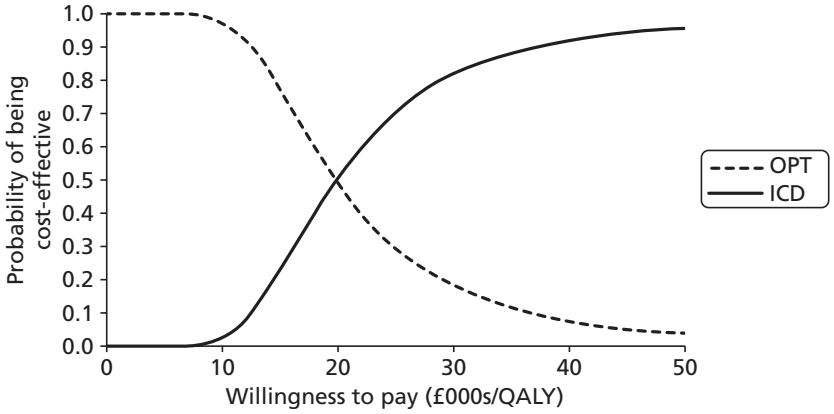

FIGURE 36 Cost-effectiveness acceptability curve: population 1.

Population 2: patients with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite receiving optimum pharmacological therapy

People with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT were modelled receiving initially OPT alone or CRT-P or CRT-D alongside OPT. This allowed the estimation of the relative cost-effectiveness of these treatment strategies, and results for the comparisons specified in the NICE scope[61] (CRT-P + OPT vs. OPT, CRT-D + OPT vs. OPT, and CRT-D + OPT vs. 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 HF was modelled receiving the relevant treatment strategies. *Table 126* 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 the incremental cost per QALY gained for the relevant comparisons.

The ICERs for initial management with CRT-P or CRT-D alongside OPT compared with initial management with OPT alone were similar (£27,584 and £27,899 per QALY gained respectively). The addition of CRT-P to OPT results in a gain of 0.68 QALYs at a cost of £18,845 compared with OPT, and the addition of CRT-D to OPT yields a gain of 1.09 QALYs at a cost of £30,548 compared with OPT. CRT-D + OPT was

TABLE 126 Base-case summary of the cost-effectiveness results: population 2

Strategy	Cost (£)	Life-years	QALYs	Incremental cost (£)	Incremental life-years	Incremental QALYs	ICER (£/QALY gained)
Vs. next best option[a]							
OPT	7615	4.86	3.48	–	–	–	–
CRT-P + OPT	26,460	5.51	4.17	18,845	0.66	0.68	27,584
CRT-D + OPT	38,163	7.21	4.58	11,703	1.69	0.41	28,420
Vs. OPT							
CRT-D + OPT	38,163	7.21	4.58	30,548	2.35	1.09	27,899

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated.
Discounted costs and benefits.

more costly (by £11,703) and more effective (resulting in an increase of 0.41 QALYs) than CRT-P + OPT, resulting in an ICER of £28,420 per QALY gained compared with CRT-P + OPT. The costs and QALYs estimated for each intervention are plotted in *Figure 37*.

Model outputs and validation Heart failure deaths and SCDs estimated in the model were compared with those reported in the CARE-HF trial[109] (see *Appendix 16* for details).

Events The percentage of time spent in the main health states by an average patient in each strategy is presented in *Table 127*. Patients in each strategy spent most time in the stable with therapy health state. The cohort initially managed with OPT alone spent slightly more time in the stable with therapy health

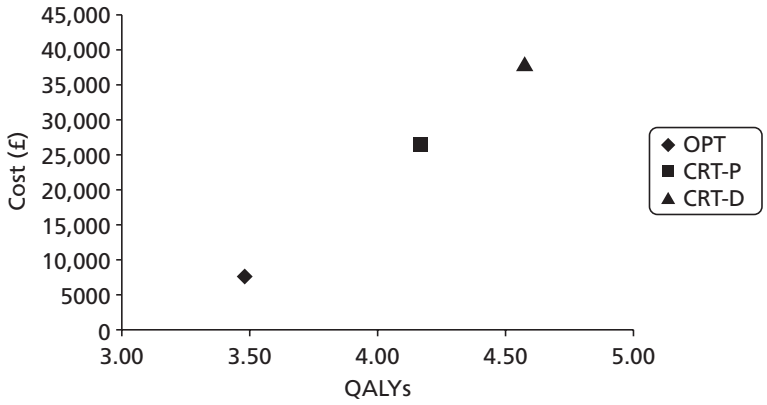

FIGURE 37 Cost-effectiveness plane: population 2.

TABLE 127 Overall distribution of an average patient's lifetime by health state category: population 2

	% of remaining life		
Health state category	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
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
CRT-D	0.03	1.02	3.14
ICD	0.00	0.17	0.48
Implant surgery	0.03	1.70	1.24
Routine replacement	0.01	0.32	0.56
Lead displacement	0.00	0.33	0.34
Postoperative complications	0.00	0.25	0.22
Infection	0.00	0.06	0.06
Device-related interventions[a]	0.05	2.65	2.42

a Sum of occupancy in implant surgery, postoperative complications, routine upgrade, lead displacement and infection.

state, but it is also the strategy with the highest proportion of remaining life spent in hospital. The CRT cohorts spent slightly less time hospitalised; however, they spent more time in the device-related intervention health state (i.e. because of implant surgery, postoperative 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 128 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 the CRT-P + OPT group required fewer device replacements than the CRT-D + OPT group given the longer lifetime of CRT-P, more upgrades were needed than in the CRT-D + OPT arm. The 228 ICDs reported as upgrades from CRT-D in the CRT-D + OPT strategy in *Table 128* are assumed to be successful ICD implants after CRT-D implant failures.

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 mixed-gender cohort of patients with HF. The distribution of patients with HF by age group reported by Cowie and colleagues[20] was used, and the proportion of men with HF was derived from the prevalence of HF per sex in the UK from British Heart Foundation Statistics.[29] Age-dependent variables in the population 2 model were those that determined SCD, HF death, other-cause mortality and RR of death by age group.

The model results for different starting ages are detailed in *Table 129*. These results show that the ICER increases non-linearly with age and the ICERs of the three comparisons are consistently similar among age groups. For most age groups, CRT-P + OPT compared with OPT alone is the strategy with the lowest ICER and CRT-D + OPT compared with CRT-P + OPT is the strategy with the highest ICER. The exception is for 80-year-old patients, for whom the opposite is estimated to occur, as CRT-D + OPT compared with CRT-P + OPT shows a smaller QALY gain (0.33) at a lower cost (£10,757) than that estimated for CRT-P + OPT relative to OPT alone (0.49 QALYs gained at a cost of £16,000).

Univariate sensitivity analysis *Tables 130–132* 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 per QALY in the ICER). The other parameters were varied but had a smaller impact on the results.

Table 130 shows that the risk of hospitalisation for a serious arrhythmic event for HF patients managed with CRT-P, the RRs of HF death for patients managed with CRT-P and CRT-D, and the RR of SCD for HF patients managed with CRT-P have the most impact on the cost-effectiveness results for the comparison between CRT-P + OPT and OPT alone as initial treatment.

The results for this comparison are particularly sensitive to the risk of hospitalisation for non-fatal arrhythmia for HF patients managed with CRT-P, as the ICER decreases to £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 the 95% CI is used, as the cost of the CRT-P + OPT cohort increases substantially whereas that for the OPT alone cohort stays the same. Patients being managed with CRT-P who are hospitalised because of arrhythmias are assumed to be referred for CRT-D implantation. The cost increment for the CRT-P cohort is hence accompanied by a small health gain.

The RR of SCD for patients managed with CRT-P was varied between the RRs reported in the CARE-HF[109] and COMPANION[116] trials, as these indicate a relative effect in opposite directions. The ICER for CRT-P + OPT compared with OPT alone decreases to £19,825 per QALY gained when the RR of SCD for

TABLE 128 Number of events[a] for cohorts of 1000 patients: population 2

Event	Strategy		
	OPT	CRT-P + OPT	CRT-D + OPT
Initial implant	0	1000	1000
ICD	0	0	0
CRT-P	0	1000	0
CRT-D	0	0	1000
Hospitalisation	3043	2349	3385
OPT	3013	299	6
CRT-P	9	1057	0
CRT-D	18	854	2929
ICD	3	140	450
Upgrade	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 displacement	3	275	315
ICD	0	4	12
CRT-P	2	183	0
CRT-D	2	88	303
Infection	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
Replacement	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
Total no. of devices[b]	27	1737	1736
ICD	2	89	228
CRT-P	11	1063	0
CRT-D	14	584	1508

a Undiscounted number of events.
b Sum of initial implants, upgrades, infections (required new device) and replacements.

TABLE 129 Base-case results by age and for a mixed-age cohort: population 2

Starting age (years)	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	7615	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	5882	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	4075	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	8218	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

patients managed with CRT-P from the CARE-HF trial[109] (0.54) is used, that is, 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[116] (1.13) is used, a scenario in which CRT-P would increase the risk of SCD.

Generally, the results for the addition of CRT-D to OPT were robust to the variation of most of the parameters (see *Table 131*) compared with the results for the other two comparisons (CRT-P + OPT vs. OPT and CRT-D + OPT vs. CRT-P + OPT). They were mainly sensitive to the RR of HF death and the RR of SCD for patients managed with CRT-D, and to the lifetime of the CRT-D device, confirming that the cost-effectiveness of the addition of CRT-D to OPT is determined by the survival benefit associated with this device. The most influential parameter for this comparison was the RR of HF death associated with CRT-D (0.73). Varying the RR between 0.47 and 1.11 resulted in the ICER ranging between £20,671 and £52,082, respectively, a difference of £31,411. When the upper limit of this estimate is considered (1.11), the preventative benefit of CRT-D for HF death disappears and the ICER for CRT-D + OPT compared with OPT alone rises to > £50,000 per QALY gained.

TABLE 130 Univariate sensitivity analysis for CRT-P + OPT vs. 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	8765	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

DSA, deterministic sensitivity analysis.

TABLE 131 Univariate sensitivity analysis for CRT-D + OPT vs. 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 (~7 years)	–16.000, 1.863 (~13 years)	25,309	1.12	22,643
		–14.931, 2.006 (~4 years)	39,322	1.05	37,363

DSA, deterministic sensitivity analysis.

The results for the comparison between CRT-D and CRT-P alongside OPT were the most sensitive to the variation of individual parameters, with eight parameters that made the ICER range by > £10,000 (see *Table 132*). The most influential parameter for this comparison was the RR of HF death for patients managed with CRT-D compared with OPT alone, followed by the RRs of SCD for both CRT-D and CRT-P devices relative to OPT alone.

The estimate of the RR of HF death for patients managed with CRT-D was sourced from the COMPANION trial[116] (RR 0.73, 95% CI 0.47 to 1.11). When a higher risk of HF death for CRT-D than 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), resulting in an extremely high ICER.

The ICER for CRT-D + OPT compared with CRT-P + OPT also becomes extremely high when the RR of SCD for patients managed 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 reported in *Chapter 4* (see *People with heart failure*, *Assessment of effectiveness*, *Sudden cardiac death*). Given its wide 95% CI, a RR of 1 was

TABLE 132 Univariate sensitivity analysis for CRT-D + OPT vs. 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	9545	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	9912	0.08	129,220
Device lifetime (CRT-D), ln(λ), γ	–15.465, 1.935 (~7 years)	–16, 1.863 (~13 years)	8608	0.43	20,238
		–14.931, 2.006 (~4 years)	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	6335	0.34	18,707
Baseline mortality from 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 from 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

DSA, deterministic sensitivity analysis.

used in the model and this value was varied in the sensitivity analysis between the mean estimates of RR reported in the most relevant trials (0.54 from the CARE-HF trial[109] and 1.13 from the COMPANION trial).[116] Under the CARE-HF trial scenario, the preventative effect of CRT-P on SCD becomes higher than that of CRT-D, that is, 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 patients managed with CRT-D is increased to 0.86 (the upper limit of its 95% CI, sourced from the COMPANION trial),[116] only 0.08 incremental QALYs are estimated for CRT-D + OPT compared with CRT-P + OPT, resulting in a particularly high ICER.

Varying the life expectancy of the CRT-D device, the RR of HF death for patients managed with CRT-P and the risk of hospitalisation for severe arrhythmia for patients managed with CRT-P also had a substantial influence on the ICER, making it range by > £20,000. The ICER for CRT-D + OPT compared with CRT-P + OPT decreased substantially when a longer device lifetime was used (13 years) for CRT-D, the RR of HF death with CRT-P was increased or the risk of hospitalisation for arrhythmia with CRT-P was higher.

Overall, the ICERs for the comparisons relevant for population 2 are sensitive mainly to survival-related parameters that determine the incremental benefit of the devices for patient survival, such as the RRs of SCD and HF death for CRT-P and CRT-D, the risk of hospitalisation because of arrhythmia for CRT-P and the lifetime of the device for CRT-D. Device lifetime was also influential because of the incremental costs incurred if a device needs replacing more frequently.

Scenario analysis

Device longevity Clinical advice indicated that the device longevity estimates used in the base-case analysis could be overestimated, particularly for CRT-P. *Table 133* presents the device lifetime estimates used in the previous model by Fox and colleagues[64] and those used in the current model.

A scenario analysis was conducted using the mean device lifetime estimates used by Fox and colleagues.[64] The results for this scenario are presented in *Table 134*. Compared with the base-case analysis, higher costs are estimated for CRT-D and CRT-P alongside OPT because of the shorter device lifetime (by approximately £4500 and £2000 respectively). Also, slightly fewer QALYs (–0.02) are estimated to be accrued than in the base-case analysis as patients are estimated to spend more time in the device-related interventions health state and less time stable with therapy.

Utilities A scenario using the utility estimates from the study by Fox and colleagues[64] (presented in *Table 135*) was explored. The utility estimates used in the base-case analysis can be found in *Table 108*.

Table 136 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 between CRT-P and CRT-D

TABLE 133 Device lifetime estimates

	Lifetime (years)	
Device	Fox *et al.*,[64] mean	SHTAC, mean (95% CI)
ICD	5.0	8.2 (5.4 to 12.8)
CRT-D	5.5	7.2 (4.1 to 13.1)
CRT-P	6.5	11.8 (6.6 to 22.2)

TABLE 134 Shorter device lifetime scenario analysis results: population 2

Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs. OPT	ICER (£/QALY gained) vs. CRT-P + OPT
OPT	7652	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

TABLE 135 Utility values used in the scenario analysis: population 2

Health state	Mean utility value	Source
NYHA class I	0.93	Kirsch and McGuire 2000[210]
NYHA class II	0.78	Kirsch and McGuire 2000[210]
NYHA class III	0.61	Calvert *et al.*[211]
NYHA class IV	0.44	Calvert *et al.*[211]
Hospitalisation and transplantation	0.57	McAllister *et al.*[194]
Decrement from surgery	0.05	Assumption
Decrement from infection	0.1	Assumption

TABLE 136 Utilities scenario analysis results: population 2

Intervention	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs. OPT	ICER (£/QALY gained) vs. CRT-P + OPT
OPT	7615	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

and OPT alone are explained by the greater differences in QALYs gained among strategies than in the base-case analysis. As both CRT cohorts had similar QALY increments in this scenario, the ICER for CRT-D compared with CRT-P in this scenario (£27,893 per QALY gained) does not differ as much from the ICER in the base case (£28,420 per QALY gained).

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% CIs (see *Table 114*). 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 compared with OPT, and from £28,090 to £61,967 per QALY gained for CRT-D + OPT compared with CRT-P + OPT. Considering a willing-to-pay threshold of £30,000 per QALY gained, when the upper limits of the 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 of the device-related costs resulted in a reduction in costs of > £4500 for both CRT strategies and of < £100 for OPT alone. Thus, the ICERs for the comparisons between the CRT devices and OPT alone are reduced much more substantially than the ICER for the comparison between CRT-D and CRT-P.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis 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 CIs) included in the probabilistic sensitivity analysis, the form of distribution used for sampling and the parameters of the distribution. *Table 137* reports the estimated probabilistic results of 10,000 iterations in terms of costs and QALYs for each strategy and their relative cost-effectiveness.

The probabilistic results are consistent with the deterministic base-case analysis. Both CRT-P + OPT and CRT-D + OPT have ICERs of < £30,000 per QALY gained compared with initial management with OPT alone, as well as CRT-D + OPT compared with CRT-P + OPT. The IQR estimated for the probabilistic ICER for the comparison between CRT-D + OPT and CRT-P + OPT reflects the overlap in model results for CRT-P and CRT-D.

The probabilistic sensitivity analysis results are presented in *Figure 38* in terms of incremental costs and QALYs, showing their dispersion on the cost-effectiveness scatterplot and the partial overlap of the cost-effectiveness results for the three strategies, particularly between CRT-P and CRT-D.

Figure 39 shows the variation in the probability of the three treatment strategies being cost-effective as the WTP threshold increases from £0 to £50,000 per QALY gained. At a WTP threshold of £20,000 per QALY

TABLE 137 Base-case summary of the probabilistic cost-effectiveness results: population 2

Strategy	Cost (£)	QALYs	ICER (£/QALY gained) vs. OPT (IQR)	ICER (£/QALY gained) vs. CRT-P + OPT (IQR)
OPT	7604	3.48	–	–
CRT-P + OPT	25,874	4.14	27,434 (16,314 to 47,527)	–
CRT-D + OPT	38,156	4.56	28,158 (17,431 to 49,839)	27,899 (–175 to 159,172)

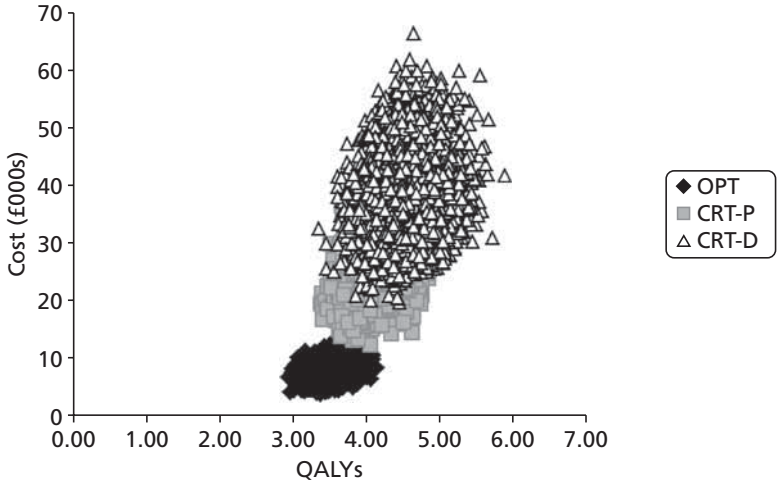

FIGURE 38 Cost-effectiveness scatterplot: population 2.

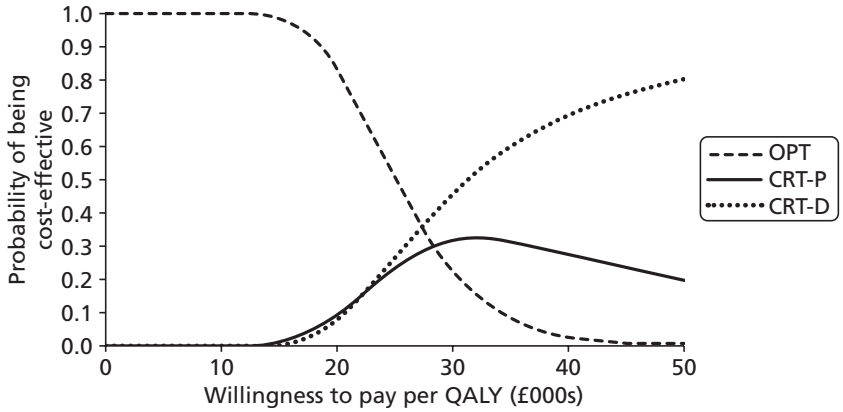

FIGURE 39 Cost-effectiveness acceptability curve: population 2.

gained, the probability of OPT alone (with subsequent upgrades), CRT-P + OPT and CRT-D + OPT being cost-effective is 83%, 9% and 8% respectively. Above a WTP threshold of £28,000 per QALY gained, the intervention with the highest probability of being cost effective is CRT-D + OPT (38%). At a WTP threshold of £30,000 per QALY gained, CRT-D + OPT and CRT-P + OPT have a 46% and 31% probability of being cost-effective, respectively, whereas OPT alone has a 23% probability of being cost-effective.

Population 3: people 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 compared with OPT alone (allowing for subsequent device implantations) or CRT-P or ICD alongside OPT.

Base-case analysis

The RAFT trial[140] provided the estimates for all-cause mortality and the distribution of patients by NYHA class used for our base-case analysis for population 3. *Table 138* presents the estimated discounted costs, life-years and QALYs gained for each strategy, as well as the ICERs 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 subsequent device implants as necessary) had a similar estimated cost (£287 more) to that of ICD + OPT and resulted in 0.10 more QALYs. Thus, each additional QALY gained with OPT alone is estimated to cost £2824 more. A significant proportion of population 3 patients initially managed with OPT alone are estimated to be referred for

TABLE 138 Base-case summary of the cost-effectiveness results: population 3

Strategy	Cost (£)	Life-years	QALYs	Incremental cost (£)	Incremental life-years	Incremental QALYs	ICER (£/QALY gained)
Vs. next best option[a]							
ICD + OPT	39,719	7.45	5.57	–	–	–	–
OPT	40,006	7.59	5.67	287	0.14	0.10	2824
CRT-P + OPT	51,202	7.96	5.94	11,196	0.37	0.27	Dominated
CRT-D + OPT	50,911	8.01	5.98	10,906	0.42	0.31	35,193
Vs. ICD + OPT							
CRT-P + OPT	51,202	7.96	5.94	11,483	0.51	0.37	Dominated
CRT-D + OPT	50,911	8.01	5.98	11,193	0.56	0.41	27,195

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated.
Discounted costs and benefits.

CRT-D over their lifetime. These patients will therefore benefit from lower risks of death and hospitalisation for HF than patients receiving ICD + OPT. They are estimated to spend more time stable with therapy and to have a slightly higher QALY gain (0.10) than those managed with ICD + OPT.

Similar costs and QALYs are estimated for the CRT-P + OPT and CRT-D + OPT strategies. As a marginally higher cost and slightly fewer QALYs are estimated for CRT-P + OPT than for CRT-D + OPT, CRT-P + OPT is dominated by CRT-D + OPT.

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.

The costs and QALYs gained per strategy are presented graphically in *Figure 40*, in which the proximity between the CRT strategies and the proximity between the OPT alone and ICD + OPT strategies is noticeable.

Model outputs and validation

The overall survival estimated in the model was compared with that reported in the relevant trials (see *Appendix 16* for details).

Events The percentage of time spent in the main health state categories by an average patient for each strategy is presented in *Table 139*. All strategies being compared show similar occupancies for the stable with therapy health state (most of the patient's lifetime) or the device-related interventions health state (implant surgery, postoperative complications, routine replacements, lead displacements and infections). The model also estimates small differences between strategies in the time spent in hospital.

The numbers of the most relevant events estimated for each arm of the population 3 model are presented in *Table 140*. The cohort of patients initially managed with OPT alone is estimated to receive 1850 implants (1552 CRT-D, 297 ICD and one CRT-P), of which 820 are estimated to be associated with routine replacements according to the estimated battery lifetime. In the cohort initially implanted with an ICD, 47 are expected to upgrade to CRT-D and nine are expected to receive an ICD subsequently because of CRT-D implant failure. Both strategies in which 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.

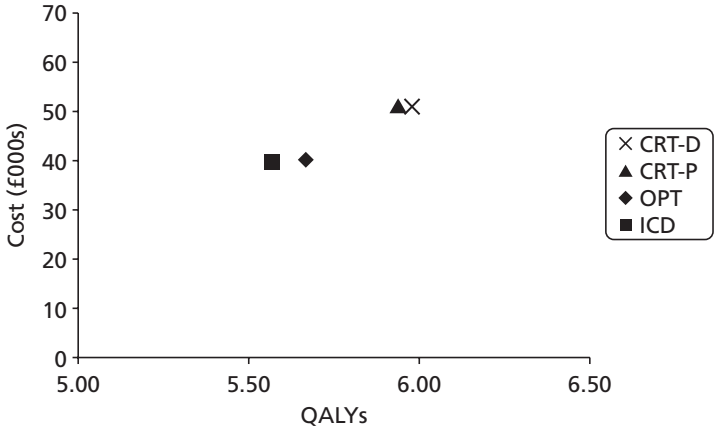

FIGURE 40 Cost-effectiveness plane for population 3.

TABLE 139 Overall distribution of an average patient's lifetime by health state category for population 3

	% of remaining life			
Health state categories	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	20.59	0
CRT-D	61.10	3.15	60.50	80.26
Hospitalisation	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	0.76	0
CRT-D	0.65	0.04	0.65	0.76
Routine replacement	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
Infection	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, postoperative complications, routine upgrades, lead displacements and infections.

Deterministic sensitivity analysis

Mixed-age cohort Cost-effectiveness results were estimated for a scenario of a mixed-age and mixed-gender cohort of population 3 patients. The distribution of ICD and CRT implants by age in the UK reported by the British Cardiovascular Society, the British Heart Foundation and the Cardio & Vascular Coalition[225] was used as a proxy for the distribution of population 3 patients. Age-dependent variables in the population 3 model were those that determined all-cause mortality (baseline risk and RR of death by age group).

TABLE 140 Number of events[a] for cohorts of 1000 patients: population 3

Event	Strategy			
	OPT	ICD	CRT-P	CRT-D
Initial implant	0	1000	1000	1000
ICD	0	1000	0	0
CRT-P	0	0	1000	0
CRT-D	0	0	0	1000
Hospitalisation	5446	4957	4797	4790
OPT	1171	21	110	4
ICD	578	4776	603	757
CRT-P	808	15	1072	3
CRT-D	2889	144	3012	4025
Upgrade	974	56	1025	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 displacement	313	151	432	435
ICD	17	137	17	22
CRT-P	0	0	106	0
CRT-D	296	15	309	413
Infection	57	59	76	78
ICD	7	57	7	9
CRT-P	0	0	17	0
CRT-D	50	2	52	69
Replacement	820	647	874	919
ICD	130	609	137	148
CRT-P	0	0	4	0
CRT-D	690	38	733	771
Number of devices[b]	1850	1762	2974	2201
ICD	297	1674	313	353
CRT-P	1	0	1021	0
CRT-D	1552	88	1640	1848

a Undiscounted number of events.
b Sum of number of initial implants, upgrades, infections (required new device) and replacements.

Table 141 summarises the model results for different starting ages. For most age groups, ICD + OPT is the strategy with the least estimated benefit. Compared with the next best option or with ICD + OPT in most age groups, OPT alone is the strategy with the lowest ICER, CRT-P + OPT is dominated and CRT-D + OPT is that with the highest ICER.

TABLE 141 Results by age and for a mixed-age cohort: population 3

Starting age (years)	Strategy	Cost (£)	Life-years	QALYs	ICER (£/QALY gained) vs. next best option[a]	ICER (£/QALY gained) vs. ICD + OPT
30	OPT	55,173	10.67	7.98	18,499	18,499
	ICD + OPT	51,560	10.40	7.78	–	–
	CRT-P + OPT	66,193	11.01	8.23	Dominated	Dominated
	CRT-D + OPT	65,417	11.08	8.28	34,236	28,020
40	OPT	54,428	10.51	7.86	19,094	19,904
	ICD + OPT	51,012	10.26	7.68	–	–
	CRT-P + OPT	65,414	10.84	8.10	Dominated	Dominated
	CRT-D + OPT	64,637	10.90	8.15	34,872	28,887
50	OPT	52,222	10.02	7.49	19,708	19,708
	ICD + OPT	49,165	9.81	7.34	–	–
	CRT-P + OPT	63,107	10.34	7.72	Dominated	Dominated
	CRT-D + OPT	62,323	10.40	7.77	36,881	30,672
60	OPT	46,012	8.77	6.55	13,715	13,715
	ICD + OPT	43,844	8.55	6.39	–	–
	CRT-P + OPT	56,718	9.05	6.75	Dominated	Dominated
	CRT-D + OPT	55,951	9.09	6.79	41,328	30,376
70	OPT	38,026	7.21	5.38	835	835
	ICD + OPT	37,938	7.06	5.27	–	–
	CRT-P + OPT	49,140	7.56	5.64	Dominated	Dominated
	CRT-D + OPT	48,856	7.61	5.68	36,625	27,196
80	OPT	33,517	6.35	4.74	Dominant	Dominant
	ICD + OPT	35,152	6.30	4.70	–	–
	CRT-P + OPT	44,963	6.77	5.05	Extendedly dominated	Extendedly dominated
	CRT-D + OPT	45,139	6.82	5.08	33,761	26,092
90	OPT	29,415	5.37	4.00	–	Extendedly dominated
	ICD + OPT	32,257	5.42	4.05	Extendedly dominated	–
	CRT-P + OPT	40,388	5.68	4.23	Extendedly dominated	Extendedly dominated
	CRT-D + OPT	40,599	5.72	4.26	43,438	38,916
Mixed	OPT	41,612	7.92	5.92	6489	6489
	ICD + OPT	40,888	7.77	5.81	–	–
	CRT-P + OPT	52,673	8.27	6.17	Dominated	Dominated
	CRT-D + OPT	52,297	8.32	6.21	36,697	28,330

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated.
Discounted costs and benefits.

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronisation Therapy trial

All-cause mortality reported for men in the CRT-D arm of the MADIT-CRT trial[130] and the respective HR for ICD therapy for the whole population of the MADIT-CRT trial (1.00, 95% CI 0.69 to 1.44) were used as an alternative scenario to the outcomes from the RAFT trial[140] used in the base-case analysis. *Table 142* summarises the cost-effectiveness results for this scenario.

Generally, most strategies became more costly and yielded a 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 dominated by ICD + OPT compared with OPT alone. Therefore, the results obtained with the MADIT-CRT trial data indicate that ICD + OPT is the most cost-effective strategy, with an ICER of £154 per QALY gained compared with OPT alone.

As the MADIT-CRT trial found no statistically significant difference in all-cause mortality between the ICD arm and the CRT-D arm, for this scenario the model assumed the same risk of death for the ICD and CRT-D cohorts. A similar benefit was therefore estimated for the ICD + OPT and CRT-D + OPT strategies (the 0.04 difference in QALYs gained is because less time is spent in the device-related interventions health state in the ICD + OPT cohort than in the CRT-D + OPT cohort). A much lower cost was estimated for ICD + OPT than for CRT-D + OPT as the first is estimated to involve fewer device upgrades and replacements.

Univariate sensitivity analysis

Comprehensive univariate sensitivity analyses were performed on the parameters informing the population 3 model. *Tables 143–146* present the sensitivity analysis results for the most influential parameters (i.e. those that when varied between the 95% CI limits caused a variation of > £20,000 per QALY in the ICER) for each of the relevant comparisons: CRT-D + OPT compared with OPT alone (allowing for subsequent device implantations), CRT-D + OPT compared with CRT-P + OPT and CRT-D + OPT compared with ICD + OPT.

The cost-effectiveness results for the comparison between initial treatment with CRT-D + OPT and initial treatment with OPT alone (see *Table 143*) were quite robust to the variation of the parameters in the model, with only two parameters varying the ICER by > £20,000. The comparison between CRT-D + OPT and OPT alone showed great sensitivity to the RR of all-cause mortality for the OPT alone arm. The ICER for CRT-D + OPT decreased to £22,240 per QALY gained when a greater risk of death is assumed for OPT than for CRT-D + OPT (because of the incremental QALY gain with the latter). When a shorter time horizon was considered (assuming the same as the lifetime of the CRT-D device), less benefit from CRT-D + OPT relative to OPT alone was accrued and therefore the ICER increased.

Table 144 shows the univariate sensitivity analysis results for CRT-D + OPT compared with ICD + OPT. The most influential parameters for this comparison were the RR of all-cause mortality for patients managed with an ICD and the lifetime of the CRT-D and ICD devices.

Assuming a lower RR of death for patients managed with an ICD would substantially increase the ICER for CRT-D + OPT compared with ICD + OPT, as there is a very small QALY gain (0.07). Also, assuming a 4-year device lifetime for the CRT-D device would almost double the ICER for CRT-D + OTP compared with ICD + OPT.

Varying the lifetime of the ICD device also had a substantial impact on the incremental cost of CRT-D compared with ICD. When the ICD was assumed to have a longer lifetime (13 years), a higher incremental cost for CRT-D was estimated and this strategy became non-cost-effective (ICER £35,034 per QALY gained). The opposite happened when the ICD was assumed to have a lifetime of 5 years (alongside the 7-year lifetime of the CRT-D device).

TABLE 142 The MADIT-CRT trial[130] scenario analysis 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	Dominated
CRT-D + OPT	60,051	9.97	7.45	Dominated
ICD + OPT	49,957	10.01	7.49	154

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated

TABLE 143 Univariate sensitivity analysis 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	9109	0.07	124,733
		2.083	12,972	0.58	22,240
Time horizon	Lifetime	CRT-D lifetime (7 years)	9347	0.15	63,837

DSA, deterministic sensitivity analysis.

TABLE 144 Univariate sensitivity analysis 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	9407	0.07	127,299
		1.37	12,981	0.75	17,262
Device lifetime (CRT-D), ln(λ), γ	–15.465, 1.935 (7 years)	–16.000, 1.863 (13 years)	3841	0.44	8784
		–14.931, 2.006 (4 years)	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)	5951	0.42	14,218

DSA, deterministic sensitivity analysis.

Table 145 shows the univariate sensitivity analysis for CRT-D + OPT compared with CRT-P + OPT, with 10 parameters that made the ICER range by > £20,000. As the estimated costs and benefits of these strategies are so similar, the comparison between 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 the preventative effect of the devices on arrhythmia (baseline risk of hospitalisation for arrhythmia with CRT-D and RR of hospitalisation for arrhythmia of CRT-P) and the lifetime of the CRT-D device.

TABLE 145 Univariate sensitivity analysis 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	3993	0.04	93,501
		0.0424	–1823	0.04	Dominant
Device lifetime (CRT-D), ln(λ), γ	–15.465, 1.935 (~7 years)	–16, 1.863 (~13 years)	–866	0.04	Dominant
		–14.931, 2.006 (~4 years)	1840	0.03	58,794
RR of hospitalisation for non-fatal arrhythmia (CRT-P)	1	0.80	1374	0.04	38,915
		1.20	–1457	0.04	Dominant
Risk of lead displacement (CRT-D)	0.004	0.0004	–926	0.05	Dominant
		0.0071	313	0.03	9393
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	–1054	0.05	Dominant
		6, 1.5	207	0.05	4370
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	6432
Risk of lead displacement (CRT-P)	0.0037	0.0004	188	0.03	5513
		0.0071	–764	0.04	Dominant
Time horizon	Lifetime	CRT-D lifetime (7 years)	–613	0.02	Dominant

DSA, deterministic sensitivity analysis.

For the base-case analysis, the baseline risk of hospitalisation for arrhythmia for patients managed with CRT-D (0.0285) was derived from the relevant trials included in the systematic review. As no evidence on hospitalisation for arrhythmia was found for the comparison between CRT-P and CRT-D, the risk for patients managed with CRT-P was assumed to be the same as that for CRT-D, given that clinical advice suggested that population 3 patients are likely to be hospitalised for arrhythmia irrespective of whether or not they have a device with a defibrillator function implanted. When a lower baseline risk of hospitalisation for arrhythmia is used, the ICER for CRT-D + OPT compared with 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 in the estimated costs; however, the costs of strategies without a defibrillator function (CRT-P and OPT alone) are reduced by more (about £10,000 less) than the cost of those with a defibrillator function (CRT-D and ICD), which incur costs of about £5000 less than in the base case. When the RR of hospitalisation for arrhythmia for patients managed with CRT-P is assumed to be 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.

TABLE 146 Univariate sensitivity analysis for OPT alone vs. ICD + OPT

Parameter	Base-case value	DSA value	Incremental cost (£)	Incremental QALYs	ICER (£/QALY gained)
Base case	–	–	287	0.10	2824
Time horizon	Lifetime	CRT-D lifetime (7 years)	–4395	–0.05	94,341
Device lifetime (CRT-D), ln(λ), γ	–15.465, 1.935 (~7 years)	–16, 1.863 (~13 years)	–6129	0.12	Dominant
		–14.931, 2.006 (~4 years)	8653	0.07	123,385
Device lifetime (ICD), ln(λ), γ	–15.78, 1.94 (~ 8 years)	–16.182, 1.889 (~13 years)	3505	0.10	35,868
		–15.385, 1.996 (~5 years)	–5086	0.11	Dominant
Baseline risk of hospitalisation for non-fatal arrhythmia (CRT-D)	0.0285	0.0146	–4565	–0.09	49,987
		0.0424	2086	0.19	10,896
RR of hospitalisation for non-fatal arrhythmia (OPT)	1	0.8	–1978	0.04	Dominant
		1.2	1923	0.15	13,107
RR of hospitalisation for non-fatal arrhythmia (ICD)	1.11	0.88	2330	0.10	22,346
		1.41	–2334	0.10	Dominant
Baseline risk of all-cause mortality (CRT-D), ln(λ), γ	–6.334, 1.234	–6.467, 1.198	2047	0.14	14,124
		–6.202, 1.270	–1092	0.06	Dominant
Risk of lead displacement (CRT-D)	0.0037	0.0004	–1083	0.11	Dominant
		0.0071	1600	0.09	17,916
Discount rates of costs and benefits (%)	3.5, 3.5	0, 0	3183	0.22	14,529
		6, 1.5	–1212	0.16	Dominant

DSA, deterministic sensitivity analysis.

As for the previous comparison of two strategies both involving initial treatment with a device, varying the lifetime of the CRT-D device had a great impact on the ICER for the comparison between CRT-D + OPT and CRT-P + OPT. The incremental cost associated with a 4-year time period for replacement led to an ICER of £58,794 per QALY gained.

The comparison between OPT and ICD + OPT was also sensitive to many parameters (see *Table 146*), given that the estimated costs and QALYs for these strategies were very similar. It showed particular sensitivity to the time horizon, the lifetime of the CRT-D and ICD devices, the baseline risk of hospitalisation for non-fatal arrhythmia (CRT-D) and the RR of hospitalisation for non-fatal arrhythmia (OPT and ICD).

Assuming a shorter time horizon resulted in a substantial increase in the ICER for the comparison between OPT alone and ICD + OPT, as the first strategy showed a cost saving associated with a very small reduction in the health benefits accrued. When the 8-year ICD lifetime was assumed as the time horizon for the model, there was an increase in the incremental cost for OPT alone and less benefit compared with

ICD + OPT. This increase in incremental cost with OPT alone is mainly a result of referrals for CRT-D implants because of severe arrhythmic events.

A substantial increase in the incremental cost for OPT alone compared with ICD + OPT is also estimated when CRT-D devices are assumed to require replacement every 4 years, associated with a small reduction in incremental QALYs compared with the base case, resulting in an ICER of £123,385 per QALY gained. When the lifetime of the ICD device is assumed to be longer than in the base case (13 years), the incremental cost of OPT increases 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 impacts on the comparison between OPT alone and ICD + OPT. With a lower baseline risk of hospitalisation, the estimated costs and QALYs for all strategies decreased (strategies without a defibrillator function have a greater reduction in costs than those with a defibrillator function) compared with the base case. Mainly because of fewer referrals for CRT-D implants, OPT alone (followed by the subsequent implants) was the strategy that was the most cost saving relative to the base case and also the one with the greatest loss of QALYs accrued, hence the high ICER estimated for it compared with ICD + OPT when a lower baseline risk of hospitalisation for severe arrhythmia was used. The ICER for OPT alone compared with ICD + OPT also increases when the RR of hospitalisation for arrhythmia is assumed to be higher for OPT or lower for ICD + OPT, as the additional cost associated with OPT increases substantially (and the additional benefit rises slightly or does not change respectively).

Table 147 presents the parameters that result in a change in the most cost-effective strategy as their value is varied between their 95% CI limits. These relate mainly to the longevity of the devices with a defibrillator function (these have a shorter estimated lifetime relative to that of CRT-P), the RR of all-cause mortality for ICD and OPT, the baseline risk of hospitalisation for arrhythmia for CRT-D and the RR of hospitalisation for arrhythmia for ICD, and the discount rates for costs and benefits.

Overall, ICD + OPT becomes the most cost-effective strategy at a WTP threshold of £20,000 per QALY gained when an 8-year time horizon (the lifetime of an ICD device), a shorter CRT-D device lifetime (approximately 4 years), a longer ICD device lifetime (approximately 13 years), a lower RR of all-cause mortality for patients managed with ICD (RR = 1.04), a higher RR of all-cause mortality for patients managed with OPT (RR = 2.08) or a lower RR of hospitalisation for arrhythmia for patients managed with ICD (RR = 0.88) is used.

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 threshold of £30,000 per QALY gained (ICERs of £25,602 and £29,650 per QALY gained, respectively, compared with OPT alone). If a higher RR of all-cause mortality for patients being managed with OPT compared with those being managed with CRT-D is used (RR = 2.08), CRT-D becomes the optimal strategy at a WTP threshold of £30,000 per QALY gained, with an ICER of £22,240 per QALY gained.

The strategy of CRT-P + OPT became the most cost-effective strategy at a WTP threshold of £30,000 per QALY gained when the lower limit of the baseline risk of hospitalisation for arrhythmia for patients managed with CRT-D was used (ICER of £26,200 per QALY gained compared with OPT alone).

Scenario analysis

Device longevity Clinical advice indicated that device longevity estimates in the base-case analysis could be overestimated. A scenario analysis using the mean device lifetime estimates used by Fox and colleagues[64] (see *Table 133*) was conducted and the results are presented in *Table 148.* 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 compared with OPT alone is higher (£43,274 per QALY

TABLE 147 Most cost-effective strategies according to the variation of the most influential parameters

Parameter	Base-case value	DSA value	Most cost-effective strategy at £20,000/QALY	Most cost-effective 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 (~7 years)	UL: –14.934, 2.006 (~4 years)	ICD + OPT	ICD + OPT
Device lifetime (ICD), ln(λ), γ	–15.784, 1.943 (~8 years)	LL: –16.182, 1.889 (~13 years)	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
Discount rates of costs and benefits (%)	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

DSA, deterministic sensitivity analysis; LL, lower limit; UL, upper limit.

TABLE 148 Shorter device lifetime scenario analysis 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

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated.

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 compared with OPT alone. Compared with ICD + OPT, CRT-D + OPT has an ICER of £23,690 per QALY gained and CRT-P + OPT is also extendedly dominated in this case.

Effect of cardiac resynchronisation therapy devices on heart failure progression The population 3 base-case analysis is based on the conservative assumption that CRT devices have no impact on the distribution of patients by NYHA class over time. This scenario analysis assumes similar HF progression as used in the population 2 model. The population 2 model assumes a given initial distribution of patients by NYHA class (initially more severe than that in the population 3 model). At 9 months and 18 months,

different distributions by NYHA class (derived from the CARE-HF trial[109] and the BRESCIA study[223]) are assumed, capturing the effect of CRT on patients' HRQoL.

Table 149 shows the cost-effectiveness results for this scenario. The results show an ICER of £27,396 per QALY gained for CRT-D + OPT compared with OPT alone, similar to that seen in the population 2 model (£27,899 per QALY gained).

Utilities A scenario using the utility estimates used by Fox and colleagues[64] (presented in *Table 135*) was explored. *Table 150* shows the cost-effectiveness results for this scenario. Using the same utility values as Fox and colleagues did not effect the model results significantly (a reduction of 0.02 QALYs for OPT alone and 0.03 QALYs for all of the strategies beginning with implantation of a device). The ICERs obtained with this scenario are similar to those in the base-case analysis.

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% CIs (see *Table 114*). When all costs were varied, the range in the ICER was > £25,000 per QALY gained for all relevant comparisons except for OPT compared with ICD + OPT, which showed a 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 compared with CRT-P + OPT, and from £28,200 to £60,864 for CRT-D + OPT compared with OPT alone.

Under a scenario using the upper limit of all costs, ICD + OPT and OPT alone are the most cost-effective strategies at a WTP threshold of £20,000 and £30,000 per QALY gained respectively. When the lower limit of all costs (including device-related costs, health state costs and pharmacological therapy costs) is used, the most cost-effective strategy at a threshold of £30,000 per QALY gained is CRT-D + OPT.

TABLE 149 The effect of CRT devices on HF scenario analysis results: population 3

				Incremental			
Strategy	Cost (£)	Life-years	QALYs	Cost (£)	Life-years	QALYs	ICER (£/QALY gained)
Vs. next best option[a]							
ICD + OPT	39,719	7.45	5.37	–	–	–	–
OPT	40,006	7.59	5.68	287	0.14	0.31	936
CRT-P + OPT	51,202	7.96	6.04	11,196	0.37	0.36	Dominated
CRT-D + OPT	50,911	8.01	6.08	10,906	0.42	0.40	27,396

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated.
Discounted costs and benefits.

TABLE 150 Utilities scenario analysis results: 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	Dominated	Dominated
CRT-D + OPT	50,911	8.01	5.95	35,515	27,859

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated.

Probabilistic sensitivity analysis

Table 151 reports the base-case probabilistic sensitivity analysis for population 3. *Appendix 15* reports the variables (mean values and CIs) included in the probabilistic sensitivity analysis and the form of distribution used for sampling and the parameters of the distribution. Overall, the probabilistic results are consistent with the deterministic results. The results show that an additional QALY gained with OPT alone is estimated to cost £13,053 more than with ICD + OPT. The estimated ICER for CRT-D + OPT compared with OPT alone is £34,988 per QALY gained. Compared with ICD + OPT, the ICER for CRT-D + OPT is £23,133 per QALY gained.

The probabilistic sensitivity analysis results of 10,000 iterations are presented in *Figure 41* in terms of average costs and QALYs, showing the overlap of the results for the different strategies on the scatterplot.

Figure 42 shows the variation in the probability of being cost-effective for the different treatment strategies as the WTP threshold increases from £0 to £50,000 per QALY gained. At a WTP threshold of £20,000 per QALY gained, the probability of OPT alone, ICD + OPT, CRT-D + OPT and CRT-P + OPT being cost-effective is 57%, 37%, 3% and 3% respectively. Above a WTP of £42,000 per QALY gained, the intervention with the highest probability of being cost effective is CRT-D + OPT (31%). At a WTP threshold of £30,000 per QALY gained, OPT alone, ICD + OPT, CRT-D + OPT and CRT-P + OPT have a probability of being cost-effective of 44%, 31%, 15% and 10% respectively.

TABLE 151 Base-case summary of the probabilistic cost-effectiveness results: population 3

Strategy	Cost (£)	QALYs	ICER (£/QALY gained) vs. next best option[a] (IQR)	ICER (£/QALY gained) vs. ICD + OPT (IQR)
ICD + OPT	44,310	5.58	–	–
OPT	38,732	5.63	13,053 (–515,869 to 471,462)	–
CRT-P + OPT	51,286	5.94	Extendedly dominated	Extendedly dominated
CRT-D + OPT	51,690	5.98	34,988 (–191,681 to 264,108)	23,133 (–196,334 to 222,149)

a Treatments compared with the preceding best option, that is, the preceding treatment that is neither dominated nor extendedly dominated.

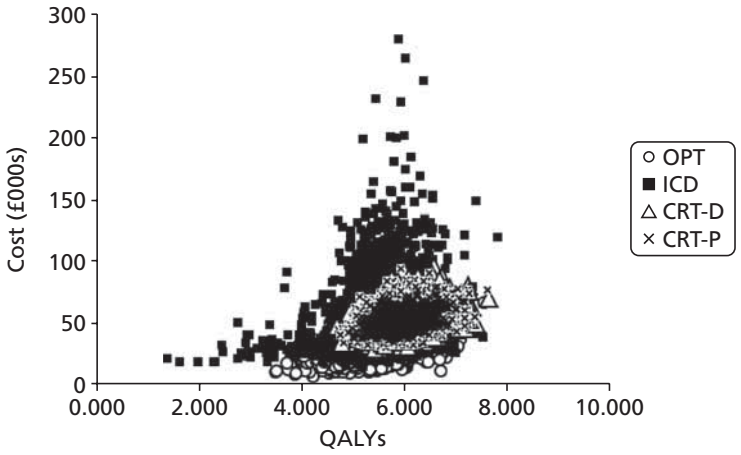

FIGURE 41 Cost-effectiveness scatterplot: population 3.

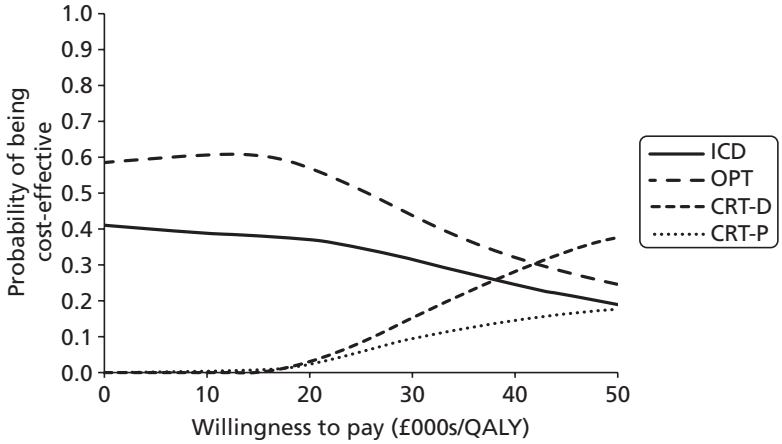

FIGURE 42 Cost-effectiveness acceptability curve: population 3.

Summary of the independent economic evaluation

Population 1

- The addition of ICD to OPT for the 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 per QALY gained) as it increased with age and 52% of these patients are expected to be aged > 65 years.
- Subgroup analysis using MADIT II trial data shows that ICD + OPT is cost-effective (ICER of £14,231 per QALY gained) for the primary prevention of SCD in patients with remote MI.
- For the SCD-HeFT trial data (patients with mild to moderate HF), 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 that have the greatest 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 HF) resulted in an ICER of £27,584 per QALY gained compared with initial management with OPT alone (allowing for subsequent implants). Similarly, initial implantation of a CRT-D device alongside OPT resulted in 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, initial management with OPT alone followed by implantation of the clinically necessary devices is the strategy with the highest probability of being cost-effective (81%). Above a WTP of £28,000 per QALY, the strategy with the 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 for patient survival, such as the RRs of SCD and HF death for patients managed with CRT-P. The lifetime of the CRT-D device was also particularly influential because of the incremental costs incurred when it became shorter.
- In a scenario assuming the upper limit estimates of device-related costs or the lower limit 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

- In the base case the most cost-effective strategy for people with both conditions at a WTP of £20,000–30,000 per QALY is initial management with OPT alone (followed by device implantation and subsequent upgrades as necessary). Both strategies including initial implantation of a CRT device have ICERs that are greater than the WTP range of £20,000–30,000 per QALY gained compared with OPT alone (CRT-D £35,193 per QALY gained; CRT-P £41,414 per QALY gained). 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 per QALY (ICER of £27,195 per QALY gained).
- At a WTP of £30,000 per QALY, OPT alone, ICD + OPT, CRT-D + OPT and CRT-P + OPT have a probability of being cost-effective of 44%, 31%, 15% and 10% respectively. Above a WTP of £42,000 per QALY, the intervention with the highest probability of being cost effective is CRT-D + OPT (31%).
- In an alternative scenario analysis using MADIT-CRT trial data, CRT-P and CRT-D are dominated by ICD + OPT, which is the most cost-effective strategy (ICER of £154 per QALY gained vs. OPT).
- Overall, the relative cost-effectiveness of the strategies compared for population 3 was most sensitive to costs and the lifetime of the CRT-D device. The risk of all-cause mortality for OPT relative to CRT-D was the most influential parameter for the comparison between CRT-D + OPT and OPT alone (followed by the subsequent updates). Similarly, the preventative effect on all-cause mortality estimated for ICD therapy was particularly important for the comparison between CRT-D + OPT and ICD + OPT.
  The preventative effect of the devices on hospitalisation for arrhythmia, as well as the longevity of the CRT-D device, were particularly prominent for the comparison between CRT-D + OPT and CRT-P + OPT.
  The most influential parameters for the comparison between OPT alone (and subsequent device implantations) and ICD + OPT were the lifetime of the CRT-D and ICD devices and the risk of hospitalisation for arrhythmia associated with CRT-D, ICD and OPT.

Chapter 6 Assessment of factors relevant to the NHS and other parties

Factors relevant to service provision

The possible extension of indications for ICD and CRT devices is likely to lead to an increase in the demand for their use. This will have the potential to impact on the organisation and provision of the service and the cost of the service to the NHS. The implications are likely to be greater given the recognition that current rates of implantation of the devices remain below national targets in the UK (see *Table 3*), there are regional variations in utilisation[55] and there is a growing ageing population that is likely to place additional pressure on the service. Any development will need to take account of the reasons for the low implantation rates as well as increasing provision for any extension of the indications. Factors thought to underlie the low implantation rates include a shortage of implantation centres and electrophysiologists, poorly developed referral strategies/care pathways and problems with specialist health-care investment.[60] Further expansion to accommodate any additional development in the service would necessitate an increase in appropriately trained cardiologists, associated clinical staff and technicians, and properly equipped implantation centres. Access to service provision and location of services are issues for consideration.

Factors relevant to patients and carers

The sudden death of a wage earner results in costs to his or her 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 HF on the lives of individuals and their families.

Chapter 7 Discussion

Statement of principal findings

Clinical effectiveness

People at risk of sudden cardiac death: implantable cardiac defibrillators compared with optimum pharmacological therapy

Thirteen RCTs were included that compared ICDs with medical therapy, four RCTs in people at increased risk of SCD because of previous ventricular arrhythmias (secondary prevention) and nine RCTs in people who have not suffered a life-threatening arrhythmia but who are at risk (primary prevention). Risk of bias was noted in the RCTs, specifically performance bias because of lack of blinding, detection bias with regard to QoL outcomes and possible selection bias because of 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 size 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 CHF, with 50–80% of those in the secondary prevention RCTs in NYHA classes I and II and 50–66% in the primary prevention RCTs in NYHA class II or II/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 that they used to identify people at risk of SCD.

Ventricular arrhythmia/cardiac arrest (secondary prevention)

Four RCTs compared ICDs with AAD. Meta-analysis found that ICDs significantly reduced the risk of all-cause mortality (four RCTs; RR 0.75, 95% CI 0.61 to 0.93; $p = 0.01$), SCD (four RCTs; RR 0.49, 95% CI 0.34 to 0.69; $p < 0.001$) and total cardiac deaths (two RCTs; RR 0.74, 95% CI 0.61 to 0.91; $p = 0.004$). No significant differences were found between ICDs and AAD for non-arrhythmic cardiac deaths (two RCTs; RR 0.97, 95% CI 0.72 to 1.31; $p = 0.83$) or other non-cardiac causes of death (two RCTs; RR 0.79, 95% CI 0.45 to 1.37; $p = 0.40$). Two RCTs reported significant benefits for ICDs compared with AAD for overall survival at 3 years (difference 11%; $p < 0.02$), survival free of cardiac death at 2 years (difference 4%; $p = 0.004$), survival from arrhythmic death at 2 years (difference 5%, $p = 0.0002$) and survival free of sudden death at 57 months (HR 0.423; $p = 0.005$). In terms of QoL, one RCT found significant improvements in the SF-36 PCS and MCS and patient concerns checklist for both groups up to the 1-year follow-up, with no significant between-group differences. Using the MHI and NHP, another RCT showed benefits for ICDs but not OPT at 1 year of follow-up. Both RCTs showed a worsening QoL with increasing numbers of shocks. Prespecified 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.[62] The population in this trial, 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.[62]

People with a recent myocardial infarction (within 6–41 days or ≤ 31 days)

Two RCTs compared ICD + OPT with OPT. Meta-analysis of two trials found no difference between the groups for 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; $p = 0.8$) and non-cardiac deaths (RR 1.39, 95% CI 0.86 to 2.27; $p = 0.18$). People with an ICD + OPT 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; $p = 0.0002$) than people receiving OPT alone. One trial reporting cumulative mortality found no statistically significant difference between groups. QoL was not reported. One trial reported no significant differences for 13 prespecified

subgroups
(age, sex, CHF 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.[62]

People with remote myocardial infarction (> 3 weeks or > 1 month previously)

Meta-analysis of the two trials in this group 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 SCDs (RR 0.36, 95% CI 0.23 to 0.55; $p < 0.00001$) with ICD + OPT compared with OPT. There was no difference between the groups in non-arrhythmic cardiac deaths (RR 0.95, 95% CI 0.41 to 2.18; $p = 0.1$) or non-cardiac deaths (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 receiving an ICD (11.3 vs. 9.4; $p = 0.09$), with higher HF hospitalisations (19.9% vs. 14.9%; *p*-value not reported). One trial assessed QoL using the HUI3, finding a worsening QoL for both the ICD + OPT group and the OPT group annually over 3 years, with no statistically significant differences. One trial reported prespecified subgroup analyses for all-cause mortality. The HRs in all 12 of the subgroups (age, sex, ejection fraction, NYHA class or QRS interval, hypertension, diabetes, LBBB, 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[62] and no additional RCTs in this population were identified in the present review.

People with non-ischaemic or idiopathic dilated cardiomyopathy

Three RCTs compared ICD + OPT with OPT or ICD + OPT with amiodarone + OPT. Meta-analysis found no significant difference between the groups 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 deaths (RR 1.13, 95% CI 0.42 to 3.03; $p = 0.81$) or non-cardiac deaths (RR 0.65, 95% CI 0.13 to 3.29; $p = 0.60$). However, a statistically significant reduction was found in SCDs (RR 0.26, 95% CI 0.09 to 0.77; $p = 0.02$) with ICD therapy. No statistically significant differences were found for measures of survival or QoL using the QWBS, STAI, SF-12 MCS or PCS and MLWHFQ. One trial reported six prespecified subgroup analyses for all-cause mortality (age, sex, LVEF, QRS interval, NHYA class and history of atrial fibrillation). None of the differences between subgroups was statistically significant

An additional meta-analysis was undertaken on the advice of clinical experts, combining data on all-cause mortality from the non-ischaemic CHF subgroup of the SCD-HeFT trial with data from the three cardiomyopathy trials. The SCD-HeFT non-ischaemic subgroup strongly influenced the analysis and a statistically significant effect in favour of ICDs 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 (CAT) was included in the previous TAR;[62] the other two RCTs (AMIOVIRT, DEFINITE) were excluded from the previous TAR[62] on the basis of the populations included in the trials. There were no SCDs 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 SCDs with ICDs in people with non-ischaemic cardiomyopathy and moderate to severe left ventricular dysfunction.

People scheduled for coronary artery bypass graft surgery

No significant difference between groups 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 deaths (RR 1.26, 95% CI 0.87 to 1.82; $p = 0.21$), non-cardiac deaths (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

SCD were lower in the ICD group 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 receiving 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. HRs for ICDs compared with the control for all-cause mortality were found to be similar among 10 prespecified subgroups (age, sex, HF, NYHA class, LVEF, diabetes mellitus, QRS complex duration, use of ACE inhibitors, use of class I or class III AADs and use of beta-adrenergic-blocking drugs).

This trial was included in the previous TAR[62] and no additional RCTs in this population were identified in the present review.

People with mild to moderate heart failure

All-cause mortality was significantly lower in the ICD + OPT group than in the placebo + OPT group (HR 0.77, 97.5% CI 0.62 to 0.96; $p = 0.007$) in one trial. A significant reduction in total cardiac deaths (HR 0.76, 95% CI 0.60 to 0.95; $p < 0.018$) and SCDs (compared with the placebo and amiodarone groups combined; RR 0.44, 95% CI 0.31 to 0.61; $p < 0.00001$) was also found for ICDs. There was no statistically significant difference in non-arrhythmic cardiac deaths (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; $p = 0.60$) between the ICD + OPT group and the placebo and amiodarone groups combined. QoL was assessed using the DASI, MHI and global health status measures, with either a limited difference or no long-term difference between the interventions. ICD shock resulted in a significant decrease in QoL. Prespecified subgroup analyses found no interaction between ICD therapy ($p = 0.68$) and the cause of CHF (ischaemic or non-ischaemic) for all-cause mortality, cardiac deaths, sudden deaths presumed to be ventricular tachyarrhythmic, HF deaths or non-cardiac deaths. There was a statistically significant interaction between ICD therapy and NYHA class, with ICDs reducing the risk of all-cause mortality, cardiac mortality and sudden death presumed to be ventricular tachyarrhythmic in people in NYHA class II but not in those in NYHA class III. The interaction between ICD therapy and NYHA class was not statistically significant for HF or non-cardiac deaths.

This trial was in progress at the time of the previous TAR.[62]

All four RCTs of people with previous ventricular arrhythmias reported adverse events, showing higher rates for the ICD groups (up to 30%), with most related to the placement and operation of the device. The nine primary prevention RCTs reported adverse event rates of between 5% and 61% for 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% and 55% in the three RCTs reporting this. Lead-, electrode- or defibrillator generator-related problems affected 1.8–14% of people in five trials.

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony: CRT-P or CRT-D compared with each other or with optimum pharmacological therapy

Four RCTs were included that compared CRT-P with OPT in people with HF as a result of LVSD and cardiac dyssynchrony. One of these RCTs included a third arm (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 because of inadequate reporting. Length of follow-up in the four RCTs varied: 3 months, 6 months, a median of 11.9–15.7 months and a mean of 37.4 months including an extension period, respectively. 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 $\leq 35\%$ in the trials, with an average baseline LVEF of 22–25% where this was reported. QRS interval was required to be ≥ 120 milliseconds (two trials), ≥ 130 milliseconds or > 150 milliseconds. The average baseline QRS interval was between 160 milliseconds and 175 milliseconds. Where reported, the proportion of participants with ischaemic heart disease varied from around 40% to around 60%.

CRT-P compared with optimum pharmacological therapy

Meta-analysis found that CRT-P reduced the risk of all-cause mortality (RR 0.75, 95% CI 0.58 to 0.96, $p = 0.02$), HF deaths (RR 0.67, 95% CI 0.51 to 0.88, $p = 0.004$) and HF 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 SCDs (RR 0.97, 95% CI 0.44 to 2.14, $p = 0.94$). One RCT 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 receiving CRT-P had an improvement of one or more NYHA class (RR 1.68, 95% CI 1.52 to 1.86, $p < 0.00001$). One RCT reported change in LVEF and reported a statistically significant improvement with CRT-P compared with OPT (4.6% vs. –0.2%, $p < 0.001$) at 6 months. There was a greater improvement in exercise capacity with CRT-P, as measured by the distance walked in 6 minutes (meta-analysis of three trials; change from baseline or final values: MD 38.14 m, 95% CI 21.74 to 54.54 m, $p < 0.00001$). A statistically significant improvement in VO_2max was also reported by two of these RCTs. All four RCTs found statistically significant improvements in QoL (using the MLWHFQ) with CRT-P (change from baseline or final values: MD –10.33, 95% CI –13.31 to –7.36). One trial also reported a statistically significant improvement in EQ-5D score and increased QALYs with CRT-P.

One trial reported prespecified subgroup analysis. A significant interaction between CRT-P and aetiology was found, with people with non-ischaemic heart disease having 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 predefined subgroups (age, sex, NHYA class, dilated cardiomyopathy, systolic blood pressure, N-terminal pro-B-type natriuretic peptide, 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 compared with optimum pharmacological therapy

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; $p = 0.02$), SCDs (HR 0.44, 95% CI 0.23 to 0.86; $p = 0.02$) and HF hospitalisations (RR 0.77, 95% CI 0.63 to 0.93; $p = 0.008$) were reduced with CRT-D compared with OPT. There was no significant difference in HF 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%; $p = 0.717$) between the CRT-D group and the OPT group. The proportion of people with an improvement of one or more NYHA class (57% vs. 38%; $p < 0.001$) and the improvements in exercise capacity [change in 6-minute walk distance: 46 m (SD 98 m) vs. 1 m (SD 93 m); $p < 0.001$] and QoL score (using the MLWHFQ) [–26 (SD 28) vs. –12 (SD 23); $p < 0.001$] were statistically significantly greater with CRT-D than with OPT.

CRT-P compared with 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 between CRT-P and 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 SCDs (RR 2.72, 95% CI 1.58 to 4.68; $p = 0.0003$) were higher with CRT-P than with CRT-D. All-cause mortality (RR 1.20, 95% CI 0.96 to 1.52; $p = 0.12$), HF deaths (RR 0.98, 95% CI 0.68 to 1.42; $p = 0.93$) and HF hospitalisations (28% vs. 29%) were similar between the CRT-P group and the CRT-D group. 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 a rate of device-related deaths of between 0.2% and 0.8% for those receiving CRT-P and 0.5% for those receiving CRT-D. The rate of moderate or severe adverse events related to the implantation procedure was reported by one trial as 10% for those receiving CRT-P and 8% for those receiving CRT-D, with 13% and 9% of CRT-P and CRT-D implantations being unsuccessful respectively. Moderate or severe

adverse events from any cause were more common among those receiving CRT-D than among those receiving 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 TAR[64] 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 on people with both conditions. Despite this difference, the results from the present review concur with those of the previous review.[64]

People with both conditions: CRT-D compared with optimum pharmacological therapy, CRT-P or implantable cardiac defibrillator

Nine RCTs were included that compared CRT-D with ICD in people at risk of SCD as a result of ventricular arrhythmias and with HF 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 because of inadequate reporting. Length of follow-up was 6 months in five trials, 1 year in two trials and an average of 2.4 years and 3.3 years in the remaining two trials. Sample size ranged from 31 to 1820 participants. The trials differed in their eligibility criteria for HF: the majority of participants were in NYHA class II in three trials, in NYHA class III in four trials, described as having mild to moderate HF in one trial (NYHA class not reported) and in NYHA class IV in one trial. The eligibility cut-off for LVEF was $\leq 35\%$ in seven trials and $\leq 30\%$ in two trials, with a mean LVEF at baseline of between 21% and 26%. One trial (RethinQ) differed from the others in the criteria used to define cardiac dyssynchrony, recruiting people with a narrow QRS interval (< 130 milliseconds) and evidence of mechanical dyssynchrony on ECG. Of the other trials, the QRS interval was ≥ 120 milliseconds (four trials), ≥ 130 milliseconds (three trials) or ≥ 150 milliseconds (one trial). The mean QRS interval at baseline was 107 milliseconds in one trial (RethinQ) and between 156 milliseconds and 169 milliseconds in the remaining trials where reported. The proportion of participants with ischaemic heart disease varied from just over 50% to 100%.

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 HF hospitalisations (RR 0.75, 95% CI 0.64 to 0.88; $p = 0.0005$) compared with ICD therapy. Fewer trials reported HF deaths or SCDs separately, and no HF deaths or SCDs occurred in some of these trials. Combining three RCTs in a meta-analysis found little difference in SCDs between the CRT-D group and the ICD group (RR 1.45, 95% CI 0.43 to 4.92; $p = 0.55$).

Meta-analysis of four trials found no statistically significant difference between groups in the proportion of people experiencing at least one episode of VT or VF (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 who 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 ml; $p < 0.0.002$) and left ventricular end-systolic volume (MD –20.9 ml, 95% CI –32.9 to –8.8 ml; $p < 0.0007$) was found with CRT-D. There was no overall difference in end-diastolic diameter (MD –0.29 mm, 95% CI –1.67 to 1.08 mm; $p = 0.67$) or end-systolic diameter (MD –1.88 mm, 95% CI –4.39 to 0.62 mm; $p = 0.14$). 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 HF found a significantly greater reduction in QRS interval with CRT-D than with ICD (–20 milliseconds vs. 0 milliseconds; $p < 0.001$). The QRS interval was similar in the CRT-D and ICD groups in two trials of people with mild or mild to moderate HF.

There was a greater improvement in exercise capacity (change in peak VO_2: MD 0.75 ml/kg/minute, 95% CI 0.23 to 1.27 ml/kg/minute; $p = 0.005$; change in 6-minute walk distance: MD 14.5 m, 95% CI 2.9 to 26.1 m; $p = 0.01$) and QoL (change in MLWHFQ score: MD –6.9, 95% CI –10.4 to –3.4; $p = 0.0001$) with CRT-D than with ICD. One small trial of people with mild to moderate HF reporting other measures of QoL (DASI, one-item Global Visual Analogue Scale and SF-36) found that the comparisons of baseline to 6-month changes were statistically significantly different for the general health component of the SF-36 only.

When the large RAFT trial contributed data to the meta-analyses, the results were strongly influenced by it. The RAFT trial included people with mild to moderate HF despite receiving OPT, a LVEF of ≤ 30% from ischaemic or non-ischaemic causes, a wide QRS interval and planned ICD implantation for indicated primary or secondary prevention of SCD.

The 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 the device received. The large RAFT trial reported adverse events for all implanted participants and found that the rate of device- or implantation-related complications within 30 days of implantation was significantly higher in the CRT-D group than in the ICD group (13.3% vs. 6.8%; $p < 0.001$), as was the rate of device-related hospitalisations (20% vs. 12.2%, HR 1.68, 95% CI 1.32 to 2.13; $p < 0.001$).

Three trials reported prespecified subgroup analyses. Two trials reported that CRT-D was associated with a greater benefit in people with a QRS duration of ≥ 150 milliseconds than in those with a QRS duration of < 150 milliseconds; the third trial found a significant increase in the proportion of people with an improvement in peak oxygen uptake among those with a QRS duration of ≥ 120 milliseconds but not among those with a QRS duration of < 120 milliseconds. CRT-D was associated with a greater benefit in women than in men (one trial) and with a greater benefit in people with LBBB than in those with non-specific intraventricular conduction delay (one trial). One trial found a statistically significant improvement with CRT-D in distance walked in 6 minutes for those with non-ischaemic cardiomyopathy (55.0 m vs. 2.5 m; $p = 0.01$) but not for those with ischaemic cardiomyopathy (4.2 m vs. 5.8 m; $p = 0.57$). Other evaluated subgroups showed no statistically significant effects.

This evidence (apart from the CONTAK-CD trial) has not been previously evaluated in a TAR.[62,64]

Summary of the industry-submitted individual patient data network meta-analysis

The MS reported an IPD NMA that assessed the effectiveness of ICDs, CRT-P and CRT-D compared with OPT for people with HF. As people with HF vary considerably, the NMA aimed to identify subgroups who may benefit from the different interventions. The NMA assessed the outcomes of all-cause mortality, all-cause hospitalisation 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 patients in the network) from the network for which IPD were available. The network excluded seven RCTs identified in this 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 clinical 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 subgroups to be identified. When possible, the MS assessed the validity of the results against other evidence, making adjustments when considered necessary because of counterintuitive results or a lack of data.

The results of the NMA showed that there was a benefit for people receiving a device compared with OPT for the three outcomes; however, the extent of the benefit and the subgroups most affected remained uncertain. Fixed-effects NMA without the covariables for all-cause mortality estimated HRs that showed a statistically significant benefit for all devices compared with OPT (commercial-in-confidence information has been removed). HRs showed a statistically significant benefit for CRT-D compared with CRT-P (commercial-in-confidence information has been removed) and ICD (commercial-in-confidence information has been removed). NMA models including covariables (treatment modifiers) reported findings that were more equivocal and the MS states that they should be interpreted with caution. Although HRs showed that all devices appeared to have a beneficial effect compared with OPT, rarely were the differences statistically significant. CRT-D appeared to have a statistically significant effect for people with QRS duration of ≥ 150 milliseconds. It also had an effect for people with a QRS duration from ≥ 120 milliseconds to < 150 milliseconds, 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 duration from ≥ 120 milliseconds to < 150 milliseconds and without LBBB. CRT-P provided a statistically significant effect for women with a QRS duration of ≥ 150 milliseconds and LBBB. Similar benefits from all devices when compared with OPT were shown for all-cause hospitalisations, although limited data meant that some comparisons were not possible. All-cause hospitalisations were reduced in people in NYHA classes I–III receiving an ICD (commercial-in-confidence information has been removed), in NYHA classes III and IV with CRT-P (commercial-in-confidence information has been removed) and in all NYHA groups with CRT-D (commercial-in-confidence information has been removed). Results for HRQoL were less clear because of 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 produced counterintuitive results. As a consequence, the MS adjusted values to show that ICDs had benefit for people in NYHA class I/II and that CRT-P and CRT-D had the same effect for people in NYHA classes III and IV. Given that most utility values were changed and that limited comparisons can be made with other evidence, these data 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 HF. Unfortunately, limitations in the data available and lack of detail concerning the methods used render the findings uncertain. It is clear that all of the devices are beneficial compared with 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 subgroups remain unclear. When some benefits are shown, the warnings in the MS concerning the analysis cause some concern. In addition, the subgroups identified in the NMA differ from those outlined in the scope for the appraisal, making translation of the results between them difficult.

Cost-effectiveness

Summary of previously published economic evaluations

The systematic review of the cost-effectiveness of ICDs for the treatment of arrhythmia and of CRT for treatment of HF 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 of the studies reported that ICDs were cost-effective, with the remaining studies finding that ICDs were cost effective only in high-risk groups or were not-cost effective or that it was uncertain whether they were cost-effective. One high-quality study was conducted for a UK setting and

perspective and reported a mean ICER for ICDs compared with AADs 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 are now out of date. Almost all studies reported that CRT was cost-effective, with only two studies uncertain whether it 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.

Summary of the systematic review of quality-of-life studies

The systematic review found six relevant HRQoL studies that measured EQ-5D in HF, stratified by NYHA class, or that 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 the EQ-5D scores of primary and secondary prevention patients and that QoL for ICD patients was similar to that of the general population. Four cohort studies reported EQ-5D scores in HF, with baseline scores ranging from 0.44 to 0.66 depending on NYHA classification. Overall, the results show decreased EQ-5D scores in HF compared with those of the general population, particularly in NYHA classes III and IV.

Summary of the 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 HF 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 the probabilistic sensitivity analysis is not described in sufficient detail to determine whether or not joint parameter uncertainty was properly assessed. The cost-effectiveness results presented in the submission (according to subgroups specified by ABHI) do not directly address questions posed in NICE's scope,[61] as it is unclear how the subgroups selected relate to the groups scoped by NICE. Overall, the results show that for most subgroups there is at least one device with an ICER of < £30,000 per QALY gained, and in some cases a different device might have an ICER of < £20,000 per QALY gained.

Summary of the independent economic model

We developed an independent state transition model based on that created by Fox and colleagues[64] for 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 SCD as a result of ventricular arrhythmias and/or HF as a result of LVSD and cardiac dyssynchrony.

People at risk of sudden cardiac death

The current economic model indicates that the initial management of patients at increased risk of SCD with an ICD alongside OPT is a cost-effective strategy compared with initial treatment with OPT alone (ICER £19,479 per QALY). The use of ICDs for the secondary prevention of SCD had a 51% and 82% probability of being cost-effective at a WTP of £20,000 and £30,000 per QALY gained respectively. ICDs were also estimated as being cost-effective (within the WTP range of £20,000–30,000 per QALY gained) for the primary prevention subgroups analysed (people with remote MI, a broad population with mild to moderate HF, 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 left ventricular systolic dysfunction and cardiac dyssynchrony

For patients with HF as a result of LVSD and cardiac dyssynchrony, the base-case analysis found that the addition of either CRT-P or CRT-D to OPT (in the initial stage of management of HF) may be considered

cost-effective at a WTP of £30,000 compared with OPT alone (allowing for subsequent device implantation), with ICERs of £27,584 per QALY and £27,899 per QALY respectively. The use of CRT-D + OPT compared with CRT-P + OPT was also likely to be cost-effective (ICER £28,420 per QALY). At a WTP of £20,000 per QALY, initial management with OPT alone (followed by the clinically necessary device implants) was the strategy with the highest probability of being cost-effective (81%). Above a WTP of £28,000 per QALY, the strategy with the 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, whereas OPT alone had a 23% probability of being cost-effective.

The parameters with the most influence on the model results for the comparison between CRT-P and OPT were the risk of hospitalisation for a serious arrhythmic event for patients receiving CRT-P, the risk of HF death for both patients receiving CRT-P and patients receiving CRT-D and the risk of SCD for patients receiving CRT-P. The results of the comparison between CRT-D and OPT were most influenced by the risks of HF death and SCD death in CRT-D patients and the lifetime of the device. The results of the comparison between CRT-D and CRT-P were the most sensitive to the variation of individual parameters, with eight parameters causing the ICER to range by > £10,000, the most influential being the risk of HF death for CRT-D patients and the risk of SCD for both CRT-D and CRT-P patients.

People with both conditions

The base-case analysis found that the most cost-effective strategy for people with both conditions at a WTP of £20,000–30,000 per QALY was initial management with OPT alone (followed by device implantation and subsequent upgrades as necessary), with an ICER of £2824 per 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 < £30,000 when compared with ICD + OPT (ICER £27,195 per QALY) but not when compared with initial management with OPT alone (ICER £35,193 per 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 a WTP of £42,000 per QALY, the intervention with the 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 dominated by ICD + OPT compared with OPT alone. Therefore, the results obtained with the MADIT-CRT data indicate that ICD + OPT is the most cost-effective strategy, with an ICER of £154 per QALY gained compared with OPT alone. The cost-effectiveness results for the comparison between CRT-D + OPT and 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 for ICD patients and the lifetime of the CRT-D and ICD devices.

Exploration of differences in results between population 2 and population 3

In response to comments querying the face validity of the results for population 3 compared with population 2, the differences were explored.

The baseline mortality risk for population 2 was higher than that for population 3, although the RR improvement with CRT-P compared with OPT was similar in the two populations. In the original analyses there was a greater benefit in terms of survival for population 2 than for population 3 because of the high numbers of crossovers to CRT-D in the OPT group in population 3. A new scenario for population 3 was conducted using a higher baseline risk, similar to the risk of all-cause mortality for population 2. All-cause mortality for population 3 was 50% higher (all-cause mortality yearly probability: OPT 0.105, CRT-D 0.065), giving a similar ICER to the baseline ICER (£34,964 vs. £35,193).

The approach to modelling changes in QoL also differed between population 2 and population 3. The population 2 model assumed a given initial distribution of patients by NYHA class (initially more severe than that in the population 3 model). At 9 and 18 months, different distributions by NYHA class (derived

from the CARE-HF and Brescia studies) were assumed to capture the effect of CRT on patients HRQoL. In the population 3 model, the HRQoL of patients was kept constant over time, assuming an initial distribution of patients per NYHA class as reported for the RAFT trial at baseline. The effect of these differences is that there is more QoL benefit in population 2 than in population 3 for patients receiving CRT-D. It is likely that these differences in HF progression explain some of the differences between the results for populations 2 and 3. A scenario analysis was undertaken assuming that population 3 has the same HF progression as population 2. This resulted in an ICER of £27,396 per QALY gained for CRT-D compared with OPT, similar to that in the population 2 model (£27,899 per QALY).

Strengths and limitations of the assessment

Strengths

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 that 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 within one assessment report the most up-to-date evidence for the clinical effectiveness and cost-effectiveness of ICDs, CRT-P and CRT-D for people at risk of SCD as a result of ventricular arrhythmias and/or HF as a result of LVSD and cardiac dyssynchrony. 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.

Limitations

In contrast, this assessment also has certain limitations.

Limitations of the included trials

- Randomised patients with successful implantation may overestimate the benefits and underestimate adverse effects.
- Trials have not been conducted in the UK and may not be generalisable.
- The time horizon of the included trials may be inadequate.
- Blinding of participants and health-care 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 pharmacological therapy used in some of the included trials would not be considered optimal by current standards.

Limitations of the systematic review of clinical effectiveness

- Three populations were defined by the NICE scope;[61] however, there are no accepted a priori criteria that could be used to categorise trials. Clinical experts were consulted to allocate trials to the population groups and pragmatic decisions were taken to allocate trials and ensure that all relevant RCT evidence comparing eligible interventions and comparators was included.
- A decision was made to also include trials in which medical therapy would not be considered optimal by current standards. Pharmacological therapy varied between the trials and was described in detail.

- The MUSTT and MAVERIC trials were excluded from the systematic review as the intervention did not meet the scope of the review (many participants in the intervention arm did not receive an ICD); however, these trials presented subgroup data for the comparison between ICD therapy and no ICD therapy. These trials were not subjected to 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 CIs rather than mean values. Median values are similar to mean values when the distribution of data is symmetrical and so can be used directly in the meta-analyses.[65] However, means and medians can be very different from 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 included only subgroup analyses specified a priori by the trials. However, subgroup analysis lacks statistical power and may be misleading, for example because of 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[61] and followed recommended guidance provided in the NICE *Guide to the Methods of Technology Appraisal*.[67] It was based on an adaptation of a model structure used in the previous appraisal of CRT for HF (TA120[43]), developed by Fox and colleagues,[64] providing a consistent approach and comparability. Despite following recognised guidance on developing economic models,[67,68] the evaluation has some limitations:

- As the independent model was based on an adaptation of a model developed by Fox and colleagues,[64] it relies on some of the same assumptions made with regard to 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 event for a patient on CRT-P or an unsuccessful CRT-P implantation). As these were validated by Fox and colleagues by clinical advice and considered during previous appraisals, it was felt that they were of limited concern.
- Additional structural assumptions were made with regard to the risks and timing of the reimplantation of devices, alternative options for those patients with unsuccessful implantation, and perioperative complications, surgical failure, heart transplantation and death. As with the assumptions in the model by Fox and colleagues,[64] 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. 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 any possible effects, base-case and subgroup analyses were carried out to try and encompass the different patients included. Also, follow-up varied (range 18–45.5 months) in the different studies used, affecting the extent to which survival curves had to be extrapolated.
- Parameter values for the clinical effectiveness of the interventions were sourced, where possible, from the systematic review undertaken for this assessment. Unfortunately, limitations in the evidence base meant that some parameters either were 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). When 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 HF 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

between CRT-P and CRT-D meant that evidence had to be used from studies on the clinical effectiveness of CRT-P and CRT-D in patients with HF 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.[64] Device-related utility values were assessed through their effect on changes in the distribution of patients by NYHA class. Data were available only for patients receiving CRT-P or OPT alone for population 2 and so the effects of CRT-D were assumed to be the same as for CRT-P 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 for 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 the costs of the implantation of the devices, the costs of upgrades and routine replacements, the costs of operative complications and device-related complications and drug costs. Alternative data were sourced from Fox and colleagues,[64] the MS and clinical advice.
- The model structure allows patients initially managed with OPT or CRT-P to have a device upgraded to a different device according to disease progression. The result of this assumption is that there are a large number of upgrades in some population arms. This is most evident in population 3. These upgrades occur in patients who experience hospitalisation because of non-fatal arrhythmia (and then undergo ICD/CRT-D implantation) and are based on the previous modelling structure in the study by Fox and colleagues.[64]

When limitations have arisen in the evaluation, these have been identified in the report. Assumptions made or data identified from alternative sources have been checked through clinical advice, and the effects parameters thought to be influential on the results have been assessed through sensitivity analyses.

Comparison of the independent economic evaluation with other evaluations

For patients in the UK at increased risk of SCD, Buxton and colleagues[153] 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 are now out of date, these results may not be applicable to current UK practice and may not be 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 for the OPT and 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 the 0.75 assumed for both arms by Buxton and colleagues. Scenario analysis using the same average utility values as used by Buxton and colleagues[153] resulted in an ICER of £22,372 per QALY gained for ICD + OPT compared with initial management with OPT alone for the secondary prevention of SCD.

For patients with HF, Fox and colleagues[64] estimated ICERs of £16,735 per QALY gained for CRT-P compared with OPT, £22,231 per QALY gained for CRT-D compared with OPT and £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 compared with 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 compared with CRT-P at a similar cost, a smaller ICER (£24, 943 per QALY) is estimated for CRT-D compared with 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 per QALY) is estimated for CRT-D compared with OPT.

The differences in results between models can be explained by using updated costs, different estimates of the lifetime of the devices, a different set of utilities by NYHA class and structural differences between models (such as referring patients being managed with OPT alone for CRT-P implantation in case of hospitalisation for HF, instead of ICD, or for CRT-D following hospitalisation for arrhythmia). Using the same utility values as in the model of Fox and colleagues[64] 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 compared with OPT, £24,580 per QALY gained for CRT-D compared with OPT and £27,893 per QALY gained for CRT-D compared with CRT-P. The scenario using the same device lifetime estimates as in the study by Fox and colleagues[64] resulted in higher ICERs for CRT devices compared with OPT because of higher costs and slightly fewer QALYs estimated for both CRT-D + OPT and CRT-P + OPT.

The joint economic evaluation submitted by ABHI[151] concluded that for most subgroups there is at least one device with an ICER of < £30,000 per QALY gained and in some cases a different device might have an ICER of < £20,000 per QALY gained. The general approach taken in the MS seems reasonable as the model structure is consistent with the current understanding of HF and ventricular arrhythmia and the assumptions over costing are also consistent with current clinical practice. However, the cost-effectiveness results presented in the MS (according to subgroups specified by ABHI) do not directly address questions posed in NICE's scope,[61] as it is unclear how the subgroups selected relate to the groups scoped by NICE. The independent economic model was developed to address NICE's scope and was 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 MS.

Other recent systematic reviews/meta-analyses

Huang and colleagues[230] presented a meta-analysis comparing CRT-D with 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 included were not RCTs. Subgroup analysis comparing CRT-D with ICD therapy 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[230] found no significant difference in all-cause mortality between CRT-D and ICD therapy. Al-Majed and colleagues[231] assessed CRT in people with advanced HF and those with less symptomatic disease. The inclusion criteria for their systematic review differed from those in the present review (eligible comparators were inactive pacing, right or left ventricular pacing alone and ICD therapy); 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 HF hospitalisations in subgroups with NYHA class I/II and 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[232] compared CRT-D with ICD therapy or OPT and conducted subgroup analysis for NYHA class. All-cause mortality was reduced with CRT-D compared with ICD therapy or OPT. Compared with ICD therapy, CRT-D reduced all-cause mortality for people with NYHA class I or II but not class III or IV symptoms. The differences in effects for the NYHA class subgroups between these the two meta-analyses[231,232] are due to the different comparators and trials included. A meta-analysis by Bertoldi and colleagues[233] also found a significant reduction in all-cause mortality with CRT-P compared with OPT and with CRT-D compared with ICD therapy, despite including slightly different trials.

Uncertainties

- No new evidence comparing CRT-P and CRT-D devices was identified; therefore, the relative clinical effectiveness and cost-effectiveness of the devices in people with HF as a result of LVSD and cardiac dyssynchrony, with or without an established indication for an ICD, remains uncertain.
- No robust evidence was identified on the effect of CRT and ICD devices on HF progression in people with both conditions.
- No evidence was found on the RR of hospitalisation because of arrhythmia for CRT-P devices compared with CRT-D devices in people with both conditions; hence, CRT devices were assumed to have the same preventative effect on severe arrhythmia. New evidence would reduce the uncertainty associated with this parameter, to which the comparison between CRT-D + OPT and CRT-P + OPT showed particularly sensitivity.
- Utility data were not identified for patients with both conditions or for patients receiving CRT-D or an ICD. Also, no utility decrements were found for the effects of transplantation, surgery or infections.
- Routine cost data were not available for the implantation of devices, upgrades and routine device replacements or for operative complications.

Chapter 8 Conclusions

Implications for service provision

Implantable cardioverter defibrillators were found to reduce all-cause mortality in people who were at increased risk of SCD as a result of ventricular arrhythmias, in which increased risk was defined as previous ventricular arrhythmias/cardiac arrest, MI > 3 weeks previously, non-ischaemic cardiomyopathy (depending on the data included) or ischaemic or non-ischaemic CHF and a LVEF of ≤ 35%. No benefit from an 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 prespecified 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 at a WTP threshold of £20,000 in some cases.

Cardiac resynchronisation therapy – pacer and CRT-D both reduced the risk of mortality and HF hospitalisations in people with HF 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. The risk of SCD was lower with CRT-D than with CRT-P, but other outcomes, including all-cause mortality, were similar between the devices. Both CRT-P and CRT-D had ICERs of < £30,000 per QALY gained compared with OPT, as did the comparison between CRT-D and CRT-P.

Compared with ICD, CRT-D reduced the risk of all-cause mortality and HF 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 was < £30,000 per QALY for the comparison of CRT-D + OPT with ICD + OPT (unless no difference in all-cause mortality was assumed) but not for the comparison with initial management with OPT alone.

The conclusions should be considered in light of the limitations of this evaluation, such as the approach of allocating heterogeneous trials to three population groups and the uncertainties in the economic evaluation.

Suggested research priorities

One three-arm trial comparing CRT-D and CRT-P with OPT in people with HF as a result of LVSD and cardiac dyssynchrony was identified by the systematic review. The trial was not designed to directly compare CRT-D and CRT-P and no additional trials of this comparison were identified. Furthermore, the trial excluded people meeting the general indications for an ICD. A RCT comparing CRT-D and CRT-P in people with HF as a result of LVSD and cardiac dyssynchrony is required, for both those with and those without an ICD indication.

The evidence base for ICD therapy in cardiomyopathy is limited. A trial is needed into the benefits of ICDs for non-ischaemic cardiomyopathy in the absence of dyssynchrony.

Acknowledgements

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

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

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

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Jill L 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.

Diana Mendes (research fellow) 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.

Andrew J 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.

Petra Harris (research fellow) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence and drafted the report.

Keith Cooper (senior research fellow) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, developed the economic evaluation and drafted the report.

Joanna 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.

Jackie Bryant (principal research fellow) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence and drafted the report.

References

1. 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). Final Scope*. London: NICE; 2011.
2. Bonow RO, Mann DL, Zipes DP, Libby P. *Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine*. Philadelphia, PA: Elsevier Saunders; 2012.
3. Chugh S, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, *et al.* Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis* 2008;**51**:213–28. http://dx.doi.org/10.1016/j.pcad.2008.06.003
4. Office for National Statistics. *Deaths Registered in England and Wales in 2010 by Cause*. Statistical Bulletin. 28 October 2011. URL: www.ons.gov.uk/ons/dcp171778_239518.pdf (accessed 23 January 2014).
5. World Health Organization. *International Classification of Diseases, 10th Edition.* URL: www.who.int/classifications/icd/en/ (accessed April 2014).
6. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation* 2012;**125**:1043–52. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.023846
7. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, *et al.* ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006;**48**:e247–346. http://dx.doi.org/10.1016/j.jacc.2006.07.010
8. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. *Circulation* 1996;**93**:519–24. http://dx.doi.org/10.1161/01.CIR.93.3.519
9. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, *et al.* American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *Circulation* 2008;**118**:1497–518. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.189375
10. Lopshire JC, Zipes DP. Sudden cardiac death: better understanding of risks, mechanisms, and treatment. *Circulation* 2006;**114**:1134–6. http://dx.doi.org/10.1161/CIRCULATIONAHA.106.647933
11. Youngquist ST, Kaji AH, Niemann JT. Beta-blocker use and the changing epidemiology of out-of-hospital cardiac arrest rhythms. *Resuscitation* 2008;**76**:376–80. http://dx.doi.org/10.1016/j.resuscitation.2007.08.022
12. Polentini MS, Pirrallo RG, McGill W. The changing incidence of ventricular fibrillation in Milwaukee, Wisconsin (1992–2002). *Prehosp Emerg Care* 2006;**10**:52–60. http://dx.doi.org/10.1080/10903120500366961

13. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980–2000. *JAMA* 2002;**288**:3008–13. http://dx.doi.org/10.1001/jama.288.23.3008

14. Bunch TJ, White RD. Trends in treated ventricular fibrillation in out-of-hospital cardiac arrest: ischemic compared to non-ischemic heart disease. *Resuscitation* 2005;**67**:51–4. http://dx.doi.org/10.1016/j.resuscitation.2005.04.015

15. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation* 2010;**81**:1479–87. http://dx.doi.org/10.1016/j.resuscitation.2010.08.006

16. Bunch TJ, Kottke TE, Lopez-Jimenez F, Mahapatra S, Elesber AA, White RD. A comparative analysis of short- and long-term outcomes after ventricular fibrillation out-of-hospital cardiac arrest in patients with ischemic and nonischemic heart disease. *Am J Cardiol* 2006;**98**:857–60. http://dx.doi.org/10.1016/j.amjcard.2006.04.023

17. Dumas F, Rea TD. Long-term prognosis following resuscitation from out-of-hospital cardiac arrest: role of aetiology and presenting arrest rhythm. *Resuscitation* 2012;**83**:1001–5. http://dx.doi.org/10.1016/j.resuscitation.2012.01.029

18. Goldberger JJ, Buxton AE, Cain M, Costantini O, Exner DV, Knight BP, *et al.* Risk stratification for arrhythmic sudden cardiac death: identifying the roadblocks. *Circulation* 2011;**123**:2423–30. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.959734

19. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–46. http://dx.doi.org/10.1136/hrt.2003.025270

20. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, *et al.* Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;**20**:421–8. http://dx.doi.org/10.1053/euhj.1998.1280

21. Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR, *et al.* Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J* 2001;**22**:228–36. http://dx.doi.org/10.1053/euhj.2000.2289

22. Hobbs FD, Roalfe AK, Davis RC, Davies MK, Hare R. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). *Eur Heart J* 2007;**28**:1128–34. http://dx.doi.org/10.1093/eurheartj/ehm102

23. Taylor CJ, Roalfe AK, Iles R, Hobbs FD. Ten-year prognosis of heart failure in the community: follow-up data from the Echocardiographic Heart of England Screening (ECHOES) study. *Eur J Heart Fail* 2012;**14**:176–84. http://dx.doi.org/10.1093/eurjhf/hfr170

24. Madsen BK, Hansen JF, Stokholm KH, Brons J, Husum D, Mortensen LS. Chronic congestive heart failure. Description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. *Eur Heart J* 1994;**15**:303–10.

25. Bouvy ML, Heerdink ER, Leufkens HG, Hoes AW. Predicting mortality in patients with heart failure: a pragmatic approach. *Heart* 2003;**89**:605–9. http://dx.doi.org/10.1136/heart.89.6.605

26. Ahmed A, Aronow WS, Fleg JL. Predictors of mortality and hospitalization in women with heart failure in the Digitalis Investigation Group trial. *Am J Ther* 2006;**13**:325–31. http://dx.doi.org/10.1097/00045391-200607000-00009

27. Holland R, Rechel B, Stepien K, Harvey I, Brooksby I. Patients' self-assessed functional status in heart failure by New York Heart Association class: a prognostic predictor of hospitalizations, quality of life and death. *J Card Fail* 2010;**16**:150–6. http://dx.doi.org/10.1016/j.cardfail.2009.08.010

28. Miller-Davis C, Marden S, Leidy NK. The New York Heart Association classes and functional status: what are we really measuring? *Heart Lung* 2006;**35**:217–24. http://dx.doi.org/10.1016/j.hrtlng.2006.01.003

29. Scarborough P, Bhatnagar P, Wickramasinghe K, Smolina K, Mitchell C, Rayner M. Coronary heart disease statistics: heart failure supplement. London: British Heart Foundation; 2010. URL: www.bhf.org.uk/research/statistics.aspx (accessed 11 May 2012).

30. Boehmer JP. CRT only or CRT plus ICD? *Eur Heart J* 2004;**6**:D83–7. http://dx.doi.org/10.1016/j.ehjsup.2004.05.003

31. Schaer BA, Koller MT, Sticherling C, Altmann D, Joerg L, Osswald S. Longevity of implantable cardioverter-defibrillators, influencing factors, and comparison to industry-projected longevity. *Heart Rhythm* 2009;**6**:1737–43. http://dx.doi.org/10.1016/j.hrthm.2009.09.013

32. Horlbeck FW, Mellert F, Kreuz J, Nickenig G, Schwab JO. Real-world data on the lifespan of implantable cardioverter-defibrillators depending on manufacturers and the amount of ventricular pacing. *J Cardiovasc Electrophysiol* 2012;**23**:1336–42. http://dx.doi.org/10.1111/j.1540-8167.2012.02408.x

33. Hauser R, Hayes D, Parsonnet V, Furman S, Epstein A, Hayes J, *et al.* Feasibility and initial results of an internet-based pacemaker and ICD pulse generator and lead registry. *Pacing Clin Electrophysiol* 2001;**24**:82–7. http://dx.doi.org/10.1046/j.1460-9592.2001.00082.x

34. Olde NLR, Knops RE, Bardy GH, Blaauw Y, Boersma LV, Bos JS, *et al.* Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. *Am Heart J* 2012;**163**:753–60. http://dx.doi.org/10.1016/j.ahj.2012.02.012

35. Pedersen SS, Lambiase P, Boersma LV, Murgatroyd F, Johansen JB, Reeve H, *et al.* Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD: design and rationale of the EFFORTLESS S-ICD Registry. *Pacing Clin Electrophysiol* 2012;**35**:574–9. http://dx.doi.org/10.1111/j.1540-8159.2012.03337.x

36. Gras D, Bocker D, Lunati M, Wellens HJ, Calvert M, Freemantle N, *et al.* Implantation of cardiac resynchronization therapy systems in the CARE-HF trial: procedural success rate and safety. *Europace* 2007;**9**:516–22. http://dx.doi.org/10.1093/europace/eum080

37. Biffi M, Moschini C, Bertini M, Saporito D, Ziacchi M, Diemberger I, *et al.* Phrenic stimulation: a challenge for cardiac resynchronization therapy. *Circ Arrhythm Electrophysiol* 2009;**2**:402–10. http://dx.doi.org/10.1161/CIRCEP.108.836254

38. van Rees JB, de Bie MK, Thijssen J, Borleffs CJ, Schalij MJ, van Erven L. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. *J Am Coll Cardiol* 2011;**58**:995–1000. http://dx.doi.org/10.1016/j.jacc.2011.06.007

39. Dewland TA, Pellegrini CN, Wang Y, Marcus GM, Keung E, Varosy PD. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR Implantable Cardioverter-Defibrillator Registry. *J Am Coll Cardiol* 2011;**58**:1007–13. http://dx.doi.org/10.1016/j.jacc.2011.04.039

40. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, *et al.* 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States. *J Am Coll Cardiol* 2011;**58**:1001–6. http://dx.doi.org/10.1016/j.jacc.2011.04.033

41. Wilkoff BL, Auricchio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM, *et al.* HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations. *Europace* 2008;**10**:707–25. http://dx.doi.org/10.1093/europace/eun122

42. National Institute for Health and Clinical Excellence. *Implantable Cardioverter Defibrillators for Arrhythmias (TA95)*. London: NICE; 2006.

43. National Institute for Health and Clinical Excellence. *Cardiac Resynchronisation Therapy for the Treatment of Heart Failure (TA120)*. London: NICE; 2007.

44. National Institute for Health and Clinical Excellence. *Chronic Heart Failure: Management of Chronic Heart Failure in Adults in Primary and Secondary Care*. NICE clinical guidelines CG108, August 2010. URL: http://publications.nice.org.uk/chronic-heart-failure-cg108 (accessed 23 January 2014).

45. Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Guidelines for cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2007;**28**:2256–95. http://dx.doi.org/10.1093/eurheartj/ehm305

46. Stevenson WG, Hernandez AF, Carson PE, Fang JC, Katz SD, Spertus JA, *et al.* Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America guideline committee. *J Card Fail* 2012;**18**:94–106. http://dx.doi.org/10.1016/j.cardfail.2011.12.004

47. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NAM, *et al.* 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012;**60**:1297–313. http://dx.doi.org/10.1016/j.jacc.2012.07.009

48. Department of Health. *Coronary Heart Disease: National Service Framework for Coronary Heart Disease – Modern Standards and Service Models*. London: Department of Health; 2000.

49. Heart Rhythm UK. *Standards for Implantation and Follow-Up of Cardiac Rhythm Management Devices*. Heart Rhythm UK; 2011.

50. Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2009;**30**:1245–53. http://dx.doi.org/10.1093/eurheartj/ehp100

51. Lane RE, Cowie MR, Chow AWC. Prediction and prevention of sudden cardiac death in heart failure. *Heart* 2005;**91**:674–80. http://dx.doi.org/10.1136/hrt.2003.025254

52. National Institute for Health and Clinical Excellence. *NICE Pathway: Chronic Heart Failure*. London: NICE; 2010.

53. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012;**33**:1787–847. http://dx.doi.org/10.1093/eurheartj/ehs104

54. National Institute for Health and Clinical Excellence. *Short-Term Circulatory Support with Left Ventricular Assist Devices as a Bridge to Cardiac Transplantation or Recovery*. London: NICE; 2006.

55. Cunningham D, Charles R, Cunningham M, de Lange A. *Cardiac Rhythm Management: UK National Clinical Audit 2010*. London: National Institute for Cardiovascular Outcomes Research; 2012.

56. Cunningham D, Charles R, Cunningham M, Whittaker T. *Cardiac Rhythm Management: UK National Clinical Audit Report*. London: National Institute for Cardiovascular Outcomes Research; 2012.

57. Scott PA, Turner NG, Chung A, Morgan JM, Roberts PR. Varying implantable cardioverter defibrillator referral patterns from implanting and non-implanting hospitals. *Europace* 2009;**11**:1048–51. http://dx.doi.org/10.1093/europace/eup145

58. McDonagh T, Standing M, Cleland J, Mitchell P, Dargie H, Cunningham D, *et al. National Heart Failure Audit April 2010–March 2011*. London: National Institute for Cardiovascular Outcomes Research; 2012.

59. Scott PA, Whittaker A, Zeb M, Watts E, Yue AM, Roberts PR, *et al.* Rates of upgrade of ICD recipients to CRT in clinical practice and the potential impact of the more liberal use of CRT at initial implant. *Pacing Clin Electrophysiol* 2012;**35**:73–80. http://dx.doi.org/10.1111/j.1540-8159.2011.03255.x

60. Camm JA, Nisam S. European utilization of the implantable defibrillator: has 10 years changed the 'enigma'? *Europace* 2010;**12**:1063–9. http://dx.doi.org/10.1093/europace/euq282

61. National Institute for Health and Care Excellence. *Arrhythmias – ICDs & Heart Failure – Cardiac Resynchronisation: Final Scope*. URL: www.nice.org.uk/guidance/ta314/resources/arrythmias-icds-heart-failure-cardiac-resynchronisation-final-scope2 (accessed 19 September 2012).

62. Bryant J, Brodin H, Loveman E, Payne E, Clegg A. The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review. *Health Technol Assess* 2005;**9**(36).

63. Parkes J, Bryant J, Milne R. Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review. *Health Technol Assess* 2000;**4**(26).

64. Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al.* The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model. *Health Technol Assess* 2007;**11**(47).

65. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. URL: www.cochrane-handbook.org (accessed February 2014).

66. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83. http://dx.doi.org/10.1136/bmj.313.7052.275

67. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal, 2013*. London: NICE; 2013.

68. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36).

69. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, *et al.* Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. *J Am Coll Cardiol* 2003;**41**:1707–12. http://dx.doi.org/10.1016/S0735-1097(03)00297-3

70. Wijetunga M, Strickberger SA; Amiodarone Versus Implantable Defibrillator Randomized Trial. Amiodarone versus Implantable Defibrillator (AMIOVIRT): background, rationale, design, methods, results and implications. *Card Electrophysiol Rev* 2003;**7**:452–6. http://dx.doi.org/10.1023/B:CEPR.0000023158.52511.76

71. AVID investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**:1576–83. http://dx.doi.org/10.1056/NEJM199711273372202

72. AVID investigators. Causes of death in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *J Am Coll Cardiol* 1999;**34**:1552–9. http://dx.doi.org/10.1016/S0735-1097(99)00376-9

73. Hallstrom AP. Antiarrhythmics Versus Implantable Defibrillators (AVID) – rationale, design, and methods. *Am J Cardiol* 1995;**75**:470–5. http://dx.doi.org/10.1016/S0002-9149(99)80583-9

74. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, *et al.* Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation* 2002;**105**:589–94. http://dx.doi.org/10.1161/hc0502.103330

75. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch trial investigators. *N Engl J Med* 1997;**337**:1569–75. http://dx.doi.org/10.1056/NEJM199711273372201

76. The Coronary Artery Bypass Graft (CABG) Patch trial. The CABG Patch trial investigators and coordinators. *Prog Cardiovasc Dis* 1993;**36**:97–114.

77. Bigger JT Jr, Parides MK, Rolnitzky LM, Meier P, Levin B, Egan DA. Changes in sample size and length of follow-up to maintain power in the Coronary Artery Bypass Graft (CABG) Patch trial. *Control Clin Trials* 1998;**19**:1–14. http://dx.doi.org/10.1016/S0197-2456(97)00124-4

78. Bigger JT, Whang W, Rottman JN, Kleiger RE, Gottlieb CD, Namerow PB, *et al.* Mechanisms of death in the CABG Patch trial – a randomized trial of implantable cardiac defibrillator prophylaxis in patients at high risk of death after coronary artery bypass graft surgery. *Circulation* 1999;**99**:1416–21. http://dx.doi.org/10.1161/01.CIR.99.11.1416

79. Spotnitz HM, Herre JM, Raza ST, Hammon JW Jr, Baker LD Jr, Fitzgerald DM, *et al.* Effect of implantable cardioverter-defibrillator implantation on surgical morbidity in the CABG Patch trial. Surgical investigators of the Coronary Artery Bypass Graft Patch trial. *Circulation* 1998;**98**(Suppl. 19):II77–80.

80. Namerow PB, Firth BR, Heywood GM, Windle JR, Parides MK. Quality-of-life six months after CABG surgery in patients randomized to ICD versus no ICD therapy: findings from the CABG Patch trial. *Pacing Clin Electrophysiol* 1999;**22**:1305–13. http://dx.doi.org/10.1111/j.1540-8159.1999.tb00623.x

81. Kuck K-H, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;**102**:748–54. http://dx.doi.org/10.1161/01.CIR.102.7.748

82. Bänsch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, *et al.* Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation* 2002;**105**:1453–8. http://dx.doi.org/10.1161/01.CIR.0000012350.99718.AD

83. German Dilated Cardiomyopathy Study investigators. Prospective studies assessing prophylactic therapy in high risk patients: the German Dilated CardioMyopathy Study (GDCMS) – study design. *Pacing Clin Electrophysiol* 1992;**15**:697–700. http://dx.doi.org/10.1111/j.1540-8159.1992.tb05166.x

84. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, *et al.* Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1297–302. http://dx.doi.org/10.1161/01.CIR.101.11.1297

85. Connolly SJ, Gent M, Roberts RS, Dorian P, Green MS, Klein GJ, *et al.* Canadian Implantable Defibrillator Study (CIDS): study design and organization. CIDS Co-Investigators. *Am J Cardiol* 1993;**72**:103–8F. http://dx.doi.org/10.1016/0002-9149(93)90972-F

86. Sheldon R, Connolly S, Krahn A, Roberts R, Gent M, Gardner M. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy: the Canadian Implantable Defibrillator Study. *Circulation* 2000;**101**:1660–4. http://dx.doi.org/10.1161/01.CIR.101.14.1660

87. Irvine J, Dorian P, Baker B, O'Brien BJ, Roberts R, Gent M, *et al.* Quality of life in the Canadian Implantable Defibrillator Study (CIDS). *Am Heart J* 2002;**144**:282–9. http://dx.doi.org/10.1067/mhj.2002.124049

88. Bokhari F, Newman D, Greene M, Korley V, Mangat I, Dorian P. Long-term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). *Circulation* 2004;**110**:112–16. http://dx.doi.org/10.1161/01.CIR.0000134957.51747.6E

89. Nademanee K, Veerakul G, Mower M, Likittanasombat K, Krittayapong R, Bhuripanyo K, *et al.* Defibrillator Versus beta-Blockers for Unexplained Death in Thailand (DEBUT): a randomized clinical trial. *Circulation* 2003;**107**:2221–6. http://dx.doi.org/10.1161/01.CIR.0000066319.56234.C8

90. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, *et al.* Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;**350**:2151–8. http://dx.doi.org/10.1056/NEJMoa033088

91. Kadish A, Quigg R, Schaechter A, Anderson KP, Estes M, Levine J. Defibrillators in nonischemic cardiomyopathy treatment evaluation. *Pacing Clin Electrophysiol* 2000;**23**:338–43. http://dx.doi.org/10.1111/j.1540-8159.2000.tb06759.x

92. Schaechter A, Kadish AH; DEFibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation. DEFibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE). *Card Electrophysiol Rev* 2003;**7**:457–62. http://dx.doi.org/10.1023/B:CEPR.0000023162.45506.c4

93. Ellenbogen KA, Levine JH, Berger RD, Daubert JP, Winters SL, Greenstein E, *et al.* Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;**113**:776–82. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.561571

94. Passman R, Subacius H, Ruo B, Schaechter A, Howard A, Sears SF, *et al.* Implantable cardioverter defibrillators and quality of life: results from the defibrillators in nonischemic cardiomyopathy treatment evaluation study. *Arch Intern Med* 2007;**167**:2226–32. http://dx.doi.org/10.1001/archinte.167.20.2226

95. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, *et al.* Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;**351**:2481–8. http://dx.doi.org/10.1056/NEJMoa041489

96. Hohnloser SH, Connolly SJ, Kuck KH, Dorian P, Fain E, Hampton JR, *et al.* The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT): study protocol. *Am Heart J* 2000;**140**:735–9. http://dx.doi.org/10.1067/mhj.2000.110088

97. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, *et al.* Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009;**361**:1427–36. http://dx.doi.org/10.1056/NEJMoa0901889

98. Steinbeck G, Andresen D, Senges J, Hoffmann E, Seidl K, Brachmann J, *et al.* Immediate Risk-Stratification Improves Survival (IRIS): study protocol. *Europace* 2004;**6**:392–9. http://dx.doi.org/10.1016/j.eupc.2004.04.008

99. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation trial investigators. *N Engl J Med* 1996;**335**:1933–40. http://dx.doi.org/10.1056/NEJM199612263352601

100. MADIT Executive Committee. Multicenter Automatic Defibrillator Implantation Trial (MADIT): design and clinical protocol. MADIT Executive Committee. *Pacing Clin Electrophysiol* 1991;**14**:920–7. http://dx.doi.org/10.1111/j.1540-8159.1991.tb04136.x

101. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83. http://dx.doi.org/10.1056/NEJMoa013474

102. Moss AJ, Cannom DS, Daubert JP, Hall WJ, Higgins SL, Klein H, *et al.* Multicenter Automatic Defibrillator Implantation Trial II (MADIT II): design and clinical protocol. *Ann Noninvasive Electrocardiol* 1999;**4**:83–91. http://dx.doi.org/10.1111/j.1542-474X.1999.tb00369.x

103. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML, *et al.* Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). *J Am Coll Cardiol* 2004;**43**:1459–65. http://dx.doi.org/10.1016/j.jacc.2003.11.038

104. Noyes K, Corona E, Zwanziger J, Hall J, Zhao HW, Wang HK, *et al.* Health-related quality of life consequences of implantable cardioverter defibrillators – results from MADIT II. *Med Care* 2007;**45**:377–85. http://dx.doi.org/10.1097/01.mlr.0000257142.12600.c1

105. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–37. [Erratum published in *N Engl J Med* 2005;**352**:2146.] http://dx.doi.org/10.1056/NEJMoa043399

106. Mitchell JE, Hellkamp AS, Mark DB, Anderson J, Poole JE, Lee KL, *et al.* Outcome in African Americans and other minorities in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Am Heart J* 2008;**155**:501–6. http://dx.doi.org/10.1016/j.ahj.2007.10.022

107. Mark DB, Anstrom KJ, Sun JL, Clapp-Channing NE, Tsiatis AA, Davidson-Ray L, *et al.* Quality of life with defibrillator therapy or amiodarone in heart failure. *N Engl J Med* 2008;**359**:999–1008. http://dx.doi.org/10.1056/NEJMoa0706719

108. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, *et al.* Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation* 2009;**120**:2170–6. [Erratum published in *Circulation* 2010;**121**:e39.] http://dx.doi.org/10.1161/CIRCULATIONAHA.109.853689

109. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49. http://dx.doi.org/10.1056/NEJMoa050496

110. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al.* The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end-points. *Eur J Heart Fail* 2001;**3**:481–9. http://dx.doi.org/10.1016/S1388-9842(01)00176-3

111. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al.* Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;**27**:1928–32. http://dx.doi.org/10.1093/eurheartj/ehl099

112. Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, *et al.* Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response: a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial. *J Am Coll Cardiol* 2008;**52**:438–45. http://dx.doi.org/10.1016/j.jacc.2008.04.036

113. Cleland JG, Calvert MJ, Verboven Y, Freemantle N. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the CArdiac Resynchronisation-Heart Failure (CARE-HF) study. *Am Heart J* 2009;**157**:457–66. http://dx.doi.org/10.1016/j.ahj.2008.11.006

114. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, *et al.* Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail* 2009;**11**:699–705. http://dx.doi.org/10.1093/eurjhf/hfp074

115. Ghio S, Freemantle N, Scelsi L, Serio A, Magrini G, Pasotti M, *et al.* Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. *Eur J Heart Fail* 2009;**11**:480–8. http://dx.doi.org/10.1093/eurjhf/hfp034

116. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, *et al.* Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50. http://dx.doi.org/10.1056/NEJMoa032423

117. Bristow MR, Feldman AM, Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators. *J Card Fail* 2000;**6**:276–85. http://dx.doi.org/10.1054/jcaf.2000.9501

118. US Food and Drug Administration. *Summary of Safety and Effectiveness Data. P010012/SO26*. Washington, DC: US Food and Drug Administration; 2004.

119. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, Lwin A, *et al.* Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *J Am Coll Cardiol* 2005;**46**:2329–34. [Erratum appears in *J Am Coll Cardiol* 2008;**51**:2197.] http://dx.doi.org/10.1016/j.jacc.2005.09.016

120. Anand IS, Carson P, Galle E, Song R, Boehmer J, Ghali JK, *et al.* Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. *Circulation* 2009;**119**:969–77. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.793273

121. Abraham WT, Fisher WG, Smith AL, DeLurgio DB, Leon AR, Loh E, *et al.* Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–53. http://dx.doi.org/10.1056/NEJMoa013168

122. Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *J Card Fail* 2000;**6**:369–80. http://dx.doi.org/10.1054/jcaf.2000.20841

123. US Food and Drug Administration. *Summary of Safety and Effectiveness. P010015*. Washington, DC: US Food and Drug Administration; 2001.

124. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, *et al.* Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;**107**:1985–90. http://dx.doi.org/10.1161/01.CIR.0000065226.24159.E9

125. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, *et al.* Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–80. http://dx.doi.org/10.1056/NEJM200103223441202

126. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, *et al.* Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;**42**:1454–9. http://dx.doi.org/10.1016/S0735-1097(03)01042-8

127. Saxon LA, Boehmer JP, Hummel J, Kacet S, De Marco T, Naccarelli G, *et al.* Biventricular pacing in patients with congestive heart failure: two prospective randomized trials. The VIGOR CHF and VENTAK CHF investigators. *Am J Cardiol* 1999;**83**:120–3D. http://dx.doi.org/10.1016/S0002-9149(98)01012-1

128. Lozano I, Bocchiardo M, Achtelik M, Gaita F, Trappe HJ, Daoud E, *et al.* Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias. *Pacing Clin Electrophysiol* 2000;**23**:1711–12. http://dx.doi.org/10.1111/j.1540-8159.2000.tb07001.x

129. US Food and Drug Administration. *Summary of Safety and Effectiveness. Original PMA P010012*. Washington, DC: US Food and Drug Administration; 2002.

130. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–38. http://dx.doi.org/10.1056/NEJMoa0906431

131. Moss AJ, Brown MW, Cannom DS, Daubert JP, Estes M, Foster E, *et al.* Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT): design and clinical protocol. *Ann Noninvasive Electrocardiol* 2005;**10**:34–43. http://dx.doi.org/10.1111/j.1542-474X.2005.00073.x

132. Solomon SD, Foster E, Bourgoun M, Shah A, Viloria E, Brown MW, *et al.* Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: Multicenter Automatic Defibrillator Implantation Trial: Cardiac Resynchronization Therapy. *Circulation* 2010;**122**:985–92. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.955039

133. Goldenberg I, Moss AJ, Hall WJ, Foster E, Goldberger JJ, Santucci P, *et al.* Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**124**:1527–36. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.014324

134. Goldenberg I, Hall WJ, Beck CA, Moss AJ, Barsheshet A, McNitt S, *et al.* Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011;**58**:729–37. http://dx.doi.org/10.1016/j.jacc.2011.04.024

135. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, *et al.* Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol* 2011;**57**:813–20. http://dx.doi.org/10.1016/j.jacc.2010.06.061

136. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, *et al.* Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. *JAMA* 2003;**289**:2685–94. http://dx.doi.org/10.1001/jama.289.20.2685

137. Abraham WT, Young JB, Leon AR, Adler S, Bank AJ, Hall SA, *et al.* Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;**110**:2864–8. http://dx.doi.org/10.1161/01.CIR.0000146336.92331.D1

138. Piccirillo G, Magri D, di Carlo S, De Laurentis T, Torrini A, Matera S, *et al.* Influence of cardiac-resynchronization therapy on heart rate and blood pressure variability: 1-year follow-up. *Eur J Heart Fail* 2006;**8**:716–22. http://dx.doi.org/10.1016/j.ejheart.2006.01.008

139. Pinter A, Mangat I, Korley V, Connolly S, Connors S, Gardner M, *et al.* Assessment of resynchronization therapy on functional status and quality of life in patients requiring an implantable defibrillator. *Pacing Clin Electrophysiol* 2009;**32**:1509–19. http://dx.doi.org/10.1111/j.1540-8159.2009.02543.x

140. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, *et al.* Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–95. http://dx.doi.org/10.1056/NEJMoa1009540

141. Tang AS, Wells GA, Arnold M, Connolly S, Hohnloser S, Nichol G, *et al.* Resynchronization/defibrillation for ambulatory heart failure trial: rationale and trial design. *Curr Opin Cardiol* 2009;**24**:1–8. http://dx.doi.org/10.1097/HCO.0b013e32831bc63b

142. Beshai JF, Grimm RA, Nagueh SF, Baker JH, Beau SL, Greenberg SM, *et al.* Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;**357**:2461–71. http://dx.doi.org/10.1056/NEJMoa0706695

143. Beshai JF, Grimm R. The resynchronization therapy in narrow QRS study (RethinQ study): methods and protocol design. *J Interv Card Electrophysiol* 2007;**19**:149–55. [Erratum published in *J Interv Card Electrophysiol* 2008;**21**:69.] http://dx.doi.org/10.1007/s10840-007-9156-3

144. US Food and Drug Administration. *Summary of Safety and Effectiveness Data. P030054.* Washington, DC: US Food and Drug Administration; 2004.

145. US Food and Drug Administration. *Summary of Safety and Effectiveness Data. P030054_S10.* Washington, DC: US Food and Drug Administration; 2005.

146. 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. *N Engl J Med* 1999;**341**:1882–90. [Erratum published in *N Engl J Med* 2000;**342**:1300.] http://dx.doi.org/10.1056/NEJM199912163412503

147. Lau EW, Griffith MJ, Pathmanathan RK, Ng GA, Clune MM, Cooper J, *et al.* The Midlands Trial of Empirical Amiodarone versus Electrophysiology-Guided Interventions and Implantable Cardioverter-Defibrillators (MAVERIC): a multi-centre prospective randomised clinical trial on the secondary prevention of sudden cardiac death. *Europace* 2004;**6**:257–66. http://dx.doi.org/10.1016/j.eupc.2004.03.009

148. Lee KL, Hafley G, Fisher JD, Gold MR, Prystowsky EN, Talajic M, *et al.* Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. *Circulation* 2002;**106**:233–8. http://dx.doi.org/10.1161/01.CIR.0000021920.73149.C3

149. Wang K, Yamauchi K, Li P, Kato H, Kobayashi M, Kato K, *et al.* Cost-effectiveness of implantable cardioverter-defibrillators in Brugada syndrome treatment. *J Med Syst* 2008;**32**:51–7. http://dx.doi.org/10.1007/s10916-007-9107-7

150. Cleland JG, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L, *et al.* Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. *Eur J Heart Fail* 2012;**14**:628–34. http://dx.doi.org/10.1093/eurjhf/hfs055

151. Association of British Healthcare Industries. *Implantable Cardioverter Defibrillators for the Treatment of Arrhythmias and Cardiac Resynchronisation Therapy for the Treatment of Heart Failure (Review of TA95 and TA120)*. London: ABHI; 2012.

152. Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D*. *CHE Discussion Paper 172*. York: University of York, Centre for Health Economics; 1999.

153. Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al.* A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context. *Health Technol Assess* 2006;**10**(27).

154. Al-Khatib SM, Anstrom KJ, Eisenstein EL, Peterson ED, Jollis JG, Mark DB, *et al.* Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. *Ann Intern Med* 2005;**142**:593–600. http://dx.doi.org/10.7326/0003-4819-142-8-200504190-00007

155. Bertoldi EG, Rohde LE, Zimerman LI, Pimentel M, Polanczyk CA. Cost-effectiveness of cardiac resynchronization therapy in patients with heart failure: the perspective of a middle-income country's public health system. *Int J Cardiol* 2011;**163**:309–15. http://dx.doi.org/10.1016/j.ijcard.2011.06.046

156. Caro JJ, Ward A, Deniz HB, O'Brien JA, Ehreth JL. Cost–benefit analysis of preventing sudden cardiac deaths with an implantable cardioverter defibrillator versus amiodarone. *Value Health* 2007;**10**:13–22. http://dx.doi.org/10.1111/j.1524-4733.2006.00140.x

157. Chan PS, Stein K, Chow T, Fendrick M, Bigger JT, Vijan S. Cost-effectiveness of a microvolt T-wave alternans screening strategy for implantable cardioverter-defibrillator placement in the MADIT-II-eligible population. *J Am Coll Cardiol* 2006;**48**:112–21. http://dx.doi.org/10.1016/j.jacc.2006.02.051

158. Chan PS, Nallamothu BK, Spertus JA, Masoudi FA, Bartone C, Kereiakes DJ, *et al.* Impact of age and medical comorbidity on the effectiveness of implantable cardioverter-defibrillators for primary prevention. *Circ Cardiovasc Qual Outcomes* 2009;**2**:16–24. http://dx.doi.org/10.1161/CIRCOUTCOMES.108.807123

159. Chen L, Hay JW. Cost-effectiveness of primary implanted cardioverter defibrillator for sudden death prevention in congestive heart failure. *Cardiovasc Drugs Ther* 2004;**18**:161–70. http://dx.doi.org/10.1023/B:CARD.0000029034.65769.f7

160. Cowie MR, Marshall D, Drummond M, Ferko N, Maschio M, Ekman M, *et al.* Lifetime cost-effectiveness of prophylactic implantation of a cardioverter defibrillator in patients with reduced left ventricular systolic function: results of Markov modelling in a European population. *Europace* 2009;**11**:716–26. http://dx.doi.org/10.1093/europace/eup068

161. Deniz HB, Ward A, Jaime CJ, Alvarez P, Sadri H. Cost–benefit analysis of primary prevention of sudden cardiac death with an implantable cardioverter defibrillator versus amiodarone in Canada. *Curr Med Res Opin* 2009;**25**:617–26. http://dx.doi.org/10.1185/03007990802695037

162. Feingold B, Arora G, Webber SA, Smith KJ. Cost-effectiveness of implantable cardioverter-defibrillators in children with dilated cardiomyopathy. *J Card Fail* 2010;**16**:734–41. http://dx.doi.org/10.1016/j.cardfail.2010.04.009

163. Filion KB, Xie X, van der Avoort CJ, Dendukuri N, Brophy JM. Microvolt T-wave alternans and the selective use of implantable cardioverter defibrillators for primary prevention: a cost-effectiveness study. *Int J Technol Assess Health Care* 2009;**25**:151–60. http://dx.doi.org/10.1017/S0266462309090205

164. Gandjour A, Holler A, Dipl GO, Adarkwah CC. Cost-effectiveness of implantable defibrillators after myocardial infarction based on 8-year follow-up data (MADIT II). *Value Health* 2011;**14**:812–17. http://dx.doi.org/10.1016/j.jval.2011.02.1180

165. Goldenberg I, Moss AJ, Maron BJ, Dick AW, Zareba W. Cost-effectiveness of implanted defibrillators in young people with inherited cardiac arrhythmias. *Ann Noninvasive Electrocardiol* 2005;**10**(Suppl. 4):83. http://dx.doi.org/10.1111/j.1542-474X.2005.00070.x

166. Kuppermann M, Luce BR, McGovern B, Podrid PJ, Bigger JT Jr, Ruskin JN. An analysis of the cost effectiveness of the implantable defibrillator. *Circulation* 1990;**81**:91–100. http://dx.doi.org/10.1161/01.CIR.81.1.91

167. Kupersmith J, Hogan A, Guerrero P, Gardiner J, Mellits ED, Baumgardner R, *et al.* Evaluating and improving the cost-effectiveness of the implantable cardioverter-defibrillator. *Am Heart J* 1995;**130**:507–15. http://dx.doi.org/10.1016/0002-8703(95)90359-3

168. Larsen GC, Manolis AS, Sonnenberg FA, Beshansky JR, Estes NA, Pauker SG. Cost-effectiveness of the implantable cardioverter-defibrillator: effect of improved battery life and comparison with amiodarone therapy. *J Am Coll Cardiol* 1992;**19**:1323–34. http://dx.doi.org/10.1016/0735-1097(92)90341-J

169. Larsen G, Hallstrom A, McAnulty J, Pinski S, Olarte A, Sullivan S, *et al.* Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular tachyarrhythmias: results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) economic analysis substudy. *Circulation* 2002;**105**:2049–57. http://dx.doi.org/10.1161/01.CIR.0000015504.57641.D0

170. Mark DB, Nelson CL, Anstrom KJ, Al Khatib SM, Tsiatis AA, Cowper PA, *et al.* Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2006;**114**:135–42. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.581884

171. McGregor M, Chen J. Should the implantable cardiac defibrillator be used for primary prevention of sudden death? A review of the issues relevant to hospital decision making. *Can J Cardiol* 2004;**20**:1199–204.

172. Medical Services Advisory Committee. *Implantable Cardioverter Defibrillators for Prevention of Sudden Cardiac Death*. Canberra: Australian Government Department of Health and Ageing; 2006.

173. Mushlin AI, Hall WJ, Zwanziger J, Gajary E, Andrews M, Marron R, *et al.* The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. *Circulation* 1998;**97**:2129–35. http://dx.doi.org/10.1161/01.CIR.97.21.2129

174. Neyt M, Thiry N, Ramaekers D, Van Brabandt H. Cost effectiveness of implantable cardioverter-defibrillators for primary prevention in a Belgian context. *Appl Health Econ Health Policy* 2008;**6**:67–80. http://dx.doi.org/10.2165/00148365-200806010-00006

175. O'Brien BJ, Buxton MJ, Rushby JA. Cost effectiveness of the implantable cardioverter defibrillator: a preliminary analysis. *Br Heart J* 1992;**68**:241–5. http://dx.doi.org/10.1136/hrt.68.8.241

176. Owens DK, Sanders GD, Harris RA, McDonald KM, Heidenreich PA, Dembitzer AD, *et al.* Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. *Ann Intern Med* 1997;**126**:1–12. http://dx.doi.org/10.7326/0003-4819-126-1-199701010-00001

177. Owens DK, Sanders GD, Heidenreich PA, McDonald KM, Hlatky MA. Effect of risk stratification on cost-effectiveness of the implantable cardioverter defibrillator. *Am Heart J* 2002;**144**:440–8. http://dx.doi.org/10.1067/mhj.2002.125501

178. Ribeiro RA, Stella SF, Zimerman LI, Pimentel M, Rohde LE, Polanczyk CA. Cost-effectiveness of implantable cardioverter defibrillators in Brazil in the public and private sectors. *Arq Bras Cardiol* 2010;**95**:577–86. http://dx.doi.org/10.1590/S0066-782X2010005000134

179. Sanders GD, Hlatky MA, Every NR, McDonald KM, Heidenreich PA, Parsons LS, *et al.* Potential cost-effectiveness of prophylactic use of the implantable cardioverter defibrillator or amiodarone after myocardial infarction. *Ann Intern Med* 2001;**135**:870–83. http://dx.doi.org/10.7326/0003-4819-135-10-200111200-00007

180. Sanders GD, Hlatky MA, Owens DK. Special report: cost-effectiveness of implantable cardioverter defibrillators in a MADIT-II population. *Technol Eval Cent Assess Program Exec Summ* 2004;**19**:1–22.

181. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med* 2005;**353**:1471–80. http://dx.doi.org/10.1056/NEJMsa051989

182. Sanders GD, Kong MH, Al-Khatib SM, Peterson ED. Cost-effectiveness of implantable cardioverter defibrillators in patients ≥ 65 years of age. *Am Heart J* 2010;**160**:122–31. http://dx.doi.org/10.1016/j.ahj.2010.04.021

183. Sheldon R, O'Brien BJ, Blackhouse G, Goeree R, Mitchell B, Klein G, *et al.* Effect of clinical risk stratification on cost-effectiveness of the implantable cardioverter-defibrillator: the Canadian implantable defibrillator study. *Circulation* 2001;**104**:1622–6. http://dx.doi.org/10.1161/hc3901.096720

184. Weiss JP, Saynina O, McDonald KM, McClellan MB, Hlatky MA. Effectiveness and cost-effectiveness of implantable cardioverter defibrillators in the treatment of ventricular arrhythmias among Medicare beneficiaries. *Am J Med* 2002;**112**:519–27. http://dx.doi.org/10.1016/S0002-9343(02)01078-1

185. You JJ, Woo A, Ko DT, Cameron DA, Mihailovic A, Krahn M. Life expectancy gains and cost-effectiveness of implantable cardioverter/defibrillators for the primary prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy. *Am Heart J* 2007;**154**:899–907. http://dx.doi.org/10.1016/j.ahj.2007.06.026

186. Zwanziger J, Hall WJ, Dick AW, Zhao H, Mushlin AI, Hahn RM, *et al.* The cost effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006;**47**:2310–18. http://dx.doi.org/10.1016/j.jacc.2006.03.032

187. Banz K. Cardiac resynchronization therapy (CRT) in heart failure – a model to assess the economic value of this new medical technology. *Value Health* 2005;**8**:128–39. http://dx.doi.org/10.1111/j.1524-4733.2005.03092.x

188. Callejo D, Guerra M, Hernandez-Madrid A, Blasco JA. Economic assessment of cardiac resynchronization therapy. *Rev Esp Cardiol* 2010;**63**:1235–43. http://dx.doi.org/10.1016/S0300-8932(10)70293-1

189. Calvert MJ, Freemantle N, Yao G, Cleland JG, Billingham L, Daubert JC, *et al.* Cost-effectiveness of cardiac resynchronization therapy: results from the CARE-HF trial. *Eur Heart J* 2005;**26**:2681–8. http://dx.doi.org/10.1093/eurheartj/ehi662

190. Caro JJ, Guo S, Ward A, Chalil S, Malik F, Leyva F. Modelling the economic and health consequences of cardiac resynchronization therapy in the UK. *Curr Med Res Opin* 2006;**22**:1171–9. http://dx.doi.org/10.1185/030079906X112516

191. Blomstrom P, Ekman M, Lundqvist CB, Calvert MJ, Freemantle N, Lonnerholm S, *et al.* Cost effectiveness of cardiac resynchronization therapy in the Nordic region: an analysis based on the CARE-HF trial. *Eur J Heart Fail* 2008;**10**:869–77. http://dx.doi.org/10.1016/j.ejheart.2008.06.018

192. Feldman AM, de Lissovoy G, Bristow MR, Saxon LA, De Marco T, Kass DA, *et al.* Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. *J Am Coll Cardiol* 2005;**46**:2311–21. http://dx.doi.org/10.1016/j.jacc.2005.08.033

193. Heerey A, Lauer M, Alsolaiman F, Czerr J, James K. Cost effectiveness of biventricular pacemakers in heart failure patients. *Am J Cardiovasc Drugs* 2006;**6**:129–37. http://dx.doi.org/10.2165/00129784-200606020-00007

194. McAlister F, Ezekowitz J, Wiebe N, Rowe B, Spooner C, Crumley E, *et al. Cardiac Resynchronization Therapy for Congestive Heart Failure: Summary. AHRQ Evidence Report Summaries 106*. Rockville, MD: Agency for Healthcare Research; 2004.

195. Medical Services Advisory Committee. *Cardiac Resynchronisation Therapy for Severe Heart Failure*. Canberra: Australian Government Department of Health and Ageing; 2006.

196. Neyt M, Stroobandt S, Obyn C, Camberlin C, Devriese S, De Laet C, *et al.* Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure: a lifetime Markov model. *BMJ Open* 2011;**1**:e000276. http://dx.doi.org/10.1136/bmjopen-2011-000276

197. Nichol G, Kaul P, Huszti E, Bridges JF. Cost-effectiveness of cardiac resynchronization therapy in patients with symptomatic heart failure. *Ann Intern Med* 2004;**141**:343–51. http://dx.doi.org/10.7326/0003-4819-141-5-200409070-00102

198. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J* 2007;**28**:42–51. http://dx.doi.org/10.1093/eurheartj/ehl382

199. Aidelsburger P, Grabein K, Klauss V, Wasem J. Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator (CRT-D) for the treatment of chronic heart failure from a German health care system perspective. *Clin Res Cardiol* 2008;**97**:89–97. http://dx.doi.org/10.1007/s00392-007-0586-9

200. Poggio R, Augustovsky F, Caporale J, Irazola V, Miriuka S. Cost-effectiveness of cardiac resynchronization therapy: perspective from Argentina. *Int J Technol Assess Health Care* 2012;**28**:429–35. http://dx.doi.org/10.1017/S0266462312000505

201. Ribeiro RA, Stella SF, Camey SA, Zimerman LI, Pimentel M, Rohde LE, *et al.* Cost-effectiveness of implantable cardioverter-defibrillators in Brazil: primary prevention analysis in the public sector. *Value Health* 2010;**13**:160–8. http://dx.doi.org/10.1111/j.1524-4733.2009.00608.x

202. O'Brien BJ, Connolly SJ, Goeree R, Blackhouse G, Willan A, Yee R, *et al.* Cost-effectiveness of the implantable cardioverter-defibrillator: results from the Canadian Implantable Defibrillator Study (CIDS). *Circulation* 2001;**103**:1416–21. http://dx.doi.org/10.1161/01.CIR.103.10.1416

203. Bond M, Mealing S, Anderson R, Dean J, Stein K, Taylor RS. Is combined resynchronisation and implantable defibrillator therapy a cost-effective option for left ventricular dysfunction? *Int J Cardiol* 2009;**137**:206–15. http://dx.doi.org/10.1016/j.ijcard.2008.05.073

204. 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. *J Am Coll Cardiol* 2002;**39**:2026–33. http://dx.doi.org/10.1016/S0735-1097(02)01895-8

205. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, *et al.* Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;**23**:1780–7. http://dx.doi.org/10.1053/euhj.2002.3232

206. Garrigue S, Bordachar P, Reuter S, Jais P, Haissaguerre M, Clementy J. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: a prospective hemodynamic study. *Card Electrophysiol Rev* 2003;**7**:315–24. http://dx.doi.org/10.1023/B:CEPR.0000023167.11038.8f

207. Leclerq C, Cazeau S, Lellouche D, *et al. Upgrading from Right Ventricular Pacing to Biventricular Pacing in Previously Paced Patients with Advanced Heart Failure: a Randomized Controlled Study (the RD-CHF Trial)*. European Society of Cardiology Congress, Vienna, Austria, 30 August – 3 September 2003.

208. Linde C, Gold M, Abraham WT, Daubert J-C. Rationale and design of a randomized controlled trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with asymptomatic left ventricular dysfunction with previous symptoms or mild heart failure – The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *American Heart Journal* 2006;**151**:288–294. http://dx.doi.org/10.1016/j.ahj.2005.03.002

209. Moss A. MADIT-CRT: the Multicentre Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy. *Eur J Heart Fail* 2009;**11**:1217–19.

210. Kirsch J, McGuire A. Establishing health state valuations for disease-specific states: an example from heart disease. *Health Econ* 2000;**9**:149–58. http://dx.doi.org/10.1002/(SICI)1099-1050(200003)9:2<149::AID-HEC501>3.0.CO;2-N

211. Calvert MJ, Freemantle N, Cleland JG. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. *Eur J Heart Fail* 2005;**7**:243–51. http://dx.doi.org/10.1016/j.ejheart.2005.01.012

212. National Institute for Health and Care Excellence. *Guide to the Single Technology Appraisal Process*. London: NICE; 2009. URL: www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf (accessed 23 January 2014).

213. Eurich DT, Johnson JA, Reid KJ, Spertus JA. Assessing responsiveness of generic and specific health related quality of life measures in heart failure. *Health Qual Life Outcomes* 2006;**4**:89. http://dx.doi.org/10.1186/1477-7525-4-89

214. Gohler A, Geisler BP, Manne JM, Kosiborod M, Zhang Z, Weintraub WS, *et al.* Utility estimates for decision-analytic modeling in chronic heart failure – health states based on New York Heart Association classes and number of rehospitalizations. *Value Health* 2009;**12**:185–7. http://dx.doi.org/10.1111/j.1524-4733.2008.00425.x

215. Groeneveld PW, Matta MA, Suh JJ, Yang F, Shea JA. Quality of life among implantable cardioverter-defibrillator recipients in the primary prevention therapeutic era. *Pacing Clin Electrophysiol* 2007;**30**:463–71. http://dx.doi.org/10.1111/j.1540-8159.2007.00694.x

216. Holland R, Brooksby I, Lenaghan E, Ashton K, Hay L, Smith R, *et al.* Effectiveness of visits from community pharmacists for patients with heart failure: HeartMed randomised controlled trial. *BMJ* 2007;**334**:1098. http://dx.doi.org/10.1136/bmj.39164.568183.AE

217. Public Health England. *Central Cardiac Audit Database (CCAD)*. URL: http://www.sepho.org.uk/viewResource.aspx?id=6584 (accessed April 2014).

218. Department of Health. *NHS Reference Costs 2010–2011*. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_122803 (accessed 23 January 2014).

219. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. No. 61, March 2011. London: BMA and RPS; 2011.

220. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press, 2006.

221. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. *Ann Intern Med* 2003;**138**:445–52. http://dx.doi.org/10.7326/0003-4819-138-6-200303180-00007

222. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J. *Coronary Heart Disease Statistics: 2012 Edition*. London: British Heart Foundation; 2012.

223. Curnis A, Caprari F, Mascioli G, Bontempi L, Scivales A, Bianchetti F, *et al. Biventricular Cardiac Resynchronization in Moderate-to-Severe Heart Failure: Analysis of Hospital Costs and Clinical Effectiveness (Brescia Study)*. Milan: Springer-Verlag Italia; 2003.

224. Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized heart failure: rates and long-term mortality. *J Card Fail* 2004;**10**:374–9. http://dx.doi.org/10.1016/j.cardfail.2004.02.003

225. Oxford Healthcare Associates. *Access to Cardiac Care in the UK: A Report on Recent Trends, Variations in Access & Future Need*. Oxford: British Cardiac Society and the British Heart Foundation; 2009. URL: www.bcs.com/documents/C1D_Access_to_Cardiac_Care_in_the_UK_-_UK_by_Country_&_English_SHA_-_FINAL2.pdf (accessed 23 January 2014).

226. UK Cardiothoracic Transplant Audit Steering Group. *UK Cardiothoracic Transplant Audit, Annual Report*. London: Clinical Effectiveness Unit, Royal College of Surgeons of England, and Statistics and Clinical Audit, NHS Blood and Transplant; 2011.

227. Hussey JC, Bond ZC, Collett D, Wallwork J. Long term patient survival for heart transplant recipients in the UK. URL: www.organdonation.nhs.uk/statistics/presentations/pdfs/bts_2004_long-term_pt_survival_%20heart.pdf (accessed 23 January 2014).

228. Tappenden P, Chilcott J, Ward S, Eggington S, Hind D, Hummel S. Methodological issues in the economic analysis of cancer treatments. *Eur J Cancer* 2006;**42**:2867–75. http://dx.doi.org/10.1016/j.ejca.2006.08.010

229. Department of Health. *NHS UK Tariff 2012–13*. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_132654. 2012 (accessed 23 January 2014).

230. Huang Y, Wu W, Cao Y, Qu N. All cause mortality of cardiac resynchronization therapy with implantable cardioverter defibrillator: a meta-analysis of randomized controlled trials. *Int J Cardiol* 2010;**145**:413–17. http://dx.doi.org/10.1016/j.ijcard.2010.05.016

231. Al-Majed NS, McAlister FA, Bakal JA, Ezekowitz JA. Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure. *Ann Intern Med* 2011;**154**:401–12. http://dx.doi.org/10.7326/0003-4819-154-6-201103150-00313

232. Wells G, Parkash R, Healey JS, Talajic M, Arnold JM, Sullivan S, *et al.* Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *CMAJ* 2011;**183**:421–9. http://dx.doi.org/10.1503/cmaj.101685

233. Bertoldi EG, Polanczyk CA, Cunha V, Ziegelmann PK, Beck-da-Silva L, Rohde LE. Mortality reduction of cardiac resynchronization and implantable cardioverter-defibrillator therapy in heart failure: an updated meta-analysis. Does recent evidence change the standard of care? *Journal of Card Fail* 2011;**17**:860–6. http://dx.doi.org/10.1016/j.cardfail.2011.06.372

234. Kron J, Herre J, Renfroe EG, Rizo-Patron C, Raitt M, Halperin B, *et al.* Lead- and device-related complications in the antiarrhythmics versus implantable defibrillators trial. *Am Heart J* 2001;**141**:92–8. http://dx.doi.org/10.1067/mhj.2001.111261

235. Kron J. Clinical significance of device-related complications in clinical trials and implications for future trials: insights from the Antiarrhytmics Versus Implantable Defibrillators (AVID) trial. *Card Electrophysiol Rev* 2003;**7**:473–8. http://dx.doi.org/10.1023/B:CEPR.0000023163.67758.b1

236. Klein RC, Raitt MH, Wilkoff BL, Beckman KJ, Coromilas J, Wyse DG, *et al.* Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *J Cardiovasc Electrophysiol* 2003;**14**:940–8. http://dx.doi.org/10.1046/j.1540-8167.2003.01554.x

237. Curtis AB, Cannom DS, Bigger JT Jr, DiMarco JP, Estes NA III, Steinman RC, *et al.* Baseline characteristics of patients in the Coronary Artery Bypass Graft (CABG) Patch trial. *Am Heart J* 1997;**134**:787–98. http://dx.doi.org/10.1016/S0002-8703(97)80001-4

238. Siebels J, Cappato R, Ruppel R, Schneider MA, Kuck KH. ICD versus drugs in cardiac arrest survivors: preliminary results of the Cardiac Arrest Study Hamburg. *Pacing Clin Electrophysiol* 1993;**16**:552–8. http://dx.doi.org/10.1111/j.1540-8159.1993.tb01624.x

239. Siebels J, Cappato R, Ruppel R, Schneider MA, Kuck KH. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). *Am J Cardiol* 1993;**72**:109–13F. http://dx.doi.org/10.1016/0002-9149(93)90973-G

240. Siebels J, Kuck KH. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). *Am Heart J* 1994;**127**:1139–44. http://dx.doi.org/10.1016/0002-8703(94)90101-5

241. Foley PW, Patel K, Irwin N, Sanderson JE, Frenneaux MP, Smith RE, *et al.* Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. *Heart* 2011;**97**:1041–7. http://dx.doi.org/10.1136/hrt.2010.208355

242. Linde C, Gold M, Abraham WT, Daubert JC, REVERSE Study Group. Baseline characteristics of patients randomized in the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. *Congest Heart Fail* 2008;**14**:66–74. http://dx.doi.org/10.1111/j.1751-7133.2008.07613.x

243. Linde C, Abraham WT, Gold MR, St John SM, Ghio S, Daubert C, *et al.* Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–43 http://dx.doi.org/10.1016/j.jacc.2008.08.027

244. US Food and Drug Administration. *Summary of Safety and Effectiveness Data (SSED)*; 2005. URL: www.fda.gov/ohrms/dockets/dockets/05m0289/05m-0289-aav0001-03-SSED-vol1.pdf (accessed April 2014).

Appendix 1 Comparison of inclusion criteria in previous and present technology assessment reports

Parameter	ICD TAR[62]	CRT TAR[64]	Present TAR
Population	Adults at high risk of SCD as a result of arrhythmia: 'Secondary prevention': (i) cardiac arrest as a result of 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 LVEF (< 35%) but who are no worse than NYHA class III (a) 'Primary prevention': (i) a history of previous MI and (a) non-sustained VT on Holter (24-hour ECG) monitoring, (b) inducible VT on electrophysiological testing, (c) left ventricular dysfunction with an LVEF < 35% and no worse than NYHA class III; (ii) a history of previous MI and depressed heart function (LVEF ≤ 30%); (iii) non-ischaemic (dilated) cardiomyopathy with arrhythmia at high risk of SCD and depressed heart function (LVEF ≤ 30%)	People with HF (any NYHA class) as a result of LVSD with evidence of cardiac dyssynchrony (QRS duration > 120 milliseconds) and LVSD (LVEF ≤ 35%)	People at increased risk of SCD as a result of ventricular arrhythmias despite OPT; people with HF as a result of LVSD 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 HF hospitalisations, exercise capacity, NYHA class, number with adverse effects, QoL	Mortality, adverse effects, QoL, symptoms and complications related to tachyarrhythmias and/or HF, HF hospitalisations, change in NYHA class, change in LVEF

Appendix 2 Sources of information, including databases searched and search terms

All databases searched for the systematic reviews of clinical effectiveness and cost-effectiveness are presented in the following table. Searches were updated in November 2012.

Database searched	Clinical effectiveness searches	Cost effectiveness and QoL searches
Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)	All available years	
Cochrane Database of Systematic Reviews (CDSR, The Cochrane Library)	All available years	
Database of Abstracts of Reviews of Effects (DARE, CRD)	All available years	All available years
EMBASE	All available years	1990–2011
HTA database (CRD)	All available years	All available years
MEDLINE (Ovid)	All available years	All available years
MEDLINE In-Process & Other Non-Indexed Citations (MEIP)	Searched 13 November 2012	Searched 13 November 2012
NHS Economic Evaluation Database (NHS EED, CRD)		All available years
Web of Science (Science Citation Index Expanded and Conference Proceedings)	All available years	All available years
Biosis Previews (ISI Web of Knowledge)	All available years	All available years
Zetoc (Mimas)	1990–2012	
Searched for ongoing trials		
NIHR Clinical Research Network (NIHR CRN Portfolio, formally UKCRN website)		
Current Controlled Trials (CCT)		
ClinicalTrials.gov		
World Health Organization International Clinical Trials Registry Platform (ICTRP)		

The MEDLINE search strategy (presented in the following section) for the systematic review of clinical effectiveness was adjusted as necessary for the other electronic databases for both the clinical effectiveness and the cost effectiveness (including QoL information) searches. Search strategies for the systematic review are available from the authors on request. Citations identified by the searches were added to a Reference Manager database (version 12; Thomson ResearchSoft, San Francisco, CA, USA).

MEDLINE search strategy

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. (10,472)
18. or/1-17 (23,443)
19. exp arrhythmia/ (149,057)
20. Tachycardia, Ventricular/ or Arrhythmias, Cardiac/ or Tachycardia/ or Ventricular Fibrillation/ (79,877)
21. Atrial Fibrillation/ (27,947)
22. Heart Ventricles/bs, in [Blood Supply, Injuries] (878)
23. exp Ventricular Dysfunction, Left/ (18,010)
24. exp cardiomyopathy, dilated/ (11,764)
25. ventricula* remodel*.tw. (2958)
26. bundle-branch block/ (6995)
27. Heart Failure/ (73,266)
28. exp heart failure, congestive/ (74,453)
29. Death, Sudden, Cardiac/ (9241)
30. Heart Arrest/ (20,135)
31. (ventricul* adj2 (tachycardia* or fibril* or arrhythmia*)).tw. (34,555)
32. ((heart or cardiac or myocardial or coronary) adj2 (failur* or arrest* or sudden)).tw. (116,912)
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. (16,602)
38. (cardiomyopathy or cardiomyopathies).tw. (38,422)
39. Myocardial Infarction/ (128,452)
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. (30,606)
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. (10,374)
51. exp cardiomyopathies/ (64,726)
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. (93,943)
58. Heart Defects, Congenital/su [Surgery] (12,194)
59. Heart Conduction System/ (26,125)
60. exp Cardiac Pacing, Artificial/ (18,111)

61. exp Pacemaker, Artificial/ (21,156)
62. exp Heart-Assist Devices/ (6947)
63. or/19-62 (502,075)
64. 18 and 63 (17,567)
65. Randomized Controlled Trials as Topic/ (75,979)
66. randomized controlled trial.pt. (315,877)
67. controlled clinical trial.pt. (83,182)
68. Controlled Clinical Trial/ (83,182)
69. random allocation/ (72,622)
70. Double-Blind Method/ (111,942)
71. Single-Blind Method/ (15,496)
72. (random* adj2 allocat*).tw. (16,697)
73. placebo*.tw. (131,568)
74. ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (109,548)
75. Research Design/ (64,180)
76. ((random* or control*) adj5 (trial* or stud*)).tw. (414,902)
77. random*.tw. (534,613)
78. exp Placebos/ (30,269)
79. Meta-Analysis/ (30,726)
80. meta analysis.pt. (30,726)
81. meta analys*.tw. (34,905)
82. (systematic adj2 (review* or overview*)).tw. (30,123)
83. Technology Assessment, Biomedical/ (7447)
84. or/65-83 (1,030,489)
85. 64 and 84 (2873)
86. (comment or editorial or letter).pt. (1,090,861)
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. (3,739,049)
91. 89 not 90 (68)
92. 88 not 91 (2433)

Reference lists

The reference lists of retrieved articles were examined for additional studies.

Other searches

The expert advisory group was contacted to obtain information about additional references and any ongoing studies.

British societies and conferences (sources checked November 2012)

Heart Rhythm in press articles

Heart Rhythm Society conferences 2010–12

www.arrhythmiaalliance.org.uk/

www.actionheart.com/

www.cardiomyopathy.org/

www.bhf.org.uk/

www.scst.org.uk/pages/default.asp

Appendix 3 Economic evaluation checklist

No.	Item	Study	Comments
1	Is there a clear statement of the decision problem?		
2	Is the comparator routinely used in the UK NHS?		
3	Is the patient group in the study similar to those of interest in the UK NHS?		
4	Is the health-care system comparable to that of the UK?		
5	Is the setting comparable to that of 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?		

Questions are answered as yes, no or unclear.

Appendix 4 List of excluded clinical effectiveness studies and recent abstracts

Excluded studies and reasons for exclusion

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**: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. *Am J Cardiol* 2003;**91**: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). *Clin Cardiol* 2004;**27**:678–82. [Reason for exclusion: study design.]

Are implantable cardioverter-defibrillators or drugs more effective in prolonging life? The Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial Executive Committee. *Am J Cardiol* 1997;**79**:661–3. [Reason for exclusion: patient group, intervention, outcomes and 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. *J Am Coll Cardiol* 2002;**39**: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. *J Am Coll Cardiol* 2003;**42**: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. *Am J Cardiol* 2007;**99**:232–8. [Reason for exclusion: population, comparator and 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**:212–18. [Reason for exclusion: 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). *J Am Coll Cardiol* 2011;**57**:2416–23. [Reason for exclusion: study design.]

Beshai JF. Resynchronization therapy in patients with narrow QRS (RethinQ). *ACC Cardiosource Rev J* 2007;**16**:30. [Reason for exclusion: abstract (insufficient details).]

Beshai JF, Daubert J-C. RethinQ (the Resynchronization Therapy in Normal QRS Study). *Clin Cardiol* 2008;**31**:89–90. [Reason for exclusion: abstract (insufficient details).]

Beshai JF, Truong Q. Resynchronization therapy in patients with narrow QRS (RethinQ). *ACC Cardiosource Rev J* 2008;**17**:44. [Reason for exclusion: study design.]

Birnie DH, Ha A, Higginson L, Green M, Thibault B, Wells G, *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). 64th Annual Meeting of the Canadian Cardiovascular Society, Vancouver, Canada, 22–26 October 2011. [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. *J Card Fail* 2008;**14**:539–46. [Reason for exclusion: study design.]

Brachmann J, Freigang K, Saggau W. Coronary Artery Bypass Graft Patch trial. *Pacing Clin Electrophysiol* 1993;**16**:571–5. [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. *Eur Heart J* 2009;**30**: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). *J Am Coll Cardiol* 2011;**58**: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). *Am J Cardiol* 2005;**96**:691–5. [Reason for exclusion: comparator and study design.]

Brodsky MA, McAnulty J, Zipes DP, Baessler C, Hallstrom AP, AVID investigators. A history of heart failure predicts arrhythmia treatment efficacy: data from the Antiarrythmics Versus Implantable Defibrillators (AVID) study. *Am Heart J* 2006;**152**: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. *N Engl J Med* 1999;**341**:1882–90. [Erratum published in *N Engl J Med* 2000;**342**:1300.] [Reason for exclusion: intervention and comparator (although 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. *J Am Coll Cardiol* 2011;**57**(Suppl. 14):E205. [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. *J Card Fail* 2011;**17**(Suppl. 8):S57. [Reason for exclusion: abstract (insufficient details).]

Cappato R, Boczor S, Kuck KH; CASH investigators. Response to programmed ventricular stimulation and clinical outcome in cardiac arrest survivors receiving randomised assignment to implantable cardioverter defibrillator or antiarrhythmic drug therapy. *Eur Heart J* 2004;**25**:642–9. [Reason for exclusion: study design.]

Cardiomyopathy trial. The Cardiomyopathy Trial Investigators. *Pacing Clin Electrophysiol* 1993;**16**:576–81. [Reason for exclusion: outcomes.]

Cawley PJ, Al-Khatib SM. Amiodarone versus implantable cardioverter defibrillator for asymptomatic nonsustained ventricular tachycardia in nonischemic dilated cardiomyopathy. *Am Heart J* 2004;**147**: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. *Congest Heart Fail* 2007;**13:**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. *J Cardiovasc Transl Res* 2009;**2**: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. *Circ Heart Fail* 2010;**3**:650–8. [Reason for exclusion: population.]

Cleland JGF. New results from the CARE-HF programme. *ESC Congress Report* 2005, p. 13. URL: www.escardio.org/congresses/esc_congress_2005/Documents/ESC-Congress-HotLines-and-CTU-Reports-2005.pdf (accessed January 2014). [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? *Nat Clin Pract Cardiovasc Med* 2004;**1**:10–11. [Reason for exclusion: Outcome and study design.]

Cleland JG, Ghosh J, Freemantle N, Kaye GC, Nasir M, Clark AL, *et al.* Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-LIPIDS and cardiac resynchronisation therapy in heart failure. *Eur J Heart Fail* 2004;**6**:501–8. [Reason for exclusion: study design (review).]

Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al.* Baseline characteristics of patients recruited into the CARE-HF study. *Eur J Heart Fail* 2005;**7**:205–14. [Reason for exclusion: outcomes.]

Cleland JG, Freemantle N, Daubert JC, Toff WD, Leisch F, Tavazzi L. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF study. *Heart* 2008;**94**:278–83. [Reason for exclusion: study design.]

Curtis AB, Cannom DS, Bigger JT Jr, DiMarco JP, Estes NA III, Steinman RC, *et al.* Baseline characteristics of patients in the coronary artery bypass graft (CABG) Patch trial. *Am Heart J* 1997;**134**:787–98. [Reason for exclusion: outcomes.]

Cygankiewicz I, Gillespie J, Zareba W, Brown MW, Goldenberg I, Klein H, *et al.* Predictors of long-term mortality in Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) patients with implantable cardioverter-defibrillators. *Heart Rhythm* 2009;**6**:468–73. [Reason for exclusion: comparator and study design.]

Cygankiewicz I, McNitt S, Thomsen PEB, Kautzner J, Moss AJ, Zareba W. Heart rate turbulence predicts heart failure events in MADIT-CRT patients. 64th Annual Meeting of the Canadian Cardiovascular Society, Vancouver, Canada, 22–26 October 2011. [Reason for exclusion: comparator, outcomes and study design.]

Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, *et al.* Inappropriate implantable cardioverter-defibrillator shocks in MADIT II. *J Am Coll Cardiol* 2008;**51**:1357–65. [Reason for exclusion: comparator and study design.]

Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, *et al.* Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol* 2009;**54**:1837–46. [Reason for exclusion: population and intervention.]

De Marco T, Wolfel E, Feldman AM, Lowes B, Higginbotham MB, Ghali JK, *et al.* Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. *J Card Fail* 2008;**14**:9–18. [Reason for exclusion: intervention.]

Domanski MJ, Sakseena S, Epstein AE, Hallstrom AP, Brodsky MA, Kim S, *et al.* Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. AVID Investigators. Antiarrhythmics Versus Implantable Defibrillators. *J Am Coll Cardiol* 1999;**34**:1090–5. [Reason for exclusion: study design.]

Domanski MJ, Epstein A, Hallstrom A, Saksena S, Zipes DP. Survival of antiarrhythmic or implantable cardioverter defibrillator treated patients with varying degrees of left ventricular dysfunction who survived malignant ventricular arrhythmias. *J Cardiovasc Electrophysiol* 2002;**13**:580–3. [Reason for exclusion: study design (comparator).]

Dorian P, Hohnloser SH, Thorpe KE, Roberts RS, Kuck KH, Gent M, *et al.* Mechanisms underlying the lack of effect of implantable cardioverter-defibrillator therapy on mortality in high-risk patients with recent myocardial infarction: insights from the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT). *Circulation* 2010;**122**:2645–52. [Reason for exclusion: study design.]

Filho MM, Pedrosa AA, Costa R, Nishioka SA, Siqueira SF, Tamaki WT, *et al.* Biventricular pacing improves clinical behavior and reduces prevalence of ventricular arrhythmia in patients with heart failure. *Arq Bras Cardiol* 2002;**78**:110–13. [Reason for exclusion: comparator.]

Foley PW, Patel K, Irwin N, Sanderson JE, Frenneaux MP, Smith RE, *et al.* Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. *Heart* 2011;**97**:1041–7. [Reason for exclusion: abstract.]

Foster E, Solomon SD, McNitt S, Heintze J, Vogt J, Almendral J, *et al.* MADIT CRT: who are the super responders to cardiac resynchronisation therapy? *Europace* 2010;**12**:i50. [Reason for exclusion: comparator.]

Freudenberger RS, Hellkamp AS, Halperin JL, Poole J, Anderson J, Johnson G, *et al.* Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2007;**115**:2637–41. [Reason for exclusion: population and design.]

Giorgberidze I, Saksena S, Krol RB, Munsif AN, Kolettis T, Mathew P, *et al.* Risk stratification and clinical outcome of minimally symptomatic and asymptomatic patients with nonsustained ventricular tachycardia and coronary disease: a prospective single-center study. *Am J Cardiol* 1997;**80**:3–9F. [Reason for exclusion: intervention and study design.]

Gold MR, Daubert C, Sutton MSJ, Ghio S, Abraham WT, Linde C. Left ventricular reverse remodeling predicts mortality: results from the reverse study. *J Am Coll Cardiol* 2011;**57**(14 Suppl.):E11. [Reason for exclusion: population.]

Goldenberg I, Gillespie J, Moss AJ, Hall WJ, Klein H, McNitt S, *et al.* Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation* 2010;**122**:1265–71. [Reason for exclusion: study design.]

Goscinska-Bis K, Bis J, Krejca M, Ulczok R, Szmagala P, Bochenek A, *et al.* Totally epicardial cardiac resynchronization therapy system implantation in patients with heart failure undergoing CABG. *Eur J Heart Fail* 2008;**10**:498–506. [Reason for exclusion: intervention.]

Gould PA, Kong G, Kalff V, Duffy SJ, Taylor AJ, Kelly MJ, *et al.* Improvement in cardiac adrenergic function post biventricular pacing for heart failure. *Europace* 2007;**9**:751–6. [Reason for exclusion: population.]

Gradaus R, Seidl K, Korte T, Himmrich E, Wieneke H, Schuchert A, *et al.* Reduction of ventricular tachyarrhythmia by treatment of atrial fibrillation in ICD patients with dual-chamber implantable cardioverter/defibrillators capable of atrial therapy delivery: the REVERT-AF Study. *Europace* 2007;**9**:534–9. [Reason for exclusion: comparator.]

Hallstrom AP, McAnulty JH, Wilkoff BL, Follmann D, Raitt MH, Carlson MD, *et al.* Patients at lower risk of arrhythmia recurrence: a subgroup in whom implantable defibrillators may not offer benefit. Antiarrhythmics Versus Implantable Defibrillator (AVID) trial investigators. *J Am Coll Cardiol* 2001;**37**:1093–9. [Reason for exclusion: study design.]

Healey JS, Hohnloser SH, Exner DV, Birnie DH, Philippon F, Basta M, *et al.* Does cardiac resynchronization therapy improve outcomes in patients with chronic atrial tachyarrhythmias? Results from the resynchronization for ambulatory heart failure trial (RAFT). *Can J Cardiol* 2011;**27**(Suppl. 5):S335. [Reason for exclusion: abstract.]

Higgins SL, Daubert JL, Akhtar M. Who are the MADIT patients? Multicenter Automatic Defibrillator Implantation Trial. *Am J Cardiol* 1997;**80**:42–6F. [Reason for exclusion: comparator, outcomes and study design.]

Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland JG, Freemantle N, *et al.* Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. *Circulation* 2006;**114**:18–25. [Reason for exclusion: study design.]

Huang DT, Sesselberg HW, McNitt S, Noyes K, Andrews ML, Hall WJ, *et al.* Improved survival associated with prophylactic implantable defibrillators in elderly patients with prior myocardial infarction and depressed ventricular function: a MADIT-II substudy. *J Cardiovasc Electrophysiol* 2007;**18**:833–8. [Reason for exclusion: study design.]

Jiménez-Candil J, Arenal A, García-Alberola A, Ortiz M, del Castillo S, Fernández-Portales J, *et al.* Fast ventricular tachycardias in patients with implantable cardioverter-defibrillators: efficacy and safety of antitachycardia pacing. A prospective and randomized study. *J Am Coll Cardiol* 2005;**45**:460–1. [Reason for exclusion: comparator and study design.]

Kadish A, Schaechter A, Subacius H, Thattassery E, Sanders W, Anderson KP, *et al.* Patients with recently diagnosed nonischemic cardiomyopathy benefit from implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2006;**47**:2477–82. [Reason for exclusion: study design.]

Kadish AH, Bello D, Finn JP, Bonow RO, Schaechter A, Subacius H, *et al.* Rationale and design for the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) trial. *J Cardiovasc Electrophysiol* 2009;**20**:982–7. [Reason for exclusion: outcomes.]

Klein RC, Raitt MH, Wilkoff BL, Beckman KJ, Coromilas J, Wyse DG, *et al.* Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *J Cardiovasc Electrophysiol* 2003;**14**:940–8. [Reason for exclusion: comparator and study design.]

Knight BP, Desai A, Coman J, Faddis M, Yong P. Long-term retention of cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;**44**:72–7. [Reason for exclusion: comparator and study design.]

Kron J. Clinical significance of device-related complications in clinical trials and implications for future trials: insights from the Antiarrhytmics Versus Implantable Defibrillators (AVID) trial. *Card Electrophysiol Rev* 2003;**7**:473–8. [Reason for exclusion: comparator and study design.]

Kron J, Herre J, Renfroe EG, Rizo-Patron C, Raitt M, Halperin B, *et al.* Lead- and device-related complications in the Antiarrhythmics Versus Implantable Defibrillators trial. *Am Heart J* 2001;**141**:92–8. [Reason for exclusion: comparator and study design.]

Lau EW, Griffith MJ, Pathmanathan RK, Ng GA, Clune MM, Cooper J, *et al.* The Midlands Trial of Empirical Amiodarone versus Electrophysiology-Guided Interventions and Implantable Cardioverter-Defibrillators (MAVERIC): a multi-centre prospective randomised clinical trial on the secondary prevention of sudden cardiac death. *Europace* 2004;**6**:257–66. [Reason for exclusion: intervention (although the study is excluded, some details of the study are discussed in the report).]

Laveneziana P, O'Donnell DE, Ofir D, Agostoni P, Padeletti L, Ricciardi G, *et al.* Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. *J Appl Physiol* 2009;**106**:1574–83. [Reason for exclusion: outcomes.]

Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, *et al.* Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;**23**:1780–7. [Reason for exclusion: comparator.]

Lee KL, Hafley G, Fisher JD, Gold MR, Prystowsky EN, Talajic M, *et al.* Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. *Circulation* 2002;**106**:233–8. [Reason for exclusion: intervention and comparator (although the study is excluded, some details of the study are discussed in the report).]

Leon AR, Abraham WT, Curtis AB, Daubert JP, Fisher WG, Gurley J, *et al.* Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. *J Am Coll Cardiol* 2005;**46**:2348–56. [Reason for exclusion: study design (review).]

Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, *et al.* Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation In Cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;**40**:111–18. [Reason for exclusion: comparator and study design.]

Linde C, Braunschweig F, Gadler F, Bailleul C, Daubert JC. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC). *Am J Cardiol* 2003;**91**:1090–5. [Reason for exclusion: comparator and study design.]

Linde C, Gold M, Abraham WT, Daubert JC; REVERSE study group. Rationale and design of a randomized controlled trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with asymptomatic left ventricular dysfunction with previous symptoms or mild heart failure – the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Am Heart J* 2006;**151**:288–94. [Reason for exclusion: population, intervention and outcomes.]

Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, *et al.* Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–43. [Reason for exclusion: population and intervention.]

Linde C, Gold M, Abraham WT, Daubert JC; REVERSE study group. Baseline characteristics of patients randomized in the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. *Congest Heart Fail* 2008;**14**:66–74. [Reason for exclusion: population, intervention and outcomes.]

Linde C, Daubert C, Abraham WT, Gold MR, Hassager C, Herre JM, *et al.* The influence of left ventricular ejection fraction on the extent of reverse remodeling by cardiac resynchronization therapy in mild heart failure: results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *J Am Coll Cardiol* 2009;**53**(Suppl. 10):A183. [Reason for exclusion: population, intervention and outcomes.]

Linde C, Leman R, Daubert C, Abraham WT, Gold MR. Cardiac resynchronization therapy in mild heart failure: is there is difference in outcome between NYHA class I versus II? Results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial. *J Am Coll Cardiol* 2009;**53**(Suppl. 10):A188. [Reason for exclusion: abstract (insufficient details).]

Linde C, Abraham WT, Gold MR, Daubert C; REVERSE study group. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: results from the REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) study. *J Am Coll Cardiol* 2010;**56**:1826–31. [Reason for exclusion: population and intervention.]

Lindenfeld J, Feldman AM, Saxon L, Boehmer J, Carson P, Ghali JK, *et al.* Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. *Circulation* 2007;**115**:204–12. [Reason for exclusion: study design.]

Link MS, Moss AJ, Goldenburg I, Viskin S, Delnoy PP, Kutz A, *et al.* Prognostic implications of supraventricular tachycardia in CRT-D treated patients: the MADIT-CRT experience. *Europace* 2010;**12**(Suppl. 1):i136. [Reason for exclusion: comparator and outcomes.]

Martin DT, McNitt S, Nesto RW, Rutter MK, Moss AJ. Cardiac resynchronization therapy reduces the risk of cardiac events in patients with diabetes enrolled in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). *Circ Heart Fail* 2011;**4**:332–8. [Reason for exclusion: study design.]

Mathew J, Katz R, Dixit S, Gerstenfeld EP, Sutton MS, Gold MR, *et al.* Kidney disease and cardiac remodeling in patients with cardiac resynchronization therapy: results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Heart Rhythm* 2011;**8**(Suppl. 1):S496. [Reason for exclusion: abstract.]

Maynard C. Rehospitalization in surviving patients of out-of-hospital ventricular fibrillation (the CASCADE study). Cardiac Arrest in Seattle: Conventional Amiodarone Drug Evaluation. *Am J Cardiol* 1993;**72**:1295–300. [Reason for exclusion: intervention and comparator.]

Moore HJ, Fletcher RD, Platt MD, Boineau R, Anderson J, Johnson GW, *et al.* SCD-heft: non-sustained ventricular tachycardia on baseline Holter monitor association with appropriate implantable cardioverter defibrillator therapy for ventricular tachycardia and ventricular fibrillation. *Heart Rhythm* 2011;**8**(Suppl. 1):S138. [Reason for exclusion: comparator and study design.]

Moss AJ. Update on MADIT: the Multicenter Automatic Defibrillator Implantation Trial. The long QT interval syndrome. *Am J Cardiol* 1997;**79**:16–19. [Reason for exclusion: study design.]

Moss AJ. Background, outcome, and clinical implications of the Multicenter Automatic Defibrillator Implantation Trial (MADIT). *Am J Cardiol* 1997;**80**:28–32F. [Reason for exclusion: study design.]

Moss AJ, Fadl Y, Zareba W, Cannom DS, Hall WJ; Defibrillator Implantation Trial Research Group. Survival benefit with an implanted defibrillator in relation to mortality risk in chronic coronary heart disease. *Am J Cardiol* 2001;**88**:516–20. [Reason for exclusion: study design.]

Moss AJ, Greenberg H, Case RB, Zareba W, Hall WJ, Brown MW, *et al.* Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004;**110**:3760–5. [Reason for exclusion: comparator, outcomes and study design.]

Moss AJ. MADIT-CRT: the Multicentre Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy. *Eur J Heart Fail* 2009;**11**:1217–19. [Reason for exclusion: study design.]

Noyes K, Corona E, Veazie P, Dick AW, Zhao H, Moss AJ. Examination of the effect of implantable cardioverter-defibrillators on health-related quality of life: based on results from the Multicenter Automatic Defibrillator Trial-II. *Am J Cardiovasc Drugs* 2009;**9**:393–400. [Reason for exclusion: study design.]

Olshansky B, Wood F, Hellkamp AS, Poole JE, Anderson J, Johnson GW, *et al.* Where patients with mild to moderate heart failure die: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Am Heart J* 2007;**153**:1089–94. [Reason for exclusion: outcomes.]

Piccini JP, Al-Khatib SM, Hellkamp AS, Anstrom KJ, Poole JE, Mark DB, *et al.* Mortality benefits from implantable cardioverter-defibrillator therapy are not restricted to patients with remote myocardial infarction: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Heart Rhythm* 2011;**8**:393–400. [Reason for exclusion: study design.]

Piepoli MF, Villani GQ, Corra U, Aschieri D, Rusticali G. Time course of effects of cardiac resynchronization therapy in chronic heart failure: benefits in patients with preserved exercise capacity. *Pacing Clin Electrophysiol* 2008;**31**:701–8. [Reason for exclusion: intervention.]

Pietrasik G, Goldenberg I, McNitt S, Moss AJ, Zareba W. Obesity as a risk factor for sustained ventricular tachyarrhythmias in MADIT II patients. *J Cardiovasc Electrophysiol* 2007;**18**:181–4. [Reason for exclusion: study design.]

Piotrowicz K, Noyes K, Lyness JM, McNitt S, Andrews ML, Dick A, *et al.* Physical functioning and mental well-being in association with health outcome in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II. *Eur Heart J* 2007;**28**:601–7. [Reason for exclusion: study design.]

Raitt MH, Klein RC, Wyse DG, Wilkoff BL, Beckman K, Epstein AE, *et al.* Comparison of arrhythmia recurrence in patients presenting with ventricular fibrillation versus ventricular tachycardia in the

Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *Am J Cardiol* 2003;**91**:812–16. [Reason for exclusion: comparator, outcomes and study design.]

Raviele A, Bongiorni MG, Brignole M, Cappato R, Capucci A, Gaita F, *et al.* Early EPS/ICD strategy in survivors of acute myocardial infarction with severe left ventricular dysfunction on optimal beta-blocker treatment. The BEta-blocker STrategy plus ICD trial. *Europace* 2005;**7**:327–37. [Reason for exclusion: comparator.]

Saxon LA. The MIRACLE trial: an electrophysiologist's perspective. *J Card Fail* 2002;**8**:202–3. [Reason for exclusion: outcomes and study design.]

Saxon LA, Bristow MR, De Marco T, Krueger SK. Procedural outcomes and device performance in the COMPANION trial of resynchronization therapy for heart failure. *Circulation* 2004;**110**(Suppl. S):443. [Reason for exclusion: abstract (insufficient details).]

Saxon LA, Bristow MR, Boehmer J, Krueger S, Kass DA, De Marco T, *et al.* Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. *Circulation* 2006;**114**:2766–72. [Reason for exclusion: study design.]

Sesselberg HW, Moss AJ, McNitt S, Zareba W, Daubert JP, Andrews ML, *et al.* Ventricular arrhythmia storms in postinfarction patients with implantable defibrillators for primary prevention indications: a MADIT-II substudy. *Heart Rhythm* 2007;**4**:1395–402. [Reason for exclusion: comparator and study design.]

Siebels J, Cappato R, Ruppel R, Schneider MA, Kuck KH. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). CASH Investigators. *Am J Cardiol* 1993;**72**:109–13F. [Reason for exclusion: comparator.]

Siebels J, Cappato R, Ruppel R, Schneider MA, Kuck KH. ICD versus drugs in cardiac arrest survivors: preliminary results of the Cardiac Arrest Study Hamburg. *Pacing Clin Electrophysiol* 1993;**16**:552–8. [Reason for exclusion: comparator.]

Siebels J, Kuck KH. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). *Am Heart J* 1994;**127**:1139–44. [Reason for exclusion: comparator.]

Singh SN, Poole J, Anderson J, Hellkamp AS, Karasik P, Mark DB, *et al.* Role of amiodarone or implantable cardioverter/defibrillator in patients with atrial fibrillation and heart failure. *Am Heart J* 2006;**152**:974.e7–11. [Reason for exclusion: study design.]

St John Sutton M, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation* 2006;**113**:266–72. [Reason for exclusion: comparator and study design.]

St John Sutton M. Cardiac resynchronization therapy and reduced risk of death and nonfatal heart failure events. *Curr Heart Fail Rep* 2009;**6**:211–12. [Reason for exclusion: study design.]

St John Sutton M, Ghio S, Plappert T, Tavazzi L, Scelsi L, Daubert C, *et al.* Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class I/II heart failure. *Circulation* 2009;**120**:1858–65. [Reason for exclusion: population and intervention.]

Steinberg JS, Beckman K, Greene HL, Marinchak R, Klein RC, Greer SG, *et al.* Follow-up of patients with unexplained syncope and inducible ventricular tachyarrhythmias: analysis of the AVID registry and an AVID

substudy. Antiarrhythmics Versus Implantable Defibrillators. *J Cardiovasc Electrophysiol* 2001;**12**:996–1001. [Reason for exclusion: study design.]

Steinberg JS, Martins J, Sadanandan S, Goldner B, Menchavez E, Domanski M, *et al.* Antiarrhythmic drug use in the implantable defibrillator arm of the Antiarrhythmics Versus Implantable Defibrillators (AVID) study. *Am Heart J* 2001;**142**:520–9. [Reason for exclusion: comparator and study design.]

Steinberg JS, Fischer A, Wang P, Schuger C, Daubert J, McNitt S, *et al.* The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. *J Cardiovasc Electrophysiol* 2005;**16**:359–65. [Reason for exclusion: comparator and study design.]

Steinberg JS, Joshi S, Schron EB, Powell J, Hallstrom A, McBurnie M. Psychosocial status predicts mortality in patients with life-threatening ventricular arrhythmias. *Heart Rhythm* 2008;**5**:361–5. [Reason for exclusion: intervention, comparator and study design.]

Stellbrink C, Auricchio A, Butter C, Sack S, Vogt J, Bocker D, *et al.* Pacing Therapies in Congestive Heart Failure II study. *Am J Cardiol* 2000;**86**:138–43K. [Reason for exclusion: population and outcomes.]

Stellbrink C, Morgan J, Schalij M, Padeletti L, Brugada J, Boccanelli S, *et al.* Cardiac resynchronization therapy benefits patients with or without ICD indication – results from the prospective European multicenter PACMAN trial. *Circulation* 2004;**110**(Suppl. S):726. [Reason for exclusion: abstract.]

Sze E, Moss AJ, McNitt S, Barsheshet A, Andrews ML, Zareba W, *et al.* Risk factors for recurrent heart failure events in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). *J Cardiovasc Electrophysiol* 2010;**21**:1217–23. [Reason for exclusion: study design.]

Tang AS, Wells GA, Talajic M, Arnold O, Sheldon R, Connolly S, *et al.* The Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Circulation* 2010;**122**:2216. [Reason for exclusion: outcomes.]

US Food and Drug Administration. *Summary of Safety and Effectiveness Data. P030035/S3*. Washington, DC: US Food and Drug Administration; 2005. [Reason for exclusion: FDA report with insufficient details (no baseline characteristics).]

Vorobiof G, Goldenberg I, Moss AJ, Zareba W, McNitt S. Effectiveness of the implantable cardioverter defibrillator in blacks versus whites (from MADIT-II). *Am J Cardiol* 2006;**98**:1383–6. [Reason for exclusion: study design.]

Wever EF, Hauer RN, van Capelle FL, Tijssen JG, Crijns HJ, Algra A, *et al.* Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in postinfarct sudden death survivors. *Circulation* 1995;**91**:2195–203. [Reason for exclusion: comparator.]

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**:489–96. [Reason for exclusion: comparator.]

Wever EFD, Ramanna H, Hauer RNW, Robles de Medina EO. Cardioverter-defibrillator implantation: better first-choice strategy for postinfarction cardiac arrest survivors. *Cardiol Rev* 1996;**13**:28–33. [Reason for exclusion: comparator.]

Whang W, Bigger JT Jr. Diabetes and outcomes of coronary artery bypass graft surgery in patients with severe left ventricular dysfunction: results from the CABG Patch trial database. The CABG Patch Trial

Investigators and Coordinators. *J Am Coll Cardiol* 2000;**36**:1166–72. [Erratum published in *J Am Coll Cardiol* 2001;**37**:2012.] [Reason for exclusion: study design.]

Wijetunga M, Strickberger SA. Comparison of therapies for nonischemic dilated cardiomyopathy. *Cardiol Rev* 2004;**21**:18–20. [Reason for exclusion: study design.]

Wittenberg SM, Cook JR, Hall WJ, McNitt S, Zareba W, Moss AJ, *et al.* Comparison of efficacy of implanted cardioverter-defibrillator in patients with versus without diabetes mellitus. *Am J Cardiol* 2005;**96**:417–19. [Reason for exclusion: study design.]

Woo GW, Petersen-Stejskal S, Johnson JW, Conti JB, Aranda JA Jr, Curtis AB. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: analysis of the MIRACLE study. *J Interv Card Electrophysiol* 2005;**12**:107–13. [Reason for exclusion: study design.]

Zareba W, Piotrowicz K, McNitt S, Moss AJ; MADIT II Investigators. Implantable cardioverter-defibrillator efficacy in patients with heart failure and left ventricular dysfunction (from the MADIT II population). *Am J Cardiol* 2005;**95**:1487–91. [Reason for exclusion: study design.]

Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, *et al.* Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**123**:1061–72. [Reason for exclusion: study design.]

References unobtainable from The British Library

Gold MR, Linde C, Abraham WT, Gardiwal A, Daubert JC. The impact of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in mild heart failure. *Heart Rhythm* 2011;**8**:679–84.

Recent abstract or conference presentations excluded because of insufficient details to allow appraisal of methodology and assessment of results

Abraham W, Gras D, Birgersdotter-Green U, Calo L, Clyne C, Klein N, *et al.* Response to cardiac resynchronization therapy varies with gender: sub-analysis from the FREEDOM trial. *Europace* 2011; Abstract P1163.

Arnold JM, Newton G, Mielniczuk L, Talajic M, Yee R, Wells GA, *et al.* Cardiac resynchronization therapy is an effective therapy for patients with impaired renal function. *Circulation* 2011;**124**:A16054.

Bardy G, Lee K, Mark D, Poole J, Fishbein D, Boineau R, *et al.* Long term follow-up in the Sudden Cardiac Death Heart Failure Trial (SCD-HEFT). *Heart Rhythm* 2012;**9**:1579.

Birnie D, Ha A, Higginson L, Green M, Thibault B, Wells G, *et al.* Importance of ECG morphology in determining response to cardiac resynchronization therapy: results from Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Can J Cardiol* 2011;**27**(Suppl. 5):S242–3.

Chapa D, Thomas SA, Friedmann E. Results of PFOS trial. *Heart Lung* 2010;**39**:352.

Daubert JP, Hranitzky PM, McNitt S, Klein HU, Gold MR, Wilber DJ, *et al.* MADIT-CRT: resynchronization patients experience more complications than ICD-only patients but outcomes are not significantly impacted. *Circulation* 2011;**124**:A9364.

Diab I, Kamdar R, Hunter R, Berriman T, Abrams D, Dhinoja M, *et al.* Value of echocardiographic mechanical dyssynchrony assessment in selecting patients for cardiac resynchronization therapy. *J Interv Card Electrophysiol* 2010;**27**:182.

Gillis AM, Kerr C, Philippon F, Newton G, Talajic M, Froeschl M, *et al.* Impact of CRT on hospitalizations in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Heart Rhythm* 2011;**8**(Suppl. 1):S494.

Healey J, *et al.* Effect of cardiac resynchronization on the development of atrial fibrillation: a report from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Heart Rhythm* 2012;**9**(Suppl. 1):S371.

Jamerson D, Tomkins C, McNitt S, Polonsky B, Zareba W, Moss A. Early procedure-related adverse events by gender in MADIT-CRT. *J Am Coll Cardiol* 2012;**59**(Suppl. 1):E919.

Parkash R, Thibault B, Sterns L, Sapp JL, Krahn A, Talajic M, *et al.* The fidelis lead fracture occurs more frequently in patients with cardiac resynchronization therapy. Report from the device committee of the resynchronization/defibrillation for ambulatory heart failure (RAFT) study. *Heart Rhythm* 2011;**8**(Suppl. 1):S121–2.

Romanov A, Pokushalov E, Prohorova D, Cherniavsky A, Shabanov V, Goscinska-Bis K, *et al.* Coronary artery bypass grafting with concomitant cardiac resynchronization therapy in patients with ischemic heart failure: Results from a multicenter study. *Europace* 2010;**12**(Suppl. 1):i50.

Talajic M, Gillis AM, Healey JS, Mitchell LB, Sapp JL, Tung S, *et al.* Effect of CRT on mode of death in patients with heart failure receiving an ICD: Results from the resynchronization-defibrillation for ambulatory heart failure trial (RAFT). *Heart Rhythm* 2011;**8**(Suppl. 1):S63.

Talajic M, Yetisir E, Mitchell LB, Luce M, Theoret-Patrick P, Wells GA, *et al.* Long-term device-related adverse events after cardiac resynchronization therapy: insights from the resynchronization-defibrillation for ambulatory heart failure trial (RAFT). *Circulation* 2011;**124**:A13983.

Talajic M, Yetisir E, Mitchell LB, Luce M, Theoret-Patrick P, Wells GA, *et al.* Adverse events associated with cardiac resynchronization therapy (CRT): Insights from the resynchronization-defibrillation for ambulatory heart failure trial (RAFT). *Can J Cardiol* 2011;**27**(Suppl.):S243–4.

Thibault B, Ducharme A, Harel F, White M, O'Meara E, Roy D, *et al.* Resynchronization therapy does not help heart failure patients with a QRS duration < 120 ms. *Eur Heart J* 2011;**32**(Suppl. 1):148.

Appendix 5 Ongoing trials

Five relevant trials in progress were identified by the searches:

- ICD2 (Implantable Cardioverter Defibrillator in Dialysis patients) trial – 'A prospective randomised controlled trial to evaluate the prevention of sudden cardiac death using implantable cardioverter defibrillators in dialysis patients' (ISRCTN20479861). This trial aims to determine whether or not ICD therapy in dialysis patients aged 55–80 years will result in a significant reduction in sudden cardiac (arrhythmic) death rates compared with no ICD therapy. This is a multicentre RCT carried out in the Netherlands. Start date: 1 April 2007; end date: 1 April 2017. Funding: Biotronik Nederland BV.
- DANISH (Efficacy of ICD in Patients with Non-Ischemic Systolic Heart Failure) trial – '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 multicentre RCT carried out in Denmark. Start date: December 2007; end date: December 2012. Funding: not stated.
- REFINE-ICD (Risk Estimation Following Infarction, Noninvasive Evaluation) trial – 'Efficacy of implantable defibrillator therapy after a myocardial infarction' (NCT00673842). This trial aims to determine whether prophylactic ICD therapy reduces mortality in MI survivors with better-preserved left ventricular function compared with standard medical care and standard post-MI treatment. This is a multicentre RCT carried out 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) trial (NCT00683696). This trial aims to evaluate the effects of CRT-D on mortality and morbidity of patients with HF as a result of LVSD, already receiving OPT, with a narrow QRS width and echocardiographic evidence of ventricular dyssynchrony, compared with OPT only and CRT-D off. This is an international multicentre RCT (including Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, France, Germany, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, the UK and the USA). Start date: August 2008; end date: December 2012. Funding: Biotronik, Inc.
- ADOPT trial – 'Assessment of efficacies of cardiac resynchronization therapies (CRT-P/D) for heart failure patients in China' (ChiCTR-TRC-09000574). This trial aims to evaluate whether CRT-P/D in addition to OPT can further reduce mortality, improve congestive HF symptoms and enhance QoL compared with OPT alone in Chinese congestive HF patients. This is a multicentre RCT carried out in China. Start date: October 2008; end date: December 2012. Funding: Medtronik, Inc.

Appendix 6 Hospitalisations: total, cardiac and non-cardiac

People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony

Number of patients hospitalised

The CARE-HF trial[109] 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, mean days in hospital after 3 months and mean days in hospital overall during the entire study (median 29.6 months). The COMPANION trial[120] reported data for all hospital admissions, cardiac admissions and non-cardiac admissions.

CRT-P compared with optimum pharmacological therapy

In the CARE-HF trial[109] there were statistically significantly fewer unplanned hospitalisations for a major cardiovascular event with CRT-P than with OPT (31% vs. 46% respectively; HR 0.61, 95% CI 0.49 to 0.77; $p < 0.001$). The mean number of days in hospital overall was also lower with CRT-P than with OPT, but no statistical comparisons for these outcomes were reported (*Table 152*). Similarly, in the COMPANION trial,[120] the rates of all hospital admissions (CRT-P 63% vs. OPT 65%; $p = 0.02$) and cardiac admissions (CRT-P 49% vs. OPT 53%; $p < 0.01$) were both statistically significantly lower with CRT-P than with OPT. However, the rate of non-cardiac hospital admissions was higher with CRT-P than with OPT (36% vs. 27% respectively), but no statistical comparison was reported.

CRT-D compared with optimum pharmacological therapy

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 than with OPT in the COMPANION trial (see *Table 152*).[120] However, non-cardiac hospital admissions were higher with CRT-D than with OPT (35% vs. 27% respectively), but no statistical comparison was reported.

CRT-P compared with cardiac CRT-D

The authors of the COMPANION trial[120] state that no significant differences were found in any of the hospital end points for CRT-P compared with CRT-D, but no statistics were reported (see *Table 152*).

Number of events/days of admission

CRT-P compared with optimum pharmacological therapy

The CARE-HF trial[109] 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 153*). The COMPANION trial[120] found statistically significantly fewer admissions per patient-year for a cardiac procedure for those receiving CRT-P (CRT-P 0.13 vs. OPT 0.24; $p < 0.01$). The number of average admissions per patient-year of follow-up was lower for those receiving CRT-P (CRT-P 1.25 vs. OPT 1.59). The average number of hospital days per patient-year of follow-up was also lower for CRT-P (CRT-P 8.3 vs. OPT 11.0), with the average length of hospital stay per admission similar for both treatment groups (CRT-P 6.7 days vs. OPT 6.9 days). The average number of hospital admissions per patient-year of follow-up was lower with CRT-P for cardiac causes (CRT-P 0.79 vs. OPT 1.20) but higher for non-cardiac causes (CRT-P 0.46 vs. OPT 0.39 admissions). Average number of 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 treatment groups.

TABLE 152 All hospitalisations: number of patients

Study	Outcome and follow-up	CRT-P, *n*/*N* (%)	OPT, *n*/*N* (%)	Effect	95% CI; *p*-value
CARE-HF[109]	Major cardiovascular event, 29.4 months[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 of 29.6 months)	20.7, median 9 (IQR 4–26)	22.4, median 9 (IQR 0–31)	–	–
MIRACLE[121]	Hospitalisations unrelated to HF or function of left ventricular lead	37/228 (16.2)	33/225 (14.7)	–	–
COMPANION[120b]	All admissions, CRT-P 16.2 months, OPT 11.9 months[c]	388/617(63)	199/308 (65)	–	0.02
	Cardiac admissions	301/617 (49)	164/308 (53)	–	< 0.01
	Non-cardiac admissions	222/617 (36)	84/308 (27)	–	–
		CRT-D, *n*/*N* (%)	**OPT, *n*/*N* (%)**		
	All admissions, CRT-D 15.7 months, OPT 11.9 months[c]	372/595 (63)	199/308 (65)	–	0.03
	Cardiac admissions	284/595 (48)	164/308 (53)	–	< 0.01
	Non-cardiac admissions	207/595 (35)	84/308 (27)	–	

a Mean.
b The authors of the COMPANION trial[116] state that no significant differences were found in any of the end points for CRT-P vs. CRT-D (no *p*-values reported).
c Median.

TABLE 153 All hospitalisations: number of events and/or of days of admission

Study	Outcome and follow-up	CRT-P	OPT	Effect	95% CI; *p*-value
CARE-HF[109]	No. of unplanned hospitalisations for a major cardiovascular event, 29.4 months[a]	222	384	–	–
COMPANION[120b]	No. of admissions (% of total admissions), no. of average admissions per patient-year of follow-up; CRT-P 16.2 months, OPT 11.9 months[a]				
	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 hospital days per patient-year of follow-up (average length of stay per admission in days); CRT-P 16.2 months, OPT 11.9 months[a]				
	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 a 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 months, OPT 11.9 months[a]				
	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 hospital days per patient-year of follow-up (average length of stay per admission in days); CRT-D 15.7 months, OPT 11.9 months[a]				
	All admissions	8.6 (7.2)	11.0 (6.9)	–	–
	Cardiac	5.5 (7.2)	8.1 (6.8)	–	–
	Non-cardiac	3.8 (8.8)	2.8 (7.1)	–	–
	No. of admissions per patient-year for a cardiac procedure	0.09	0.24	–	< 0.01

n/a, not applicable; NS, not significant.
a Median.
b The COMPANION trial[116] states that no significant differences were found in any of the end points for CRT-P vs. CRT-D (no *p*-values reported).

CRT-D compared with optimum pharmacological therapy

The COMPANION trial[120] reported statistically significantly fewer hospital admissions per patient-year for a cardiac procedure in those receiving CRT-D (CRT-D 0.09 vs. 0.24 OPT; $p < 0.01$). The number of average admissions per patient-year of follow-up was lower in those receiving CRT-D (CRT-D 1.20 vs. 1.59 OPT). The average number of hospital days per patient-year of follow-up was also lower in those receiving CRT-D (8.6 days vs. 11.0 days OPT), with the average length of hospital stay per admission similar for both treatment groups (CRT-D 7.2 days vs. OPT 6.9 days). Those receiving 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 days vs. OPT 8.1 days) and non-cardiac (CRT-D 3.8 days vs. OPT 2.8 days) causes, and average length of stay per hospital admission for cardiac (CRT-D 7.2 days vs. OPT 6.8 days) and non-cardiac (CRT-D 8.8 days vs. OPT 7.1 days) causes were similar for both treatment groups (see *Table 153*).

CRT-P compared with CRT-D

The authors of the COMPANION study[120] state that no significant differences were found in any of the hospitalisation end points for CRT-P vs. CRT-D, but statistics were not reported.

People with both conditions

The RAFT study[140] reported that a similar proportion of participants (about 56%) in each group were hospitalised at least once (*Table 154*), 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,[136] although the mean length of stay was slightly reduced with CRT-D [mean 4.8 days (SD 4.9 days) vs. mean 5.4 days (SD 4.7 days); $p = 0.06$]. All-cause hospitalisations were slightly lower with CRT-D in the Pinter study[139] (30.6% vs. 36.1%).

TABLE 154 All hospitalisations

Study	Outcome and follow-up	CRT-D, *n*/*N* (%)	ICD, *n*/*N* (%)	Effect	95% CI; *p*-value
MIRACLE ICD[136]	Hospitalisation, 6 months	85/187 (45.5)	78/182 (42.9)	–	–
	Length of hospital stay (days), mean (SD)	4.8 (4.9)	5.4 (4.7)	–	0.06
Pinter[139]	Patients hospitalised, 6 months	11/36[a] (30.6)	13/36[a] (36.1)	–	–
RAFT[140]	One or more hospitalisations during follow-up (mostly cardiovascular reasons), 40 (SD 20) months[b]	509/894 (56.9)	509/904 (56.3)	–	–
	Hospitalisation: cardiac cause	423/894 (47.3)	404/904 (44.7)	HR 1.04	0.56

a Numerator calculated by reviewer.
b Mean.

Appendix 7 Data extraction: people at risk of sudden cardiac death as a result of ventricular arrhythmias

Amiodarone Versus Implantable Cardioverter-Defibrillator Randomized Trial (AMIOVIRT)

Reference and design	Intervention and comparator	Participants	Outcome measures
Strickberger *et al.* 2003,[69] Wijetunga and Strickberger, 2003[70] *Study design*: RCT *Country*: USA *No. of centres:* 10 *Funding*: unrestricted research grant from the guidant corporation	*Intervention*: ICD + OPT (ICDs were inserted using conventional non-thoracotomy techniques) *Comparator*: Amiodarone + OPT (dose: 800 mg/day for first week, 400 mg/day for 1 year and then 300 mg/day) *Other interventions used*: OPT with ACE inhibitors, beta-blockers and potassium-sparing diuretics was strongly encouraged and attempted throughout the duration of the study for both groups	*Indication for treatment*: NIDCM and asymptomatic NSVT *No. of randomised participants:* 103; ICD: 51 OPT: 52 *Inclusion criteria*: age ≥ 18 years; NIDCM (left ventricular dysfunction in the absence of, or disproportionate to the severity of, coronary artery disease); LVEF ≤ 0.35; asymptomatic NSVT (three or more consecutive ventricular premature depolarisations with a rate of > 100 beats per minute, lasting < 30 seconds and not associated with symptoms of cerebral hypofusion); NYHA class I–III *Exclusion criteria*: syncope; pregnancy; a contraindication to amiodarone or defibrillator therapy or concomitant therapy with a class I AAD; or NIDCM diagnosed within 6 months[70]	*Primary outcome*: total mortality *Secondary outcomes*: SCD, non-SCD, non-cardiac death, syncope, arrhythmia-free survival, QoL and costs *Method of assessing outcomes*: stored ECGs and all available clinical data were used to determine the appropriateness of ICD therapy. Causes of death were determined by an events committee, with each of the three members independently evaluating all information available regarding each death. Differences in the cause of death were adjudicated and a consensus reached QoL: completed by patients both at the time of randomisation and during follow-up visits: • QWBS – score range 0–110 (higher level of general well-being associated with a higher value) • STAI – score range 40–160 (higher 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 study entry (not data extracted)

Reference and design	Intervention and comparator	Participants	Outcome measures
			Amiodarone group: assessed for thyroid function and aspartate and alanine transaminase plasma levels; chest radiograph 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 treatment (until 30 June 2001) ICD group: defibrillator follow-up was performed every 4 months, including evaluation of stored ECGs and sensing and pacing functions *Definitions*: arrhythmia-free survival: freedom from death, syncope, appropriate ICD therapy and sustained VT or VF *Length of follow-up*: mean duration 2.0 years (SD 1.3 years, range 0.1–4.8 years); ICD 2.2 years (SD 1.2 years); amiodarone 1.8 years (SD 1.4 years), $p = 0.4$ *Recruitment:* August 1996–September 2000

NIDCM, non-ischaemic dilated cardiomyopathy.

Participant characteristics

Characteristic	ICD ($n = 51$)	Amiodarone ($n = 52$)	p-value
Age (years), mean (SD)	58 (11)	60 (12)	0.5
Sex, % male	67	74	0.3
Ethnicity	NR	NR	
NYHA classification, %			0.9
I	18	13	
II	64	63	
III	16	24	
LVEF, mean (SD)	0.22 (0.10)	0.23 (0.08)	0.5
Heart rate (bpm), mean (SD)	80 (17)	78 (14)	0.7
RBBB, %	16	8	0.2
LBBB, %	42	53	0.3
Electrophysiology findings			
No. of beats of NSVT, mean (SD)	8 (7)	12 (21)	0.2
NSVT (bpm), mean (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	NR	NR	
Duration of NIDCM (years), mean (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	NR	NR	
Comorbidities			
Diabetes mellitus, %	31	36	0.6
Hypertension, %	58	67	0.4
QWBS, mean (SD)	67 (15)	70 (17)	0.5
STAI, mean (SD)	75 (25)	79 (21)	0.5

bpm, beats per minute; CAD, coronary artery disease; NIDCM, non-ischaemic dilated cardiomyopathy; NR, not reported; RBBB, right bundle branch block.
a CAD > 70% = one major epicardial coronary artery with stenosis ≥ 70%.

Results

Outcome	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	1 (25)	2 (40)	0.7
Non-SCD	3 (75)	3 (60)	0.7
Survival rate, %			
At 1 year	96	90	0.8
At 3 years	88	87	
Arrhythmia-free survival rate, %			
At 1 year	78	82	0.1
At 3 years	63	73	
Non-cardiac death, *n* (%)	2 (33)	2 (29)	0.9
Cardiac transplant, *n* (%)	1 (2)	2 (4)	0.8
Syncope, %	3.9[a]	5.8	0.7
HRQoL			
QWBS 1 year, mean (SD)	74 (19)	70 (22)	0.5[b]
STAI 1 year, mean (SD)	61 (17)	67 (20)	0.4[b]

a VT 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).

Comments

- Kaplan–Meier estimates of cumulative survival and arrhythmia-free survival also displayed in figures for 0–55 months.
- At 1 year, the QWBS and STAI scores were not significantly different between patients treated with an ICD who did [67 (SD 15) 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

Drug therapy	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

Comment

- Amiodarone group: mean dose at the conclusion of the study: 303 (SD 93) mg/day. 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 because of adverse side effects (mean 17.8, SD 13.3, range 1.2–43.8 months)[a]

a States in the discussion that amiodarone was discontinued in one-third of patients but data not reported per treatment group.

Comments

- All ICD implants were successful.
- An appropriate ICD therapy was delivered in 16 patients for ventricular arrhythmias, which had a mean rate of 218 (SD 40, range 170–284) beats per minute.

Comments

Methodological comments

- *Allocation to treatment groups*: randomisation was stratified by centre (patients who refused study participation were followed in a voluntary registry).
- *Blinding*: unblinded 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 end points were compared between the two 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 the Student's *t*-test, except for comparisons between baseline and 1-year QoL scores within the two 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*-value of < 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/dropout*: states that no patients were lost to 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 (months): mean 26.1 (SD 16.9) after study entry. ICD patients also receiving amiodarone ($n = 11$): frequent appropriate defibrillator therapies ($n = 1$; 200 mg/day, SD 0 mg/day), atrial fibrillation ($n = 8$; 200 mg/day, SD 0 mg/day), other reasons ($n = 2$; 150 mg/day, SD 71 mg/day).

General comments

- *Generalisability*: only to patients with NIDCM and asymptomatic NSVT.
- *Outcome measures*: appear appropriate.
- *Intercentre variability*: not reported.
- *Conflict of interests*: none reported, but supported by grant from Guidant Corporation.

NIDCM, non-ischaemic dilated cardiomyopathy.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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	No blinding
QoL	High	May be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment		
Mortality	Low	Members of independent events review committee assessing causes of death were blinded
QoL	High	May be influenced by lack of blinding
Attrition bias		
Incomplete outcome data addressed	Low	States that all analyses were based on ITT; no patients lost to follow-up
Reporting bias		
Selective reporting	Low	No study protocol available but results for specified primary and secondary outcomes were reported
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Antiarrhythmics Versus Implantable Defibrillators (AVID) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
AVID investigators 1997,[71] 1999,[72] Hallstrom 1995,[73] Schron *et al*. 2002[74] *Study design*: RCT Countries: USA and Canada *No. of centres:* 56 (53 USA, three Canada) *Funding*: National Heart, Lung, and Blood Institute, Bethesda, MD; contract N01-HC-25117	*Intervention*: ICDs; investigators chose any 'state-of-the-art' ICD meeting prespecified criteria *Comparator*: best contemporary 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 electrophysiological testing, Holter monitoring or both) *Other interventions used*: aspirin, beta-blockers and ACE inhibitors when clinically appropriate	*Indication for treatment*: resuscitated from near-fatal VF; or symptomatic sustained VT with hemodynamic compromise *No. of randomised participants*: 1016; ICD: 507 (93% non-thoracotomy lead system, 5% epicardial system, 2% no device implanted), AAD: 509 [356 began immediate treatment with amiodarone; remaining 153 randomised to amiodarone ($n = 79$) or sotalol ($n = 74$)] QoL substudy:[74] 800; ICD: 416, AAD: 384 *Inclusion criteria*: VF, VT with syncope or VT without syncope but with ejection fraction ≤ 0.40 and systolic blood pressure < 80 mmHg, chest pain or near syncope.[73] If patients underwent revascularisation their ejection fraction had to be ≤ 0.40 *Exclusion criteria*: contraindication to amiodarone or ICD 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 HF, life expectancy < 1 year[73]	*Primary outcome*: overall mortality *Secondary outcomes*: cost, QoL *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[74] at baseline (before randomisation) and 3, 6 and 12 months after randomisation: • SF-36: overall score, PCS and MCS, score range 0–100; higher scores indicate superior QoL • the 46-item patient concerns checklist (disease specific), score range 0–46; higher sores indicate increased concern and poorer QoL • cardiac version of the QoL index, score range 0–30; higher score indicates superior QoL (this measure administered at baseline and 12 months only) Defibrillator shocks categorised as appropriate or inappropriate on the basis of clinical presentation, R–R intervals and ECGs *Length of follow-up*: mean 18.2 (SD 12.2) months. For QoL substudy[74] follow-up was 1 year *Recruitment*: 1 June 1993 to 7 April 1997

Main study

Participant characteristics

Characteristic	ICD ($n = 507$)	AAD ($n = 509$)	*p*-value
Age (years), mean (SD)	65 (11)	65 (10)	
Sex, % male	78	81	
Ethnicity, % white	87	86	
Index arrhythmia VF, *n*	226	229	
Index arrhythmia sustained VT, *n*	281	280	
CHF at enrolment, %			
No CHF	45	40	
NYHA class I or II	48	48	
NYHA class III[a]	7	12	
Angina at enrolment, %			
No angina	64	65	
CCS class I or II	34	33	
CCS class III	2	2	
LVEF, mean (SD)	0.32 (0.13)	0.31 (0.13)	
Median time from index event to measurement (days)	3	3	
Findings on baseline ECG[b]			
Heart rate (bpm), mean (SD)	77 (18)	78 (17)	
PR interval (milliseconds), mean (SD)	178 (37)	183 (37)	
QRS complex (milliseconds), mean (SD)	116 (26)	117 (26)	
Corrected QT interval (milliseconds), mean SD	441 (40)	445 (39)	
Paced, %	3	4	
Bundle branch block, %	23	25	
Clinical history before index arrhythmia, %			
Atrial fibrillation or flutter[a]	21	26	
VF	5	5	
VT	14	15	
Unexplained syncope	11	15	
Coronary artery disease	81	81	
MI	67	67	
CHF	46	47	
Hypertension	55	56	
Diabetes	25	24	
Angina	48	50	
Peripheral vascular disease	16	15	
AAD therapy	16	15	
Coronary revascularisation during hospitalisation for the index arrhythmia, %	10	12	

	ICD ($n = 497$)	AAD ($n = 496$)	
Therapy at discharge, %[c]			
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 AAD	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	
Acetylsalicylic acid (aspirin)	60.7	59.2	
Warfarin	21.9	34.8	

bpm, beats per minute; CCS, Canadian Cardiovascular Society.
a Paper stated that baseline characteristics are similar in the two groups except for NYHA class III HF and history of atrial fibrillation or flutter.
b Recorded when patients were taking no AADs and without cardiac pacing.
c 23 patients are excluded: 19 who died while in hospital after the index event and four who were still in hospital at the termination of the study.
d Unclear in paper whether *p*-value applies at discharge or 12 or 24 months' follow-up or overall.

Results

Outcome	ICD ($n = 507$)	AAD ($n = 509$)	p-value
Deaths, *n/N*	80/507	122/509	< 0.012
Cause of death, *n*[72]			
Cardiac death	63	94	
Arrhythmic	24	55	
Non-arrhythmic	39	39	
Non cardiac death	17	28 (three attributed to pulmonary toxicity from 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)	
Survival free of cardiac death[72] (non-cardiac deaths censored), %			0.0042
At 1 year	90.9	85.1	
At 2 years	85.0	81.2	
Survival to arrhythmic death[72] (non-cardiac and non-arrhythmic deaths censored), %			0.0002
At 1 year	96.6	91.9	
At 2 years	94.2	89.1	
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, %			< 0.02 in favour of ICD
Patients surviving at 1 year	89.3	82.3	
Patients surviving at 2 year	81.6	74.7	
Patients surviving at 3 year	75.4	64.1	
Cumulative % of patients with any activation of the ICD (antitachycardia pacing or shock)	Index VF[a] / Index VT[a]		< 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 $n = 1011$)			0.04
At 1 year	59.5	55.6	
At 2 years	74.8	64.7	
At 3 years	83.3	75.5	
Change in NYHA class	NR	NR	
Change in LVEF	NR	NR	
Exercise capacity outcomes	NR	NR	

Outcome	ICD ($n = 507$)		AAD ($n = 509$)		p-value
Crossover rate, %					
At 1 year	17.7		12.6		< 0.001
At 2 years	25.7		18.9		
At 3 years	33.7		24.3		
Therapy at follow-up, %	12 months ($n = 338$)	24 months ($n = 171$)	12 months ($n = 306$)	24 months ($n = 162$)	
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 AAD	7.1	10.0	3.8	4.0	
ACE inhibitor	68.4	68.1	65.5	63.1	
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	
Acetylsalicylic acid (aspirin)	55.4	62.5	55.4	56.4	
Warfarinftsa	24.8	22.5	35.4	30.2	

NR, not reported.

a Numbers not reported. 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).

Comments

- A Kaplan–Meier plot of overall survival is presented. The survival figures represent a decrease in death rate (±95% CI) of 39 ± 20%, 27 ± 21% and 31 ± 21% at 1, 2 and 3 years respectively. The authors note that the accuracy of long-term data is limited because few patients had been followed beyond 2 years at the time that the study ended. The average unadjusted length of additional life with an ICD (not clear if just those in the ICD group or all those with an ICD in the study) was 2.7 months at 3 years.
- The location of death (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 that the study was stopped. The groups that these patients were in are not reported.
- The study 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

Adverse effect	ICD	Amiodarone	Sotalol	*p*-value
Non-fatal torsade de pointes VT, *n*		1		
Suspected pulmonary toxicity in patients treated with amiodarone, %				
At 1 year		3		
At 2 years		5		
Death from pulmonary toxicity, *n*		1		
Thyroid replacement medication, %				
At 1 year	1	10		
At 2 years	1	16		
Death within 30 days of initiation of therapy, *n/N* (%)[a]	12/507 (2.4)	18/509 (3.5)		0.27
Bleeding requiring reoperation or transfusion, *n*	6			
Serious haematoma, *n*	13			
Infection, *n*	10			
Pneumothorax, *n*	8			
Cardiac perforation, *n*	1			
Early dislodgement or migration of leads, *n*	3			
Unsuccessful first attempt at ICD implantation without thoracotomy, *n*	5[b]			
Overall rate of non-fatal complications of implantation, % (reported in discussion)	5.7			

a Or by the time of hospital discharge if discharge occurred later than 30 days after therapy began.
b 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.

Comments

- Two linked excluded studies, Kron *et al.*[234,235] provide data on lead- and device-related complications, including time-to-event data with Kaplan–Meier curves, but these data have not been extracted.
- A linked excluded study, Klein *et al.*,[236] 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[71]

Subgroup	HR	95% CI	*p*-value
Age (years)			
< 60	0.57	0.31 to 1.05	
60–69	0.63	0.38 to 1.04	
≥ 70	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			
VF	0.57	0.38 to 0.86	
VT	0.68	0.46 to 1.02	
Overall	0.62	0.47 to 0.83	

Comments

- HRs 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, CHF, 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 differences in the presence or absence of HF, 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[72]

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, with twice as many deaths in the AAD group ($p = 0.0019$). Survival curves presented but not extracted		
Non-arrhythmic cardiac death	No difference in survival between ICD and AAD groups in patients with either VT ($p = 0.72$) or VF ($p = 0.98$)		

Quality-of-life substudy[74]

Participant characteristics

Characteristic	ICD ($n = 416$)	AAD ($n = 384$)	*p*-value
Age (years), mean (SD)	64.3 (10.5)	64.7 (10.1)	0.5
Sex, % 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
Index arrhythmia VF, %	43.5	42.4	0.8
LVEF, mean (SD)	0.33 (0.13)	0.32 (0.14)	0.6
History of HF, %	44.5	41.1	0.3
Discharge beta-blocker use, %	43.0	16.4	< 0.001

Results

Outcome	ICD ($n = 416$)	AAD ($n = 384$)	p-value
SF-36 PCS score, mean (SD)			
Baseline	37.4 (10.9)	36.5 (11.2)	0.3
12 months	40 (10.5)	38 (17)	
SF-36 MCS score, mean (SD)			
Baseline	45.9 (11.8)	47.5 (11.5)	0.006
12 months	49 (16.5)	48 (17)	
Patient concerns checklist, mean (SD)			
Baseline	15.9 (8.6)	16.2 (8.9)	0.06
Follow-up	NR	NR	0.1
QoL index baseline, mean (SD)	22.1 (4.9)	21.9 (5.0)	Similar at baseline and follow-up
Impact of adverse symptoms on QoL[a]			
SF-36 PCS score	–2.25 (–3.32, –1.18), $p < 0.001$	–1.64 (–2.89, –0.41), $p = 0.009$	
SF-36 MCS score	–2.32 (–3.76, –0.88), $p = 0.002$	–0.51 (–1.97, 0.94), $p = 0.5$	
Patient concerns	1.84 (0.91, 2.76), $p < 0.001$	0.91 (0.07, 1.75), $p = 0.03$	
Impact of ICD shocks on QoL[a,b]			
SF-36 PCS score	–1.45 (–2.74, –0.18), $p = 0.03$		
SF-36 MCS score	–1.82 (–3.56, –0.08), $p = 0.04$		
Patient concerns	2.15 (1.07, 3.23), $p < 0.001$		
ICD shocks[b]			
Experienced one or more shocks during first year of follow-up, *n/N* (%)	144/373 (39)		
Experienced one or two shocks	71/144 (49)		
Experienced three or more shocks	73/144 (51)		
Proportion of shocks considered appropriate, %	94		

NR, not reported.

a Multivariate analysis with model comparing any adverse events/ICD shock vs. none. Model includes age, sex, race, index arrhythmia, ejection fraction, history of HF 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.

b Complete data on shocks available for 373/416 (90%) ICD recipients in the QoL substudy.

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.
- The occurrence of one or more vs. no shocks was independently associated with significant reductions in mental well-being and physical functioning and an increase in patient concerns. The development of more frequent shocks (three of more vs. less than three) was associated with similar alterations in self-perceived QoL (numerical data not presented in paper).

Comments

Methodological comments

- *Allocation to treatment groups*: stratified by clinical site and index arrhythmia.[73] AAD group subrandomised to empirical amiodarone or Holter-/electrophysiology-guided sotalol (if no contraindications to sotalol, otherwise assigned to amiodarone).[71]
- *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 history of atrial fibrillation or flutter and NYHA class III HF. 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 footnote d in *Participant 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 were 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, QoL and costs;[73] 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 6 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 the first 200 participants), and the intention was to limit severely the numbers of a priori subgroup analyses.[73] Two subgroup analyses are specified: index arrhythmia (VF vs. VT) and cardiac substrate (coronary artery disease vs. cardiomyopathy). In the QoL substudy[74] both appropriate and inappropriate shocks were included in the analysis. Because follow-up QoL values cannot be reliably defined for patients who die before reassessment the primary analyses were limited to patients who survived for 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 vs. with a spouse or partner, index arrhythmia, ejection fraction, history of HF and beta-blocker use to assess the independent relationship of variables with QoL. All analyses were ITT and $p \leq 0.05$ was considered significant.
- *Sample size/power calculation*: a sample size of 1200 patients was estimated, assuming an 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 7 April 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/dropout*: 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 AAD ($n = 1$) or an ICD ($n = 2$). 25.7% of ICD group and 18.9% of AAD group 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:[74] 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 time point; 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 VF or who have symptomatic, sustained VT.

QoL substudy:[74] 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) and more likely to be male (81% vs. 70%), white (88% vs. 70%) and living with a spouse or partner (71% vs. 51%) and to have graduated from high school (73% vs. 42%) than 111 non-participants. Also reports differences between those who died in the first year vs. those who survived.

- *Outcome measures*: appear appropriate. For the QoL substudy[74] definitions and categorisation of symptoms provided.
- *Intercentre 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 to compare the randomised and non-randomised patients. The registry also followed patients with VF or VT who were not eligible for randomisation. Data on long-term mortality among the non-randomised patients could be obtained from the National Death Index.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	'Allocation is stratified by clinical site and index arrhythmia (ventricular fibrillation or ventricular tachycardia)'.[73] No other information provided
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	High	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 because of knowledge of intervention received
Detection bias		
Blinding of outcome assessment		
Overall mortality and cause of death	Low	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	
Attrition bias		
Incomplete outcome data addressed – overall mortality	Low	'Analysis was performed according to the intention-to-treat principle'.[71] Although there were crossovers between groups, no dropouts are recorded in the paper
Incomplete outcome data addressed – QoL	High	The QoL substudy did not include all randomised participants and there were some differences between those completing the QoL substudy and the whole trial population. In addition, data from those who completed the 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	Paper available describing rationale, design and methods for the study
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Coronary Artery Bypass Graft (CABG) Patch trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Bigger *et al.* 1997,[75–78] Namerow *et al.* 1999,[80] Spotnitz *et al.* 1998[79] *Study design*: RCT Countries: USA and Germany *No. of centres*: 37 (USA 35, Germany two) *Funding*: National Heart Lung and Blood Institute grants HL-48120 and HL-48159 and a grant from Guidant Corporation/CPI, St Paul, MN	*Intervention*: ICD: epicardial defibrillator. Leads and pulse generators provided by Guidant Corporation/CPI (St Paul, MN). 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 ECGs *Comparator*: control group, OPT (subject to caveats described below). No defibrillator therapy[75] and no specific therapy for ventricular arrhythmias[237] *Other interventions used*: ICD group: the protocol prohibited the use of AADs for asymptomatic ventricular arrhythmias and specified that patients without contraindications should be treated with aspirin. Clinical advice has indicated that, although the 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	*Indication for treatment*: patients scheduled for CABG surgery and at risk for sudden death (LVEF < 0.36 and abnormalities on an ECG). Prophylactic *No. of randomised participants*: 900; ICD: 446, control: 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 milliseconds; root mean square voltage in the terminal 40 milliseconds of the QRS complex < 20 μV; or duration of the terminal filtered QRS complex at < 40 μV > 38 milliseconds) *Exclusion criteria*: history of VT or VF, diabetes mellitus with poor blood glucose control or recurrent infections, previous or concomitant aortic or mitral valve surgery, concomitant cerebrovascular surgery, serum creatinine > 3 mg/dl (265 mmol/l), emergency coronary bypass surgery, non-cardiovascular condition with expected survival < 2 years, inability to attend follow-up visits	*Primary outcome*: mortality *Secondary outcomes*: not explicitly stated but QoL and adverse events reported *Method of assessing outcomes*: follow-up visits every 3 months QoL study:[80] single assessment at 6 months included (1) seven 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 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 5 February 1996.[80] Study data reported on 30 April 1997 for main trial publication[75]

Participant characteristics

Characteristic[a]	ICD ($n = 446$)	Control ($n = 454$)	p-value
Age (years), mean (SD)	64 (9)	63 (9)	
Sex, male/female, *n*	386/60	373/81	
Ethnicity, %[80]			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 milliseconds	71	74	
LBBB	10	12	
Q-wave MI	52	53	
Cardiovascular history, %			
Cigarette smoking at any time	79	76	
Angina pectoris	76	76	
MI	83	82	
Two or more previous MIs	30	33	
HF	51	49	
Treatment for HF	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 (mmHg), 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	

Characteristic[a]	ICD ($n = 446$)	Control ($n = 454$)	p-value
	ICD ($n = 430$)	Control ($n = 442$)	
Drug therapy at hospital discharge, % of patients[b]			
Oral AADs			
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	
ACE 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	

bpm, beats per minute; NS, not significant; PTCA, percutaneous transluminal coronary angioplasty.

a Baseline data for marital status, educational attainment, employment status and occupational status are reported in the paper describing QoL outcomes;[80] these characteristics did not differ between the groups and have not been data extracted.

b Data were not available for all patients.

Comment

- States that there was no significant difference between the two groups for the variables listed. States that the use of cardiac drugs was similar at the time of discharge.

Results

Outcome	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
[a]Deaths during mean (SD) follow-up of 32 (16) months,[78] *n*	102	96	
Mechanism of death,[78] *n/N* (%)			
Cardiac	76/102 (74.5)	79/96 (82.3)	
Primary arrhythmic	13/102 (12.7)	22/96 (22.9)	Arrhythmic deaths 15% vs. 29%, $\chi^2 = 5.10$, $p = 0.024$
Secondary arrhythmic	2/102 (2)	6/96 (6.3)	
Non-arrhythmic, cardiac	57/102 (55.9)	46/96 (47.9)	
Myocardial pump failure	30/102 (29.4)	23/96 (24.0)	$\chi^2 = 0.75$, $p = 0.358$
Cardiac procedure	27/102 (26.5)	23/96 (24.0)	
Unwitnessed, cardiac	0	2/96 (2.1)	
Uncertain, cardiac	4/102 (3.9)	3/96 (3.1)	
Non cardiac	25/102 (24.5)	17/96 (17.7)	
Unknown	1/102 (1.0)	0	
RR (95% CI) of cause-specific death by treatment assignment[78]			
Cardiac	0.97 (0.71 to 1.33)		0.84
Arrhythmic	0.55 (0.29 to 1.03)		0.06
Non-arrhythmic, cardiac	1.24 (0.84 to 1.84)		0.28
Myocardial pump failure	1.28 (0.74 to 2.22)		0.37
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
HR (95% CI) for death per unit time	1.07 (0.81 to 1.42)		
HR (95% CI) from Cox regression model stratified by clinical centre and LVEF	1.02 (0.76 to 1.35)		
HR (95% CI) from Cox model beginning 30 days after randomization	1.03 (0.75 to 1.41)		
Received a shock within 1 year of ICD implantation (actuarial incidence presented in a figure), %	50		
Received a shock within 2 years of ICD implantation (actuarial incidence presented in a figure), %	57		
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalizations	NR	NR	
Change in NYHA class	NR	NR	
Change in LVEF	NR	NR	

Outcome	ICD ($n = 446$)		Control ($n = 454$)		*p*-value
Exercise capacity outcomes (e.g. 6-minute walk distance, total exercise time, peak VO_2)	NR		NR		
	3 months ($n = 403$)	1 year ($n = 374$)	3 months ($n = 411$)	1 year ($n = 373$)	
Drug therapy after CABG, %[b]					
Oral AADs					
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	
ACE 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	

NR, not reported.

a Total number of deaths and number of cardiac deaths reported differs slightly between the main trial publication[75] and that specifically reporting mechanism of death.[78] Results from the latter paper are reported above (main trial publication[75] reported 101 (71 from cardiac causes) in the ICD group and 95 (72 from cardiac causes) in the control group).

b Drug therapy – data were not available for all patients.

Comments

- The HR (95% CI) derived from a Cox model after adjustment for the 10 prespecified 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 prespecified covariates showed no significant interaction with ICD therapy (i.e. HRs for the ICD group compared with the control group were similar among the predefined subgroups).
- Kaplan–Meier figures for analysis of the probability of death and the probability of the discharge of the 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 3 months and 1 year after hospital discharge. Rates of use of class I or III AADs and beta-blockers were similar in the two groups throughout the trial.

Quality-of-life outcomes

Outcome	ICD ($n = 262$)		Control ($n = 228$)	p-value[a]
HRQoL at 6 months, mean (SD)[80]				
Perception of health				
General health status	54.8 (22.9)		58.3 (23.6)	NS
Perception of health transition[b]	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 before completing the 6-month QoL instrument, *n/N* (%)	101/262 (38.5)			
	ICD device did not fire (n = 161)	***ICD device fired (n = 101)***	***Control (n = 228)***	***Control vs. ICD fired (95% CI)[c]***
HRQoL at 6 months, mean (SD)[80]				
Perception of health				
General health status	56.6 (23.3)	52.1 (22.1)	58.3 (23.6)	NS
Perception of health transition[b]	2.3 (1.2)	2.5 (1.3)	2.1 (1.2)	–0.73 to –0.01[d]
Physical limitations	44.8 (42.9)	36.8 (41.1)	49.2 (42.8)	0.31 to 24.6[e]
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 before date of 6-month QoL assessment (%)	36.0	55.5	33.8	

Outcome	ICD ($n = 262$)	Control ($n = 228$)	p-value[a]
ICDs explanted before completing 6-month QoL assessment, *n/N*	12/262		
At patient request	1		
Because of infection	8		
Other reason	3		

NS, not significant.
a *p*-values for QoL outcomes represent significance of *t*-tests comparing mean scores of control vs. ICD patients.
b 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.
c 95% CIs control the experiment-wise type 1 error rate to be 0.5 using Tukey's method.
d *F*-test for analysis of variance (ANOVA) has *p*-value of 0.0507.
e *F*-test for ANOVA has *p*-value of 0.0549.

Comments

- QoL outcomes grouped into three categories: perception of health status, ability to function and psychological well-being.
- 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 the cumulative incidence of ICD discharges is presented but has not been data extracted.
- Discussion states that, although hospitalisation affects perceived QoL, the differences in QoL scores between control patients and ICD patients whose devices had fired persisted even when rehospitalisation was controlled for in regression analyses.

Adverse effects of treatment

Adverse effect	ICD ($n = 446$)	Control ($n = 454$)	p-value[a]
Postoperative complications, %			
MI	4.0	3.5	
Sustained VT	5.8	6.8	
VF	3.4	5.3	
Bradycardia	2.9	4.4	
Atrial fibrillation	22.9	20.7	
Shock	9.2	7.5	
New or more severe HF	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	
Postpericardiotomy 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	
MI	0.5	4.2	$0.01 < p < 0.05$
New or worsening HF	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[b]	40		
Infection	19		
ICD reached end of service period and not replaced	5		
Patient request	5		

PTCA, percutaneous transluminal coronary angioplasty.
a p-values have no adjustment for multiple comparisons.
b Reason for every ICD removal not reported.

Comments

Methodological comments

- *Allocation to treatment groups*: two independent randomisation schedules were set up for each hospital, one for patients with a LVEF ≤ 0.2 and the other for those with a LVEF of 0.21–0.35. Randomisation therefore stratified by LVEF and also by centre.[76] Patients randomly assigned to ICD or control group within randomly permuted blocks. Randomisation took place in the operating room after completion of CABG surgery and patients were on partial cardiopulmonary bypass. The attending surgeon had the option not to have the patient randomly assigned if he or she thought that implanting and testing an ICD in the patient was too risky. Assignment supplied by data co-ordinating 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 for QoL because informed consent was obtained just hours before surgery, which made it impossible to obtain preoperative QoL data.
- *Method of data analysis*: data were reviewed by an independent data and safety monitoring board. Four interim analyses were scheduled and performed. These were based on sequential monitoring procedures for the groups, with prospective stopping rules defined by a Lan–DeMets boundary with an O'Brien–Fleming spending function. Cumulative survival curves were estimated by the Kaplan–Meier method. Cox proportional hazards regression models were used to estimate HRs. 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 prespecified subgroups. Ten prospectively selected covariates [age, sex, presence/absence of HF, NYHA functional class, LVEF, presence/absence of diabetes, duration of QRS complex (> 100 milliseconds or ≤ 100 milliseconds), use of ACE inhibitors, use of class I or class III AADs 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 analyses of mortality data was on 2 April 1997; 76% of the anticipated information was available. This fourth analysis showed no difference between the ICD group and the control group 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 30 April 1997 while the trial continued to pursue its secondary objectives.
- *QoL substudy*:[80] Comparisons of scales based on *t*-tests. Analysis of variance models were used to test for differences in QoL scales between three groups: (1) control, (2) ICD – device did not fire and (3) 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 of 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 the 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.[77]

- *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 the ICD group 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% and the cumulative rate of crossover 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-month 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 vs. 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:[80] 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 from those receiving 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 the study population did not benefit from an ICD. In the discussion section of the paper[75] 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[71] and MADIT[99,101] trials and this leads the study authors to conclude that there must be differences between the enrolled populations. The authors speculate that the indicator for arrhythmia used may be the important factor and that the 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[80] 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 on generalisability.
- *Outcome measures*: appear appropriate although not all (e.g. QoL outcomes) were ITT.
- *Intercentre variability*: not discussed.
- *Conflict of interests*: not explicitly stated. The leads and pulse generators were provided by the device manufacturer, Guidant Corporation/CPI, who also provided part of the grant funding for the study.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	States 'randomised' and also mentions 'randomly permuted blocks' 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	'The nature of the intervention precluded the blinding of investigators or patients'[75]
Detection bias		
Blinding of outcome assessment		
Mortality	Low	'The nature of the intervention precluded the blinding of investigators or patients'.[75] Death unlikely to be influenced by lack of blinding
QoL	High	
Attrition bias		
Mortality	Low	States analysed according to the ITT principle. 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	High	Not all participants contributed data; those who did differed from those who did not and there was a higher rate of completion in the ICD group
Reporting bias		
Selective reporting	Unclear	Protocol[76] 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	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Cardiac Arrest Study Hamburg (CASH)

Reference and design	Intervention and comparator	Participants	Outcome measures
Kuck *et al.* 2000[81] *Study design*: RCT *Country*: Germany *No. 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 an epicardial or endocardial device was performed at the time of or 7–15 (mean 10 ± 3) days after CABG surgery respectively *Comparator*: AAD, either amiodarone or metoprolol (propafenone arm originally included but eliminated). Amiodarone oral loading dose of 1000 mg/day for 7 days, followed by maintenance dose of 200–600 mg/day. Metoprolol initiated at 12.5–25 mg/day and increased within 7–14 days to a maximum of 200 mg/day if tolerated. Details reported for propafenone (study arm terminated early as a result of interim analysis) in other publications[238–240] – excluded comparator *Other interventions used*: concurrent therapies at discharge reported (see below) but doses not provided	*Indication for treatment*: patients resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias. Index arrhythmia VF in 293/349 (84%) patients and VT in 56/349 (16%) patients (entire group before termination of propafenone arm) *No. of randomised participants*: 349, but this dropped to 288 after termination of the propafenone arm; ICD: 99, amiodarone: 92, metoprolol: 97. Some evidence for error in participant numbers and/or missing data. Details in methodological comments *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 MI, cardiac surgery, electrolyte abnormalities or proarrhythmic drug effect	*Primary outcome*: 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 of 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 *Recruitment*: from March 1987 to March 1992 (propafenone arm terminated early) or to 1996 (remaining study arms)

Participant characteristics

Characteristic	ICD ($n = 99$)	Amiodarone ($n = 92$)	Metoprolol ($n = 97$)	p-value
Age (years), mean (SD)	58 (11)	59 (10)	56 (11)	
Sex, % male	79	82	79	
Ethnicity	NR	NR	NR	
Underlying disease, %				
Coronary artery disease	73	77	70	
Dilated cardiomyopathy	12	10	14	
Others	6	2	5	
No heart disease	9	11	11	
CHF 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 (milliseconds), mean (SD)	437 (42)	430 (51)	430 (48)	
Bundle branch block, %	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	
Acetylsalicylic acid (aspirin)	57	41	40	
Warfarin	9	6	9	
Coronary revascularisation during hospitalisation after index event, %	19	21		
Cardiac history	NR	NR	NR	
Previous treatment	NR	NR	NR	
Comorbidities	NR	NR	NR	
Exposure time to primary events (months)	4767.36	4169.41	5078.40	

bpm, beats per minute; NR, not reported.

Comment

- Daily maintenance doses throughout the study were 225 ± 75 mg of amiodarone and 85 ± 73 mg of metoprolol.

Results

Outcome	ICD ($n = 99$)	Amiodarone ($n = 92$)	Metoprolol ($n = 97$)	p-value
Crude death rate during mean (SD) follow-up of 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 rate, % (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 rate of non-fatal 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 HF	NR	NR	NR	
HRQoL	NR	NR	NR	
HF hospitalisations	NR	NR	NR	
Change in NYHA class	NR	NR	NR	
Change in LVEF fraction	NR	NR	NR	
Exercise capacity outcomes	NR	NR	NR	

NR, not reported.
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 One-sided p-value unadjusted for multiple looks for survival or survival free of the event for the comparison between ICD and antiarrhythmic therapy.

Comments

- 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 1–9 of follow-up were 41.9%, 39.3%, 28.4%, 27.7%, 22.8%, 11.4%, 9.1%, 10.6% and 24.7% respectively.
- The Kaplan-Maier estimates of the percentage reduction in sudden death for ICD patients at years 1–9 of follow-up were 81.8%, 86.7%, 76.2%, 78.3%, 80.8%, 73.1%, 64.3%, 56.7% and 60.6% respectively.
- The decrease in cardiac arrest rates for patients assigned to ICD were 61.8%, 65.5%, 59.2%, 53.8%, 50.4%, 58.6%, 49.2%, 52.8% and 42.1% at years 1–9 of follow up respectively.
- 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 for 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 HRs 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 a higher benefit from ICDs for subgroups with a lower LVEF and higher NYHA function class is reported.

Adverse effects of treatment

Adverse effect	ICD ($n = 99$)	Amiodarone ($n = 92$)	Metoprolol ($n = 97$)	p-value
Drug-related pulmonary toxicity, *n*		0	NR	
Hyperthyroidism, *n* (%)		3 (3.3)		
Drug discontinuation required, *n* (%)		9 (9.8)	10 (10.3)	
Perioperative death or, for drug arms, deaths within the same time frame, *n* (%)	5 (5.1); 3 (5.4) epicardial ICD, 2 (4.5) endocardial ICD	2 (1.1) 2	0	$p = 0.029$
Other complications, *n*				
Infection	3 (explantation required for 2)			
Haematoma or seroma	6			
Pericardial effusion	1			
Pleural effusion	3			
Pneumothorax	1			
Dislodgement or migration of system leads	3			
Device dysfunction	5			
Overall complication rate, %	23.0 (including an explantation rate of 2.1%)			

Comments

Methodological comments

- *Allocation to treatment groups*: randomisation ratio ICD : AAD = 1 : 3 (ICD : amiodarone : metoprolol : propafenone = 1 : 1 : 1 : 1). All patients assigned to the AAD arm underwent repeat predischarge 24-hour Holter monitoring, PES 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 and 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 ITT. 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, as 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 three drug groups was adjusted according to Bonferroni inequality. Time to clinical events (i.e. mortality, sudden death, cardiac arrest recurrence) for ICD vs. AAD was analysed using the Kaplan–Meier method. Cumulative survival functions were compared using the log-rank (Mantel–Cox) test. The Cox proportional regression model was used for calculation of HRs 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 AADs. The alpha-level for comparison of survival distributions between the ICD and drug arms was based on a one-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 two 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 the trial sample size, thus rendering the trial underpowered to test the working hypothesis. Note that data were presented and analysed separately for the two drugs and it is unclear whether the study was powered for this.
- *Attrition/dropout*: three participants are unaccounted for from the description of numbers of participants. Overall, 349 included (293 VF + 56 VT) 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 three study arms. Two in the amiodarone group refused to start drug therapy (table 2 in the paper indicates that these are included among the 92 in the amiodarone group). During follow-up six (6.1%) 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 beta-blockers during follow-up.

General comments

- *Generalisability*: the study authors suggest that the mean LVEF for the whole study population (0.46) suggests that there may have been a disproportionate representation of relatively healthy patients in the 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 the trial
- *Outcome measures*: appear appropriate.
- *Intercentre variability*: unclear as the 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 randomised controlled trials[65]

Domain	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	'For calculation of hazard ratios, the Cox proportional regression model was used with the patients grouped as randomised (intention to treat)'[81] Crossovers or addition of the other treatment was similar in the two groups (ICD 6.1%, AAD 5.8%)
Reporting bias		
Selective reporting	Low	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 or not this could have introduced any bias

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Cardiomyopathy Trial (CAT)

Reference and design	Intervention and comparator	Participants	Outcome measures
Bänsch *et al.* 2002,[82] German Dilated Cardiomyopathy Study investigators 1992[83] *Study design*: RCT (pilot phase) *Country*: Germany *No. of centres:* 15 *Funding*: grant from Guidant Corporation, Giessen, Germany	*Intervention*: ICD + OPT. Transvenous electrode systems (Endotak, Cardiac Pacemakers, Inc.). Pulse generators Ventak P2, P3, PrX II, CPI. Defibrillation threshold of < 20 J mandatory. VT zone with detection rate of 200 bpm programmed for all patients. All shocks programmed to maximum output 30 J. 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	*Indication for treatment*: recent-onset idiopathic dilated cardiomyopathy (DCM) and impaired LVEF and without documented symptomatic VT *No. of randomised participants:* 104; ICD: 50, control: 54 *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%), previous history of MI, myocarditis or excessive alcohol consumption, symptomatic bradycardia, VT, VF, on heart transplant list, significant valvular disease, hypertrophic or restricted cardiomyopathy, NYHA class I or IV, mentally unable to understand protocol	*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 tachyarrhythmias requiring antiarrhythmic treatment, complications *Method of assessing outcomes*: visits every 3 months and encouraged to make additional visit if the first shock, cluster of shocks or syncope had occurred. ECGs stored on devices *Length of follow-up*: 2 years *Recruitment*: 1991–7

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter.

Participant characteristics

Characteristic	ICD ($n = 50$)	Control ($n = 54$)	p-value
Age (years), mean (SD)	52 (12)	52 (10)	NS
Sex, male/female, *n*	43/7	40/14	NS
Ethnicity	NR	NR	
NYHA class, %			
I	66.7	64.1	NS
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	NR	NR	
Echocardiography[a]			
Left ventricular end-diastolic volume (mm), mean (SD)	69 (7)	69 (8)	NS
Left ventricular end-systolic volume (mm), mean (SD)	58 (9)	59 (10)	NS
ECG rhythm, %			NS
Sinus	79.6	86.8	
Atrial fibrillation/flutter[b]	20.4	11.3	
Paced	0	1.9	
QRS morphology, %			NS
Normal	72.9	55.1	
Not normal	27.1	44.9	
LBBB	84.6	81.8	
RBBB	7.7	0	
Other or undefined bundle branch block	7.7	18.2	
QRS width[c] (milliseconds), mean (SD)	102 (29)	114 (29)	NS
Patients with NSVT, %	53.1	58.0	NS
Median duration of NSVT (seconds) (25th–75th percentile)	5 (3.0–6.5)	3.5 (2.3–6.0)	NS
Rate of NSVT (bpm), mean (SD)	175 (39)	157 (23)	NS
Bradycardias, %	2.1	18.8	0.015
Sinoatrial block	0	4.2	
Atrioventricular block	2.1	14.6	NS
Inducible VT, %	6.1	0	NS
Inducible VF, %	16.0	3.7	NS

APPENDIX 7

Characteristic	ICD ($n = 50$)	Control ($n = 54$)	p-value
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	NR	NR	
Previous treatment	NR	NR	
Comorbidities	NR	NR	
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

bpm, beats per minute; NR, not reported; NS, not significant; NSVT, non-sustained VT; RBBB, right bundle branch block.

a States echocardiographic M-mode data available only for 70 patients; no 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.

Comment

- The following baseline characteristics were reported but not extracted: baseline violators, orthopnoe, oedema, left ventricular end-diastolic pressure, QT duration, baseline AH interval a (interval between atrial electrogram and His bundle electrogram) and HV interval (interval between His bundle electrogram and ventricular electrogram).

Results

Outcome	ICD ($n = 50$)	Control ($n = 54$)	*p*-value
All-cause mortality after 1 year (primary end point),[a] *n*	4 (all cardiac)	2 (both non-cardiac)[b]	0.3672
All-cause mortality after mean (SD) 5.5 (2.2) years' follow-up, *n*	13	17	
Cumulative survival, %			
2 year	92	93	0.554
4 years	86	80	
6 years	73	68	
HRQoL	NR	NR	
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalisations	NR	NR	
Change in NYHA class	NR	NR	
Change in LVEF	NR	NR	
Exercise capacity outcomes (e.g. 6-minute walk distance, total exercise time, peak VO_2)	NR	NR	
Received adequate therapy from ICD for VTs > 200 bpm, *n*	11	NA	
Syncope during VT, *n*	6		

bpm, beats per minute; NA, not applicable; NR, not reported.
a No sudden death occurred in either group.
b States both control group deaths are non-cardiac in text but table 1 shows one cardiac death.

Comments

- 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.[83]
- All-cause mortality for subgroups of patients with and without adequate therapies in the ICD group reported but not extracted.

Adverse effects of treatment

Adverse effect	ICD ($n = 50$)	Control ($n = 54$)	*p*-value
Complications caused by ICD therapy			
Deaths within 30 days of ICD implantation, *n*	0		
Device dislocation and bleeding requiring revision, *n*	2		
Electrode dislocation requiring revision, *n*	2		
Complications in 24 months of follow-up	10 in 7 patients		
Electrode dislocation and sensing/isolation defects, *n*	7		
Infection with total device replacement, *n*	2		
Perforation, *n*	1		

Comments

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*: no differences between groups except for bradycardias caused by sinus arrest and atrioventricular block I and II (Wenckebach), which were more common in the control group (18.8%) than the ICD group (2.1%) ($p = 0.015$) during Holter monitoring. Any other differences observed between groups were not statistically significant.
- *Method of data analysis*: no statement made regarding whether analysis ITT or not. Blind interim analysis after inclusion of 100 patients at 1 year of 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 of 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 using two-sided analysis using Mann–Whitney exact test; qualitative characteristics compared using 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 a power of 80% and a probability value of 0.05.
- *Attrition/dropout*: no details reported.

General comments

- *Generalisability*: as the trial was stopped because of futility after 1 year because of 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.
- *Intercentre variability*: not commented on.
- *Conflict of interests*: no statement other than support was by a grant from Guidant Corporation.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	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 personnel	High	Blinding unlikely
Detection bias		
Blinding of outcome assessment	Low	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	Incidence of heart transplantation specified as a secondary outcome but no reporting on this
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Canadian Implantable Defibrillator Study (CIDS)

Reference and design	Intervention and comparator	Participants	Outcome measures
Connolly *et al.* 1993[85] and 2000,[84] Irvine *et al.* 2002,[87] Sheldon *et al.* 2000[86] (no additional data extracted), Bokhari *et al.* 2004[88] *Study design*: RCT *Countries*: Canada, Australia, USA *No. of centres:* Canada: 19, Australia: 3, USA: 2 *Funding*: Medical Research Council of Canada	*Intervention*: ICD. Implant criteria met with three consecutive successful defibrillations at ≥ 10 J below maximum device output. Either thoracotomy or non-thoracotomy 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*: AADs could be used in both groups to control supraventricular or NSVTs that were symptomatic or might cause discharge of the ICD	*Indication for treatment*: previous sustained ventricular arrhythmia *No. of randomised participants:* ICD randomised: 328, ICD received implant: 310, amiodarone: 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 the absence of either recent acute MI (≤ 72 hours) 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 ≥ 150 bpm causing presyncope or angina in a patient with a LVEF ≤ 35%; or unmonitored syncope with subsequent documentation of either spontaneous VT ≥ 10 seconds or sustained (≥ 30 seconds) monomorphic VT induced by programmed ventricular stimulation. Ventricular tachyarrhythmias induced in laboratory met criteria if patient had previous 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, non-arrhythmic medical condition making 1-year survival unlikely, long QT syndrome	*Primary outcomes*: death from any cause *Secondary outcomes*: arrhythmic death (based on clinical classification of cardiac deaths by Hinkle and Thaler (reference provided), QoL,[87] 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 study:[87] emotional functioning: Rand Corporations 38-item MHI; HRQoL: NHP. Assessed in hospital 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 For long-term follow-up of subset of patients from one centre:[88] follow-up until April 2002, mean 5.6 (SD 2.6) years, median 5.92 (range 0.08–11.08) years *Recruitment*: October 1990–January 1997

bpm, beats per minute.

Participant characteristics

Characteristic	ICD ($n = 328$)	Amiodarone ($n = 331$)	p-value
Age (years), mean (SD)	63.3. (9.2)	63.8 (9.9)	
Sex, % male	85.4	83.7	
Ethnicity	NR	NR	
Index arrhythmia, %			
VF or cardiac arrest	45.1	50.1	
VT with syncope	15.9	10.6	
Other VT	23.8	26.9	
Unmonitored syncope	15.2	12.4	
Primary cardiac diagnosis, %			
Ischaemic heart disease with MI	75.6	73.1	
Ischaemic heart disease without MI	7.3	9.1	
Dilated cardiomyopathy	8.5	10.6	
Valvular heart disease	1.2	3.0	
Other heart disease	3.7	2.4	
No heart disease	3.7	1.8	
CHF, %			
None	51.2	49.5	
NYHA class I or II	37.8	39.9	
NYHA class III or IV	11.0	10.6	
LVEF (%), mean (SD)	34.3 (14.5)	33.3 (14.1)	
LVEF < 20%, %	11.3	13.3	
Heart rate	NR	NR	
Baseline electrophysiological study			
Ever done, %	62.2	62.8	
Inducible VT or VF, *n/N* (%)	154/204 (75.7)	147/208 (70.7)	
Coronary angiography, %			
Ever done	75.6	78.2	
Three-vessel disease	19.0	18.9	
Chest radiography, %			
Interstitial abnormality (document on previous standard chest radiography report)	15.5	17.6	
Other abnormality	31.4	34.6	
Current pharmacological therapy	NR	NR	

Characteristic	ICD ($n = 328$)	Amiodarone ($n = 331$)	p-value
Cardiac history, %			
Angina pectoris	51.2	57.1	
MI	77.1	75.8	
CABG surgery	31.4	28.1	
Previous treatment	NR	NR	
Medical conditions, %			
Liver disorder	1.5	2.7	
Respiratory disease	17.5	17.8	
Thyroid disease	5.8	3.9	

NR, not reported.

Comment

- Baseline characteristics are also presented for 317 English-speaking participants undertaking QoL assessment.[87] QoL results reported for 178 of these.

Results

Outcome	ICDs ($n = 328$)	Amiodarone ($n = 331$)	RRR[a] (95% CI) (%), p-value
30-day mortality in implanted patients ($n = 310$), n/N (%)			
Patients with thoracotomy ($n = 33$)	1/33 (3.3)		
Patients with non-thoracotomy lead system ($n = 277$)	1/277 (0.36)		
Outcome event rate summary, no. of events [rate/year (%)]			
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
Non-cardiac vascular death	3 (0.3)	2 (0.2)	–36.6 (–719.8 to 77.2), 0.732
Non-vascular 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
			ARR, RRR (%)
Cumulative risks over time, %			
Total mortality			
1 year	9.46	11.18	1.72, 15.4
2 years	14.75	20.97	6.22, 29.7
3 years	23.32	27.03	3.71, 13.7
Arrhythmic mortality			
1 year	4.37	6.23	1.86, 29.9
2 years	6.68	9.74	3.06, 31.4
3 years	9.77	11.88	2.11, 17.8
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalisations	NR	NR	
Change in NYHA class	NR	NR	
Change in LVEF	NR	NR	
Exercise capacity outcomes	NR	NR	
Concomitant antiarrythmic medications, % patients			
Beta-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	

APPENDIX 7

Outcome	ICDs ($n = 328$)	Amiodarone ($n = 331$)	RRR[a] (95% CI) (%), p-value
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 AAD (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	

ARR, absolute risk reduction; NR, not reported.

a Treatment effect adjusted for LVEF stratification. Total patient-years of follow-up were 957 for amiodarone group and 995 for ICD group.

Comments

- 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.
- Percentage of amiodarone group receiving amiodarone at 2 months: 96.2%; 1 year: 88.7%, 3 years: 80.3%; 5 years: 85.4%. Mean doses 390, 306, 262 and 255 mg/day respectively.
- 52/331 in the amiodarone group received an ICD.
- Cumulative proportion of the amiodarone group receiving an ICD at 1, 3 and 5 years was 9.0%, 18.6% and 21.4% respectively.
- 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 but not data extracted.
- Figure of HRs 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 prespecified and so it was not data extracted.

Health-related quality of life[87]

QoL measure	ICD ($n = 86$)	Amiodarone ($n = 92$)	Time by group p-value (ANOVA)
Domains of MHI, mean (SD)			
Total index[a]			
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[b]			
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[a]			
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 NHP, mean (SD)			
Energy level[b]	($n = 83$)	($n = 88$)	
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[b]	($n = 84$)	($n = 90$)	
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[b]	($n = 81$)	($n = 88$)	
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[b]	($n = 76$)	($n = 86$)	
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[b]	($n = 83$)	($n = 90$)	
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[b]	($n = 78$)	($n = 88$)	
Baseline	31.4 (27.4)	29.6 (31.5)	
6 months	25.0 (29.7)	30.8 (31.0)	

QoL measure	ICD ($n = 86$)	Amiodarone ($n = 92$)	Time by group p-value (ANOVA)
12 months	23.9 (29.4)	30.2 (32.4)	0.02
Life impairment[b]	($n = 78$)	($n = 83$)	
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

ANOVA, analysis of variance.
a Higher values represent better functioning.
b Higher values represent poorer functioning.

Effect of implantable cardiac defibrillator shocks on Mental Health Inventory and Nottingham Health Profile scores[87]

QoL measure	ICDs, no shocks ($n = 66$)	ICDs, one to four shocks ($n = 27$)	ICDs, five or more shocks ($n = 15$)	Amiodarone, no ICD ($n = 95$)	Between-group p-value
Domains of MHI, mean (SD)					
Total index[a]					
Baseline	175.9 (26.5)	171.7 (22.7)	171.2 (32.0)	177.9 (27.1)	
12-month follow-up	186.2 (26.9)[b,c]	186.6 (21.7)[b,c]	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-month follow-up	42.5 (15.3)[b,c]	41.4 (11.7)[b,c]	52.7 (25.2)	50.9 (17.5)	0.001
Within-group p-value	0.001	0.001	0.833		
Psychological well-being[a]					
Baseline	60.1 (12.5)	56.6 (11.6)	57.1 (15.0)	61.7 (12.0)	
12-month follow-up	62.8 (13.1)	62.1 (10.9)[c]	55.6 (16.8)	60.6 (13.3)	0.02
Within-group p-value	0.074	0.004	0.642		
Domains of NHP, 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-month follow-up	19.5 (27.1)[b]	24.8 (33.4)[b]	23.5 (29.5)	37.0 (37.6)	0.003
Within-group p-value	0.02	0.115	0.859		
Physical mobility[d]	($n = 65$)	($n = 27$)	($n = 15$)	($n = 93$)	
Baseline	13.1 (15.0)	12.4 (10.2)	7.1 (9.8)	13.18 (20.1)	
12-month follow-up	9.3 (12.4)[b]	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-month 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		

QoL measure	ICDs, no shocks ($n = 66$)	ICDs, one to four shocks ($n = 27$)	ICDs, five or more shocks ($n = 15$)	Amiodarone, no ICD ($n = 95$)	Between-group *p*-value
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-month follow-up	7.1 (14.6)[b,c]	6.8 (10.2)[b]	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-month 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-month 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-month follow-up	1.3 (1.5)[b]	1.4 (1.5)[b]	1.4 (1.6)	1.9 (1.9)	0.03
Within-group *p*-value	0.061	0.033	0.334		

a Higher values represent better functioning.
b Groups that differed significantly from the amiodarone without an ICD group ($p < 0.05$).
c Groups that differed significantly from the ICD five or more shocks group ($p < 0.05$).
d Higher values represent poorer functioning.

Adverse effects of treatment

Adverse effect	ICD ($n = 328$)	Amiodarone ($n = 331$)	p-value
ICD permanently or temporarily explanted because of infection, heart transplantation or patient preference, *n/N*	16/310		
Adverse experiences ever reported, *n/N* (%)			
Pulmonary infiltrate		18/331 (5.7) (1.9% per year)[a]	
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)[a]	
Tremor		91/331 (15.4)[a]	
Insomnia		64/331 (19.3)	
Peripheral neuropathy		1/331 (0.3)	
ICD product discomfort, *n/N* (%)	25/328 (7.6)		
ICD malfunction, *n/N* (%)	2/328 (0.6)		
ICD pocket infection, *n/N* (%)	15/328 (4.6) (1.4% per year)		
ICD dislodgement/fracture, *n/N* (%)	8/328 (2.4)		

a The numerator, denominator and percentages are as reported by the primary publication. They are incorrect; however, it is not clear where the error lies.

Long-term follow-up of subset of patients from one centre[88]

Participant characteristics

Characteristic	ICD ($n = 60$)	Amiodarone ($n = 60$)	*p*-value
Age (years), mean (SD)	64 (9.2)	64 (8.7)	NS
Sex, male, *n* (%)	50 (83)	50 (83)	NS
Index arrhythmia, %			
VF	18	27	NS
VT	35	23	0.044
Syncope/inducible VT, %	7	10	NS
History of MI, *n* (%)	36 (60)	31 (52)	NS
Coronary artery disease, *n* (%)	48 (80)	48 (80)	NS
NYHA class I or II, *n* (%)	57 (95)	57 (95)	NS
NYHA class III or IV, *n* (%)	3 (5)	3 (5)	NS
LVEF (%), mean (SD)	33.9 (12.5)	32.1 (11.1)	NS
CABG surgery, *n* (%)	19 (32)	22 (37)	NS
Percutaneous coronary intervention, *n* (%)	4 (7)	2 (3)	NS
Beta-blockers, *n* (%)	23 (38)	21 (35)	NS
Diabetes mellitus, *n* (%)	7 (12)	11 (18)	NS
Hypertension, *n* (%)	13 (22)	14 (23)	NS

NS, not significant.

Results

Outcome	ICD ($n = 60$)	Amiodarone ($n = 60$)	*p*-value
Total deaths, *n* (%)	16 (27)	28 (47)	0.0231
Total mortality per year, %	2.8	5.5	HR 2.011 (95% CI 1.087 to 3.721, $p = 0.0261$)[a]
Presumed arrhythmic death, %	2	12	0.049
Cardiac death, %	8	11	
Vascular death, %	1	1	
Non-cardiac death, %	5	4	
Symptomatic non-fatal arrhythmia recurrence, *n*		12	

a States $p = 0.0261$ in text but $p = 0.0231$ in legend of a figure.

Adverse effects of treatment

Adverse effect	ICD ($n = 60$)	Amiodarone ($n = 60$)	*p*-value
Side effects related to amiodarone, *n* patients (%)		49 (82)	
Side effects requiring dose reduction or discontinuation, *n* patients (%)		30 (50)	
Serious adverse effects requiring discontinuation, *n* patients		13	
Severe side effects requiring permanent removal of the ICD and crossover to amiodarone	0		
Procedures performed in addition to initial implants, *n* 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 two or more procedures to replace device or change a lead (up to seven procedures, details reported), *n*	41		
Perioperative death, *n*	0		
Pneumothorax, *n*	1		
Deep-vein thrombosis, *n*	1		
Pocket haematoma postoperatively, *n*	1		
ICD turned off at patients request because of terminal cancer	2		
Inappropriate therapy, *n* (%)	30 (50)		

Comments

- 19/60 amiodarone group crossed over to ICD group because of adverse events ($n = 12$) or arrhythmia ($n = 7$).
- 26/60 ICD group were receiving or had received amiodarone by the end of follow-up.

Comments

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'.[84]
- *Comparability of treatment groups*: described as well-balanced.
- *Method of data analysis*: states analysis based on the ITT principle. Study planned as a one-sided comparison with the hypothesis that ICDs would be superior to amiodarone. Two-sided statistics presented in response to review process. Cumulative mortality summarised as Kaplan–Meier survival curves. 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 three formal interim analyses of efficacy with the intention of stopping the study early in favour of ICD if one-sided $p \leq 0.001$. For QoL study,[87] 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 were assessed using analysis of covariance. Analysis based on the ITT principle.
- *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, because of completing risks, have little effect on overall survival. This change led to an increase in the patient enrolment target from 400 to 650 patients, which provided 90% power to detect a relative reduction in all-cause mortality of 33% with the ICD with an anticipated 3-year mortality rate of 30% on amiodarone. Crossover rates of 5% per year for both treatment groups were anticipated. QoL study[87] was conducted with the original 400 patients only because of cost. Of these, 317 spoke English; participation rate was 79%. In the QoL study, 9/92 receiving amiodarone received an ICD and 14/86 with an ICD received amiodarone by 12 months. The long-term follow-up of a subset of patients from one centre would not be adequately powered.[88]
- *Attrition/dropout*: of the entire trial population, 328 were randomised to the ICD group and 310 (94.5%) received an ICD. Of the 18 who did not receive an ICD, seven died in hospital awaiting ICD surgery and 10 decided against an ICD (patient or physician) after randomisation; in addition, there was one technical problem. A total of 16 patients had their ICD explanted permanently or temporarily because of infection, heart transplantation or patient preference; 52/331 (15.7%) patients randomised to amiodarone received an ICD. For QoL,[87] of the original 400 participants, 317 spoke English; participation rate was 79%. Of the 317 recruited, 287 (90.5%) were alive at the 12-month assessment; 22/287 (7.7%) were missing the baseline QoL assessment (11 from each group) and 127/287 (44%) were 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. In total, 9/92 in the amiodarone group received an ICD within the first 12months and 14/86 in the ICD group were taking amiodarone at 12 months. For the subset of patients from a single centre[87] it is stated that follow-up was complete in the ICD group and 3/60 patients were lost to follow-up in the amiodarone group. In the amiodarone group 19/60 crossed over to the ICD group because of adverse events ($n = 12$) or arrhythmia recurrence ($n = 7$). For those with an ICD, 26/60 were receiving amiodarone during follow-up.[88]

General comments

- *Generalisability*: included people with VF, sustained VT or unmonitored syncope likely because of VT. Most participants from centres in Canada.
- *Outcome measures*: mortality, QoL and adverse events only.
- *Intercentre variability*: not reported.
- *Conflict of interests*: not stated. Amiodarone supplied by Wyeth-Ayerst Pharmaceuticals, Ltd.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	'Central randomisation was stratified by clinical centre and LVEF (≤ 35% and > 35%)'.[84] Method not stated
Allocation concealment	Low	'Central randomisation'.[84] No further details given but assume allocation concealed by central allocation
Performance bias		
Blinding of participants and personnel	High	No details reported but assume participants and personnel not blinded
Detection bias		
Blinding of outcome assessment		
Mortality	Low	'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'.[84] Mortality unlikely to be influenced by lack of blinding
QoL	High	
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,[85] 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	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Defibrillator versus Beta-Blockers for Unexplained Death in Thailand (DEBUT) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Nademanee *et al.* 2003[89] *Study design*: RCT; pilot study and main study *Country*: Thailand *No. of centres:* not reported *Funding*: Grant-in-Aid from Cardiac Rhythm Management and Guidant Corporation, St Paul, MN	*Intervention*: ICD (Guidant Corporation, St Paul, MN) *Comparator*: beta-blockade (long-acting propranolol 40 mg/day up to 160 mg/day) *Other interventions used*: other beta-blocking agents or amiodarone permitted if intolerable side effects of propranolol or if frequent shocks from recurrent VF developed	*Indication for treatment*: SUDS survivors or probable survivors *No. of randomised participants:* pilot study: 20 (ICD: 10, beta-blockers: 10); main study: 66 (ICD 37, beta-blockers: 29) (155 screened, 88 not randomised, one 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 electrophysiological testing *Exclusion criteria*: no further detail	*Primary outcome*: death from all causes *Secondary outcomes*: recurrent VT/VF or cardiac arrest *Method of assessing outcomes*: first month and at 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)

RBBB, right bundle branch block.

Participant characteristics

Pilot study

Characteristic	ICD ($n = 10$)	Beta-blocker ($n = 10$)	*p*-value
Age (years), mean (SEM)	44 (11)	48 (15)	0.63
Sex, male, *n* (%)	10 (100)	10 (100)	
Ethnicity	NR	NR	
SUDS survivors, *n*	8	6	
Probable SUDS survivors, *n*	2	4	
NYHA class I, *n* (%)	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–V_3), *n* (%)	NR	NR	
Heart rate (bpm), mean (SEM)	67 (12)	64 (7)	
PR interval (milliseconds), mean (SEM)	166 (26)	169 (30)	
QRS interval (milliseconds), mean (SEM)	98 (29)	92 (12)	
QT interval (milliseconds), mean (SEM)	396 (51)	387 (31)	
Induced VF ($\geq$ 300 bpm), *n* (%)	1 (13)	1 (10)	
Induced polymorphic VT ($\leq$ 300 bpm), *n* (%)	4 (50)	8 (80)	
Non-inducible VF/VT, *n* (%)	3 (37)	1 (10)	
Electrophysiological study not carried out, *n*	2	0	
Atrio-His conduction time (milliseconds), mean (SEM)	94 (10)	94 (12)	
His-Purkinje conduction time (milliseconds), mean (SEM)	58 (18)	54 (3)	
Signal-averaging ECG performed, *n* (%)	5	8	
Positive	4 (80)	4 (50)	
Negative	1 (20)	4 (50)	

bpm, beats per minute; CPR, cardiopulmonary resuscitation; NR, not reported; RBBB, right bundle branch block; RVEF, right ventricular ejection fraction.

Comment

- No differences in baseline characteristics or index arrhythmic events.

Main study

Characteristic	ICD ($n = 37$)	Beta-blocker ($n = 29$)	
Age (years), mean (SEM)	40 (11)	40 (14)	0.95
Sex, male, *n* (%)	35 (95)	29 (100)	0.5
Ethnicity	NR	NR	
SUDS survivors, *n*	22	20	
Probable SUDS survivors, *n*	15	9	
NYHA class I, *n* (%)	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–V_3), *n* (%)	23 (62)	16 (55)	
Heart rate (bpm), mean (SEM)	64 (11)	66 (12)	0.48
PR interval (milliseconds), mean (SEM)	180 (98)	163 (27)	0.48
QRS interval (milliseconds), mean (SEM)	99 (30)	95 (16)	0.43
QT interval (milliseconds), mean (SEM)	404 (43)	394 (31)	0.33
Induced VF ($\geq$ 300 bpm), *n* (%)	8 (22)	8 (30)	0.70
Induced polymorphic VT ($\leq$ 300 bpm), *n* (%)	15 (40)	11 (41)	
Non-inducible VF/VT, *n* (%)	14 (38)	8 (30)	
Electrophysiological study not carried out	0	2	
Atrio-His conduction time (milliseconds), mean (SEM)	100 (22)	96 (22)	0.58
His-Purkinje conduction time (milliseconds), mean (SEM)	51 (8)	49 (11)	0.47
Signal-averaging ECG performed, *n* (%)	29	21	0.74
Positive	11 (38)	7 (33)	
Negative	18 (62)	14 (67)	

bpm, beats per minute; CPR, cardiopulmonary resuscitation; RBBB, right bundle branch block; RVEF, right ventricular ejection fraction.

a Reported in paper as 28 (100%); however, 28/29 would be (96.5%). Not clear which is correct.

Comment

- No differences in baseline characteristics or index arrhythmic events.

Results

Pilot study

Outcome	ICD ($n = 10$)	Beta-blocker ($n = 10$)	*p*-value
Died before main trial, *n*		1	
Death during follow-up, *n*	0	3 (2 SUDS survivors, 1 probable SUDS survivor) at 5.4, 11.8 at 24.6 months	0.07
Multiple VF episodes successfully treated by ICD, *n*	5		

Adverse effects of treatment

Adverse effect	ICD ($n = 10$)	Beta-blocker ($n = 10$)	*p*-value
Operative mortality, *n*	0		
Adverse effects, *n*/*N* (%)	2/10 (20)		
Defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia	1		
T-wave oversensing	0		
ICD replaced because of insulation break, *n*	1		

Main study

Outcome	ICD ($n = 37$)	Beta-blocker ($n = 29$)	*p*-value
Mortality during 3-year follow-up, *n* (%)	0	4 (14)	0.02
Annual death rate	0	About 10%	
Survival (months), mean (SEM)		26.2 (1.4)	
Recurrent VF (effectively treated by ICD), *n* (%)	7 (19)		

Comment
- Kaplan–Meier survival curve presented.

Adverse effects of treatment

Adverse effect	ICD ($n = 37$)	Beta-blocker ($n = 29$)	*p*-value
Operative mortality	0		
Adverse effects, *n*/*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, *n*	1		
Side-effects in beta-blocker group, *n*			
Impotence/decrease in libido		1	
Fatigue		1	
Profound bradycardia		1	
Hypotension plus central nervous system side effect		1	

Comment
- Medication compliance in beta-blocker group 98%.

Pilot and main study combined

Outcome	ICD ($n = 47$)	Beta-blocker ($n = 39$)	*p*-value
Sudden death, *n*	0	7	
Multiple VF episodes and defibrillation shocks, *n*	12		
Annual rate of VF episodes or sudden death (%)	20	10	

Comment
- Kaplan–Meier survival curve of composite of primary and secondary end points (sudden death or VF episodes) for pilot and main trial data presented.

Comments

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 ITT analysis used to contrast 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 the 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 that the annual mortality rate would be reduced 10-fold (i.e. by 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 two-sided significance level. Note that only 66 patients were randomised. The annual death rate in the beta-blocker arm was about 10%, half that used for the sample size calculation.
- *Attrition/dropout*: in total, 155 people were screened, 64 had probable SUDS, either non-inducible or unclear marker, 10 refused to be enrolled, one was randomised to the ICD group but refused, two preferred ICD treatment, five had brain anoxic encephalopathy, six had presence of heart disease and one entered after the trial was stopped. Attrition/dropout 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 that in other trials as participants are survivors of sudden unexplained death with otherwise normal hearts with no HF. All participants were of Thai origin, mostly men. Participants similar to those with Brugada syndrome (a genetic disorder characterised by abnormal ECG findings and increased risk of SCD); 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 the 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.
- *Intercentre variability*: not reported.
- *Conflict of interests*: not stated. Supported by grant-in-aid from Cardiac Rhythm Management and Guidant Corporation, St Paul, MN.
- *Other*: paper reports the results of a pilot study and main study.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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 blinded because of 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	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE)

Reference and design	Intervention and comparator	Participants	Outcome measures
Kadish *et al.* 2000[91] and 2004,[90] Schaechter *et al.* 2003[92] Ellenbogen *et al.* 2006,[93] Passman *et al.* 2007[94] *Study design*: RCT *Countries*: USA and Israel *No. of centres:* 48 (USA 44, Israel 4) *Funding*: St Jude Medical	*Intervention*: ICD + standard oral medical therapy for HF (OPT). Single chamber device. Programmed to back up VVI pacing at a rate of 40 bpm and to detect VF at a rate of 180 bpm *Comparator*: OPT. Medical therapy in both groups for HF included ACE inhibitors unless contraindicated (then hydralazine, nitrates or ARBs) and beta-blocker therapy (unless not tolerated) with carvedilol. Doses of ACE inhibitors and beta-blockers adjusted to recommended levels for HF patients or to highest tolerated doses. Digoxin and diuretics used when necessary to manage clinical symptoms. Use of AADs (e.g. amiodarone) discouraged but allowed for some patients with symptomatic atrial fibrillation or supraventricular arrhythmias. No other AADs used *Other interventions used*: none reported	*Indication for treatment*: non-ischaemic cardiomyopathy and moderate to severe left ventricular dysfunction *No. of randomised participants:* 458; ICD + OPT: 229, OPT: 229 *Inclusion criteria*: NYHA class not reported, LVEF < 36%, LVEDD not reported, QRS interval not reported, presence of ambient arrhythmias (episode of non-sustained VT 3–15 beats at a rate of > 20 bpm or an average of at least 10 premature ventricular complexes per hour on 24-hour Holter monitoring), history of symptomatic HF, presence of non-ischaemic dilated cardiomyopathy, absence of clinically significant coronary artery disease, age 21–80 years[93] *Exclusion criteria*: NYHA class IV, not a candidate for an ICD, electrophysiological testing within the last 3 months, permanent pacemaker, cardiac transplantation appeared imminent, familial cardiomyopathy associated with sudden death, acute myocarditis, congenital heart disease	*Primary outcome*: death from any cause *Secondary outcomes*: sudden death from arrhythmia, QoL[94] *Method of assessing outcomes*: at 3-month intervals. Cause of death used Epstein classification; therefore, patients with progressive symptomatic deterioration of pump failure who died from terminal VF were not considered to have had sudden death from arrhythmia. ICD shocks assessed at each follow-up or when indicated by symptoms.[94] QoL assessed with self-administered SF-12 and the MLWHFQ at baseline, 1 month after randomisation and every 3 months thereafter (to 63 months)[94] *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

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter.

Participant characteristics

Characteristic[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)	
Sex 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* (%)			
NSVT only	51 (22.3)	52 (22.7)	
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	NR	NR	
QRS interval (milliseconds), mean (range)	114.7 (78–196)	115.5 (79–192)	
LBBB, *n* (%)	45 (19.7)	45 (19.7)	
RBBB, *n* (%)	8 (3.5)	7 (3.1)	

APPENDIX 7

Characteristic[a]	ICD + OPT ($n = 229$)	OPT ($n = 229$)	p-value
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)	
ARB	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 HF (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)	
	ICD + OPT ($n = 227$)	OPT ($n = 226$)	
HRQoL[94a]			
Physical score (MLWHFQ), mean (SD)	20 (12)	20 (12)	0.98
Emotional score (MLWHFQ), mean (SD)	11 (8)	10 (8)	0.59
PCS (SF-12), mean (SD)	37 (11)	38 (10)	0.47
MCS (SF-12), mean (SD)	45 (11)	47 (11)	0.14

NR, not reported; PVC, premature ventricular complex; RBBB, right bundle branch block.

a Separate participant characteristics are reported for the QoL study, which excluded five patients with no data, but only data for baseline SF-12 and MLHFQ scores have been extracted. In common with the data above, the only significant difference between the groups was for duration of HF > 1 year ($p = 0.01$).

Results

Outcome	ICD + OPT ($n = 229$)	OPT ($n = 229$)	HR (95% CI) *p*-value
All-cause mortality, *n*	28	40	0.65 (0.40 to 1.06),[a] 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	0.20 (0.06 to 0.71), 0.006
Death from HF, *n*	9	11	
Receipt of appropriate ICD shocks[b]	41 patients, 91 shocks		
Receipt of inappropriate ICD shocks[b]	49 patients		
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalisations	NR	NR	
Change in NYHA class	NR	NR	
Change in LVEF	NR	NR	
Exercise capacity outcomes (e.g. 6-minute walk distance, total exercise time, peak VO_2)	NR	NR	
	ICD + OPT (n = 227)	**OPT (n = 226)**	***p*-value**
HRQoL[94]			
Long-term MCS score			0.89
Long-term PCS score			NS, *p*-value not reported
Long-term MLWHFQ subscale score			NS, *p*-value not reported

NR, not reported; NS, not significant.

a HR for death among ICD patients compared with OPT patients. The HR was unchanged after adjustment for duration of HF.

b Unclear whether these data are for the 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.*[93] but these data, which differ from those reported in the main study paper,[90] have not been extracted. The reason(s) for the difference between the two papers is not discussed in either paper.

Comments

- 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 or non-arrhythmic cause could not be distinguished from the available information.
- 26 deaths classified as non-cardiac were not reported by treatment group (10 from cancer, seven from pneumonia, five from stroke, one each to drug overdose, suicide, liver failure and renal failure).
- Four deaths (two in each group) could not be classified (insufficient information).
- Pairwise comparisons of unadjusted MLWHFQ and SF-12 scores by treatment group were 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 data 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 groups showed a statistically significant improvement from baseline for the ICD group and a non-statistically significant trend towards improvement in the OPT group. After this short-term improvement scores in both groups declined slowly (statistically significant) towards baseline values.
- MLWHFQ 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 second follow-up visit. After initial improvement, scores remained stable for the emotional scale in both groups; scores for the physical scale decreased equally toward baseline values.
- Potential interaction between QoL and patient variables was 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

Adverse effect	ICD + OPT ($n = 229$)	OPT ($n = 229$)	p-value
Complications during implantation of ICD,[a] n (%)	3 (1.3)		
Haemothorax	1		
Pneumothorax	1		
Cardiac tamponade	1		
Procedure-related deaths, n	0		
Complications during follow-up, n (%)	10 (4.4)		
Lead dislodgement or fracture	6		
Venous thrombosis	3		
Infection	1		
Receipt of ICD upgrade during follow-up, n	13		
Dual chamber ICD because of development of sinus node dysfunction	2		
Biventricular device for NYHA class III or IV HF and prolonged QRS interval	11		

a All resolved with medical therapy or drainage.

Prespecified subgroup analyses

Subgroup analysis	RR (95% CI)	p-value
RR of death from any cause after receipt of ICD in comparison to OPT		
For men	0.49 (0.27 to 0.90)	0.018
For NYHA class III HF patients	0.37 (0.15 to 0.90)	0.02

Comments

- Six prespecified subgroup analyses (age, sex, LVEF, QRS interval, NHYA class and history of atrial fibrillation) are presented in a figure, with data reported for men and NYHA class III only. The 95% CIs crossed 1.0 apart from for men, NYHA class III and LVEF $\geq 20\%$ (favours ICD, data in figure only).
- None of the differences between subgroups were significant.
- The study was not powered to detect differences within subgroups.
- Kaplan–Meier survival curves for NYHA class III patients in the ICD and OPT groups are provided, but have not been data extracted.
- The QoL paper[94] reports an analysis of the impact of shocks on QoL (comparing those receiving shocks with those not receiving shocks); however, this analysis is not mentioned in either of the two available papers on study design and organisation.[91,92] Therefore, it is assumed that these are post hoc analyses and they have therefore not been data extracted.

Comments

Methodological comments

- *Allocation to treatment groups*: randomisation stratified by centre and by the use or non-use of amiodarone for supraventricular arrhythmias.
- *Blinding*: cause of death determined by an events committee unaware of patients' 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 HF [ICD + OPT mean 2.39 (range 0.0–21.33) years, OPT mean 3.27 (range 0.0–38.5) years, $p = 0.04$].
- *Method of data analysis*: all analyses ITT. Data collection and analysis independently performed at Northwestern University, IL. 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. The *p*-value for significance in the final analysis was 0.041 on the basis of a two-sided test. Baseline characteristics were compared using two-sample *t*-tests for continuous variables and chi-square tests for categorical variables. Log-rank test was used to compare Kaplan–Meier survival curves. Cox proportional hazards model was used to adjust for covariates and to estimate the HR for death and corresponding 95% CI in the ICD group vs. the OPT group. Data for patients receiving a heart transplant were censored at the time of transplantation. All reported *p*-values are two-tailed. QoL outcomes were compared using hierarchical linear regression. QoL analyses were controlled for baseline differences and predetermined characteristics (sex, age, NYHA class, ethnicity, ejection fraction, duration of HF, 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 the criterion for entry and removal respectively.[94]
- *Sample size/power calculation*: designed to have statistical power of 85% based on a one-sided test. Two-year mortality rate 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/dropout*: prespecified criteria meant that the 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 an ICD 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 one 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.[94] The QoL analysis excluded five patients who did not provide any data (two from the ICD group, three from the OPT group). QoL data were missing from one or two visits for 130 patients, and 178 patients had missing QoL data from more than two visits. States no relationship between QoL and varying length of follow-up or dropping out of the study. No significant differences between complete and incomplete QoL data by patient age, sex or NYHA class but patients without missing data are more likely to be white and have a better ejection fraction 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 non-ischaemic cardiomyopathy and 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.
- *Intercentre variability*: randomisation stratified by centre but no comments regarding intercentre 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 Corporation and St Jude Medical.
- *Other:* included after receiving advice from experts who indicated that it was similar to the AMIOVERT trial investigating whether ICDs reduce mortality in a high-risk population with cardiomyopathy and no coronary disease. Note that mean QRS interval is < 120 milliseconds in each group so on average no cardiac dyssynchrony.

Criteria for assessment of risk of bias in randomised controlled trials[65]

	Judgement[a]	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		
Mortality	Low	Events committee determining cause of death blinded
QoL	High	
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[91,92] but no cost outcomes are reported in the identified papers
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)

Reference and design	Intervention and comparator	Participants	Outcome measures
Hohnloser *et al.* 2000[96] and 2004[95] *Study design*: RCT *Countries*: 12 countries worldwide *No. 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) *Funding*: Supported by a grant from St Jude Medical	*Intervention*: ICD + OPT (supplied by St Jude Medical). Single-chamber ICD implanted within 1 week of randomisation. Implanted leads were required to achieve an R wave of < 4.9 mV, a pacing threshold of > 2.1 V at 0.5 milliseconds and a defibrillation threshold with a safety margin of at least 10 J. Postoperatively, the ICD was set to detect VT and VF. The detection rate for tachycardia was set at ≥ 175 bpm per minute for ≥ 16 beats. The device was programmed to deliver all discharges at maximal output in the VF zone (≥ 200 bpm). Bradycardia pacing was programmed for activation at a minimum of 40 bpm. Antitachycardia pacing within the VT zone (175–200 bpm) could be activated to deliver four bursts of six to 10 beats beginning at 81% of the tachycardia cycle length, with 10-milliseconds 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 ACE inhibitors, beta-blockers, aspirin and lipid-lowering drugs as appropriate (reasons for not giving these medications were documented)	*Indication for treatment*: Recent MI (within 6–40 days), reduced LVEF and impaired cardiac autonomic function *No. of randomised participants:* 674; ICD: 332, OPT: 342 *Inclusion criteria*: Age 18–80 years, recent MI (within 6–40 days), LVEF ≤ 0.35, SD of normal-to-normal R–R intervals of ≤ 70 milliseconds or a mean R–R interval of ≤ 750 milliseconds (HR ≥ 80 bpm) over a 24-hour period as assessed by 24-hour Holter monitoring performed at least 3 days after the infarction *Exclusion criteria*: CHF or NYHA class IV at time of randomisation, non-cardiac disease that limited life expectancy, CABG performed since the qualifying infarction or planned to be performed within 4 weeks of randomisation, three-vessel percutaneous coronary intervention performed since the qualifying infarction, name on a waiting list for a heart transplant, current ongoing ICD therapy, previous implantation of a permanent pacemaker, requirement for an ICD (i.e. sustained VT or VF > 48 hours after the qualifying infarction), low probability that the study ICD could be implanted within 7 days of randomisation, expected poor compliance with the protocol	*Primary outcome*: Death from any cause *Secondary outcome*: Death from 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 circumstances of death and not ICD information. Deaths were classified as either arrhythmic or non-arrhythmic in nature (based on criteria from Hinkle and Thaler, reference provided). Follow-up visits were scheduled at 3 and 6 months after randomisation and at 6-monthly intervals thereafter. Follow-up ended in September 2003, about 15 months after last patient was recruited *Length of follow-up:* Mean follow-up 30 (SD 13) months, maximum 4 years from randomisation *Recruitment*: April 1998–June 2002

bpm, beats per minute.

Participant characteristics

Characteristic	ICD ($n = 332$)[a]	OPT ($n = 342$)[a]	p-value
Age (years), mean (SD)	61.5 (10.9)	62.1 (10.6)	NR
Sex male, *n* (%)	252 (75.9)	262 (76.6)	NR
Ethnicity	NR	NR	
CHF with index MI, *n* (%)	156 (47.0)	167 (48.8)	NR
NYHA class I	21 (13.5)	20 (12.0)	NR
NYHA class II	95 (60.9)	98 (58.7)	NR
NYHA class III	40 (25.6)	49 (29.3)	NR
LVEF, mean (SD)	0.28 (0.05)	0.28 (0.05)	NR
Heart rate	NR	NR	
Electrophysiology			
QRS duration (milliseconds), mean (SD)	107 (24)	105 (23)	NR
Peak creatine kinase (U/l), 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 (milliseconds), mean (SD)	61 (21)	61 (22)	NR
24-hour RR interval (milliseconds), mean (SD)	745 (106)	747 (105)	NR
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, *n* (%)			
Previous MI	123 (37.0)	111 (32.5)	NR
Previous CABG	25 (7.5)	24 (7.0)	NR
Previous PTCA	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

Characteristic	ICD ($n = 332$)[a]	OPT ($n = 342$)[a]	p-value
Comorbidities, *n* (%)			
Diabetes mellitus	102 (30.7)	98 (28.7)	NR
Hypertension	155 (46.7)	154 (45.0)	NR

NR, not reported; PTCA, percutaneous transluminal coronary angioplasty.
a Not all percentages total 100 because of rounding.

Comments

- Authors state that there were no significant differences between the treatment groups in baseline characteristics.
- The average time from MI to randomisation was 18 days and was similar in both groups.
- The average time between randomisation and ICD implantation was 6.3 (SD 7.3) days.
- The average time between implantation and hospital discharge was 4.7 (SD 6.4) days.

Results

Outcome	ICD ($n = 332$)	OPT ($n = 342$)	HR (95% CI),[a] p-value[b]
Mortality rate, *n* [rate (%/year][c,d]			
Primary outcome: death from any cause	62 (7.5)	58 (6.9)	1.08 (0.76 to 1.55), 0.66
Secondary outcome: death from arrhythmia	12 (1.5)	29 (3.5)	0.42 (0.22 to 0.83), 0.009
Secondary outcome: non-arrhythmic causes	50 (6.1)	29 (3.5)	1.75 (1.11 to 2.76), 0.02
Cardiac, non-arrhythmic	34 (4.1)	20 (2.4)	1.72 (0.99 to 2.99), 0.05
Vascular, non-cardiac	5 (0.6)	3 (0.4)	1.69 (0.40 to 7.06), 0.47
Non-vascular	11 (1.3)	6 (0.7)	1.85 (0.68 to 5.01), 0.22
Percutaneous or surgical coronary revascularisation, *n* (%)	33 (9.9)	50 (14.6)	$p = 0.08$
Prescribed amiodarone, *n* (%)	27 (8.1)	46 (13.5)	$p = 0.04$

a HRs are for the ICD group vs. the OPT group.
b *p*-values are two-sided.
c Average follow-up 30 (SD 13) months.
d The data were analysed with use of the Cox model.

Comments

- Kaplan–Meier 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.
- HRs for death from any cause also reported according to selected clinical characteristics (age, sex, diabetes, NYHA class, LVEF, rhythm, QRS duration, NSVT, heart rate, SD of normal RR intervals and early reperfusion).
- States that for each outcome the ICD effect remained consistent and did not differ significantly between or among subgroups.

Adverse effects of treatment

Adverse effect	ICD ($n = 332$)
Death related to device implantation, *n*	0
In-hospital device-related complications,[a] *n*	25/310

a Most common complications were lead dislodgement, pneumothorax and inappropriate shocks.

Comments

Methodological comments

- *Allocation to treatment groups*: central randomisation was performed at the study co-ordinating 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*: unblinded study; blinding reported for independent review committee.
- *Comparability of treatment groups*: described as well balanced for baseline clinical characteristics and early use of reperfusion therapy (states no significant differences). The ICD group had slightly higher percentages for previous MI and percutaneous transluminal coronary angioplasty (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 was 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 the use of the Kaplan–Meier procedure and were compared between groups with the use of the Mantel–Haenszel test. A single interim analysis of efficacy was performed by an external safety and efficacy monitoring committee after 66deaths (about half the anticipated number) had occurred. A one-sided *p*-value of < 0.001 would have resulted in early termination of the study. Before unblinding, 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 3-year mortality rate of 30.0% and that 40.0% of these deaths would be caused by arrhythmias. The net effect of preventing 80.0% of these deaths from arrhythmias with the use of an ICD would be to 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 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 two groups in the rate of death from all causes represents a false-negative result because of an inadequate sample size.
- *Attrition/dropout*: four patients in the OPT group had only partial follow-up data available. ICD received: 310/332; 20/332 patients refused ICD implantation, 2/332 died before receiving the ICD.

General comments

- *Generalisability*: limited to high-risk patients with a recent MI, reduced LVEF and impaired cardiac autonomic function.
- *Outcome measures*: limited to mortality. No adverse event data for the OPT group and limited adverse event data for the ICD group.
- *Intercentre 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 the 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 randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	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	Central randomisation
Performance bias		
Blinding of participants and personnel	High	Described as an unblinded study
Detection bias		
Blinding of outcome assessment	Low	Assessment of causes of death by unblinded local investigators, but all causes of deaths were reviewed by an independent blinded central validation committee
Attrition bias		
Incomplete outcome data addressed	Low	Primary outcome was evaluated according to the ITT principle; unclear how partially missing follow-up data for four OPT patients were accounted for in relation to secondary outcomes
Reporting bias		
Selective reporting	High	QoL mentioned in protocol but data not reported
Other bias		
Other sources of bias	High	Block randomisation in unblinded trial can lead to prediction of allocation

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Immediate Risk Stratification Improves Survival (IRIS) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Steinbeck *et al.* 2004[98] and 2009[97] *Study design*: RCT *Countries*: Austria, the Czech Republic, Germany, Hungary, Poland, the Russian Federation, Slovakia *No. of centres:* 92 *Funding*: grants from Medtronic Bakken Research Center, AstraZeneca and R Becker	*Intervention*: ICD + OPT. In total, 78% received Medtronic models of the GEM® family, 11% Micro Jewel II, 8% Maximo and 3% Marquis. A total of 81% were single-chamber ICDs. A Fidelis lead was used in 21% of patients. Protocol required two consecutive terminations of VF at 10 J below the maximum ICD output and 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 described further) *Other interventions used*: Not stated	*Indication for treatment*: Recent MI (within ≤ 31 days) and predefined markers of elevated risk *No. of randomised participants:* 898; ICD: 445, OPT: 453 *Inclusion criteria*: Predefined markers of elevated risk: at least one of heart rate ≥ 90 bpm on the first available ECG (within 48 hours of MI) and LVEF ≤ 40% (on one of days 5–31 after MI); NSVT of three or more consecutive ventricular premature beats during Holter ECG monitoring, with a heart rate of ≥ 150 bpm (on days 5–31) *Exclusion criteria*: Ventricular arrhythmia before the index MI or > 48 hours after the event and required treatment, NYHA class IV, interval > 31 days between the MI and presentation, no ECG within 48 hours of chest pain onset, indication for CABG surgery, psychiatric disorder, severe concomitant disease, history of poor compliance with treatment, current participation in another trial, unstable clinical condition	*Primary outcome*: Overall mortality *Secondary outcomes*: SCD [death occurred within minutes of 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)], non-SCD, non-cardiac death *Method of assessing outcomes*: 3 and 6 months after randomisation and then at 6-month intervals *Length of follow-up*: Average 37 (range 0–106) months *Recruitment*: June 1999–October 2007

bpm, beats per minute.

Participant characteristics

Characteristic	ICD ($n = 445$)	OPT ($n = 453$)	p-value
Age (years), mean (SD)	62.8 (10.5)	62.4 (10.6)	
Sex, male, *n* (%)	345 (77.5)	344 (75.9)	
Ethnicity	NR	NR	
Criteria for inclusion, *n* (%)			
Criterion 1 only (heart rate and LVEF)	299 (67.2)	303 (66.9)	
Criterion 2 only (NSVT)	99 (22.2)	109 (24.1)	
Criteria 1 and 2	47 (10.6)	41 (9.1)	
LVEF (%), mean (SD)	34.6 (9.3)	34.5 (9.4)	
Criterion 1 only	32.2 (6.3)	31.9 (6.7)	
Criterion 2 only	45.9 (10.8)	44.8 (11.0)	
Criteria 1 and 2	29.6 (7.0)	31.4 (6.7)	
Heart rate	NR	NR	
Electrophysiology findings	NR	NR	
Medical therapy on admission *n/N* (%)			
Antiplatelet agents	438/443 (98.9)	442/452 (97.8)	
Beta-blockers	394/442 (89.1)	388/453 (85.7)	
ACE inhibitors	361/443 (81.5)	373/453 (82.3)	
STEMI, *n* (%)	341 (76.6)	348 (76.8)	
Reperfusion in STEMI, *n/N* (%)			
None	43/340 (12.6)	48/348 (13.8)	
PTCA	243/340 (71.5)	253/348 (72.7)	
Thrombolytic therapy, with or without PTCA	54/340 (15.9)	47/348 (13.5)	
Anterior wall MI, *n/N* (%)	282/439 (64.2)	300/449 (66.8)	
HF 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)	
LBBB, *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

Characteristic	ICD ($n = 445$)	OPT ($n = 453$)	p-value
NYHA class at discharge (in 885 surviving patients), *n* (%)			
I	247 (28)		
II	531 (60)		
III	106 (12)		
IV	1 (0.1)		
Discharge medication, % of patients			
Antiplatelet agents	96.1	95.8	
Beta-blockers	97.1	95.3	
ACE inhibitors	90.9	91.1	
Statins	91.6	91.5	
AADs (mainly amiodarone)	13.4	17.4	0.11

NR, not reported; PTCA, percutaneous transluminal coronary angiography; STEMI, ST-elevation myocardial infarction.

Comments

- Characteristics described as well balanced although diabetes and LBBB more frequent in the ICD group.
- Randomised to study treatment a mean (SD) of 13 (7) days after infarction. Implantation performed 'as soon as possible' after randomisation.[98]
- Implantation performed during hospitalisation for index infarction in 378 (91.1%) in the ICD group.

Results

Outcome	ICD ($n = 445$)	OPT ($n = 453$)	HR (95% CI) (unadjusted), p-value
Cause of death,[a] n/n (%)			
Any cause	116/445 (26.1)	117/453 (25.8)	1.04 (0.81 to 1.35), 0.15
SCD	27/445 (6.1)	60/453 (13.2)	0.55 (0.31 to 1.00), 0.049
Non-SCD	68/445 (15.3)	39/453 (8.6)	1.92 (1.29 to 2.84), 0.001
Non-cardiac death	21/445 (4.7)	18/453 (4.0)	1.23, 0.51
Cumulative 1-year death rate, %[b]	10.6	12.5	
Cumulative 2-year death rate, %[b]	15.4	18.2	
Cumulative 3-year death rate, %[b]	22.4	22.9	
HRQoL	NR	NR	
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalisations	NR	NR	
Change in NYHA class	NR	NR	
Change in LVEF	NR	NR	
Exercise capacity outcomes (e.g. 6-minute walk distance, total exercise time, peak VO_2)	NR	NR	

NR, not reported.

a Average follow-up of 37 (range 0–106) months.

b 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.

Comments

- 13 prespecified subgroups and one post hoc subgroup. HRs and p-values for death from any cause in nine (age, sex, CHF 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 prespecified subgroups (diabetes, hypertension, lipid abnormalities, number of risk factors) not shown in figure. The 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 that was < 0.05. States that a neutral effect of the ICD on overall mortality was seen in all three prespecified subgroups (patients meeting criterion 1 or 2 or both).
- Kaplan–Meier plots for all-cause mortality, risk of SCD and risk of non-SCD are presented but have not been data extracted.
- Cause of death also reported separately for participants meeting inclusion criterion 1 or 2 only or both criteria but these data have not been extracted. States that the effects were almost identical in these three predefined subgroups (interaction $p = 0.99$ or $p = 0.71$ for SCD or non-SCD respectively).

Adverse effects of treatment

Adverse effect	ICD ($n = 445$)	OPT ($n = 453$)	p-value
No. of ICDs actually implanted	415	39 (median 7.6 months after randomisation)	
Inserted lead entangled in tricuspid valve, removed surgically	1/415 patients		
ICD explanted or permanently deactivated during follow-up (median 6.8 months after implantation)	14/415 patients		
Clinically significant complications requiring hospitalisation, surgical correction or intravenous drug administration	65/415 (15.7%) patients, 76 complications		
Up to 30 days after implantation	19 (4.6%) patients		
During follow-up	48 (11.6%) patients		
Lead-related problems requiring surgical revision (included in the above complications)	10 patients (four had lead replacements)		
Died within 30 days of implantation, *n*	7 (MI 4, HF 3)		
Died within 30 days of randomisation, *n*	9	11	

Comments

Methodological comments

- *Allocation to treatment groups*: randomisation by the data co-ordinating centre with risk stratification to ensure a balanced number of patients with ST elevation and non-ST elevation MI between the ICD and control groups within these strata.[98] No further details on allocation.
- *Blinding*: an adverse event committee unaware of treatment assignment classified deaths. An independent data co-ordinating 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 an independent data co-ordinating centre and independently repeated by one of the authors. Subdistribution hazard analyses performed using R software. Baseline comparisons were carried out using Fisher's exact tests, chi-squared tests or Wilcoxon tests as appropriate. Cumulative risks of death estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Cumulative mortality by year and annual rates calculated using an inverse Kaplan–Meier analysis. Calculation of HRs and subgroup analysis performed on the basis of Cox proportional hazards models. Proportional hazards assumption tested on the basis of Schoenfeld residuals. Subgroup analyses (13 prespecified and one post hoc added for the effect of amiodarone) were performed one 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*: the 2-year survival rate was assumed to be 70.6% for the medical therapy group and 79.4% for the ICD group (RRR approximately 30% in the 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% per year and accounting for group sequential design the number of patients required in each group was 350. Recruitment time was more than doubled because the percentage of screened patients excluded was unexpectedly high. In December 2005 the data and safety monitoring board, because of lower than anticipated mortality, recommended increasing the required number of patients to 900 and extending follow-up until the last patient had been in the study for 1 year.
- *Attrition/dropout*: 415/445 ICD group patients actually received an ICD: 14 withdrew consent; 11 refused ICD implantation; five died before implantation could take place. ICDs were removed in 15 patients and 39 in the OPT group were given ICDs.
- *Other*: to increase recruitment two modifications to the protocol were made: (1) non-ST elevation MI included from June 2002; (2) qualifying heart rate on the first ECG was reduced from 100 bpm to 90 bpm from October 2004.

General comments

- *Generalisability*: people within 31 days of a MI.
- *Outcome measures*: appear appropriate.
- *Intercentre variability*: not reported.
- *Conflict of interests*: sponsors were informed of the 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 the interpretation of results.

bpm, beats per minute.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	Details not reported
Allocation concealment	Low	Randomisation by data co-ordinating centre
Performance bias		
Blinding of participants and personnel	High	No blinding
Detection bias		
Blinding of outcome assessment	Low	No blinding but outcomes not likely to be influenced (deaths classified by blinded committee)
Attrition bias		
Incomplete outcome data addressed	Low	Primary analysis according to the ITT principle
Reporting bias		
Selective reporting	High	Protocol paper[98] indicates that the SF-36 will be used to determine QoL but this outcome is not reported
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Multicenter Automatic Defibrillator Implantation Trial (MADIT) I

Reference and design	Intervention and comparator	Participants	Outcome measures
Moss *et al.* 1996,[99] MADIT Executive Committee 1991[100] *Study design*: RCT *Countries*: USA and Europe *No. of centres:* 32 (USA 30, Europe 2) *Funding*: research grant from CPI/ Guidant Corporation, St Paul, MN (also donated ICDs)[100]	*Intervention*: ICD + medical therapy. Pulse generators (monophasic $n = 79$; biphasic $n = 11$) and lead systems supplied by CPI/Guidant Corporation. Non-thoracotomy transvenous leads included in 1993. Late in the trial, a small number of patients had pulse generators with ECG 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 AADs in both groups *Other interventions used*: none reported	*Indication for treatment*: previous MI and left ventricular dysfunction *No. of randomised participants:* 196; ICD: 95 (transthoracic stratum 45, transvenous stratum 50), OPT: 101 (transthoracic stratum 53, transvenous stratum 48). Total transthoracic stratum: 98, total transvenous stratum: 98 Crossovers: 16; ICD: 5 (no ICD fitted), deactivated ICD: 2, OPT: 11 (ICD fitted) Loss to follow up: ICD: 1, OPT: 2 *Inclusion criteria*: age 25–80 years, NYHA class I, II or III, LVEF ≤ 0.35, Q-wave or enzyme-positive MI > 3 weeks before entry, a documented episode of asymptomatic, unsustained VT (run of 3–30 ventricular ectopic beats at a rate > 120 bpm) unrelated to an acute MI, no indications for CABG surgery or coronary angioplasty within the past 3 months, sustained VT or VF reproducibly induced and not suppressed after the intravenous administration of procainamide (or equivalent) *Exclusion criteria*: previous cardiac arrest or VT causing syncope not associated with an acute MI, symptomatic hypotension while in a stable rhythm, MI within the past 3 weeks, CABG surgery within the past 2 months or coronary angioplasty within the past 3 months, non-contraceptive-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, participating in other clinical trials	*Primary outcome*: death from all causes *Secondary outcomes*: none specified *Other outcomes reported*: prevalence of medications, adverse events, impact of 11 preselected baseline characteristics and medication type on observed HR for overall mortality *Method of assessing outcomes:* causes of death: categorised as either cardiac or non-cardiac (Hinkle and Thaler classification, reference provided) by two people reviewing information on deaths on or before 24 March 1996. Cardiac causes further categorised into arrhythmic, non-arrhythmic or uncertain Follow-up visits: clinical evaluation, recorded use of medication, test of defibrillator; 1 month after randomisation, thereafter 3-monthly until trial was stopped. Final evaluation 1 month after end of trial *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 December 1990

bpm, beats per minute.

Participant characteristics

Characteristic	ICD ($n = 95$)	OPT ($n = 101$)	p-value
Age (years), mean (SD)[a]	62 (9)	64 (9)	NR
Sex, % male/female[a]	92/8	92/8	NR
Ethnicity	NR	NR	
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 > 25 mg/dl (8.92 mmol/l)[a]	22	21	NR
Cholesterol > 200 mg/dl (5.17 mmol/l)	41	49	NR
LBBB, %[a]	7	8	NR
LVEF, mean (SD)[a]	0.27 (0.07)	0.25 (0.07)	NR
Qualifying unsustained VT (no. of consecutive beats), mean (SD)	10 (9)	9 (10)	NR
Electrophysiology – initial induction, %			
Monomorphic VT	87	91	NR
Polymorphic VT	7	7	NR
VF	6	2	NR
Electrophysiology – induction after antiarrhythmic challenge, %			
Monomorphic VT	92	94	NR
Polymorphic VT	7	5	NR
VF	1	1	NR
Cardiac history, %			
Two or more previous MIs[a]	34	29	NR
Treatment for ventricular arrhythmias	42	35	NR
Treatment for CHF[a]	52	51	NR
Treatment for hypertension[a]	48	35	NR
CABG surgery[a]	46	44	NR
Coronary angioplasty	17	27	NR
Implanted pacemaker	2	7	NR
Interval of ≥ 6 months between most recent MI and enrolment[a]	75	76	NR
Insulin-dependent diabetic, %	7	5	NR
Cigarette smoking (any time), %	79	73	NR

NR, not reported.
a Denotes 11 preselected variables for inclusion in a Cox regression analysis.

Comments

- States baseline characteristics of the two treatment groups were similar; no *p*-values reported.
- States that the distribution of the qualifying Q-wave MIs in terms of anterior, inferior and posterior locations was similar in the two treatment groups; no *p*-values reported.

Results

Outcome	ICD ($n = 95$)	OPT ($n = 101$)	HR (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 to 0.82), 0.009

NR, not reported.

Comments

- 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 the 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 than in the ICD group and suggest that this could be due to an inaccuracy in the classification of cause of death or the higher rate of amiodarone use in this group.

Cardiac medication

	1 month[a]		Last contact[b]		
Medication	ICD ($n = 93$)	OPT ($n = 93$)	ICD ($n = 86$)	OPT ($n = 82$)	p-value
AADs, %					
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, %					
ACE inhibitors	60	55	57	51	NR
Digitalis	58	38	57	30	NR
Diuretics	53	52	52	47	NR

NR, not reported.

a Data missing for two patients in the ICD group and eight patients in the OPT group.

b Last contact defined as the last recorded contact with the patient at the end of the trial, at the last clinic visit before death or at the last clinic visit before the patient was lost to follow-up.

Comments

- Separate Cox regression analyses revealed that neither medication nor any of the 11 preselected baseline variables had any 'meaningful influence' on the HR ($p > 0.2$ for all interactions). However, the authors acknowledge that the power of the analysis is limited because of the small patient numbers for some of the variables.
- ICD effects did not differ between those with transthoracic leads and those with transvenous leads ($p = 0.78$).

Adverse effects of treatment

Adverse effect	ICD ($n = 95$)[a]	OPT ($n = 101$)[a]	*p*-value
Operative deaths in the first 30 days, *n*	0	0	
Hypotension, *n*	0	1	
Syncope, *n*	1	5	
Hypothyroidism, *n*	0	1	
Sinus bradycardia, *n*	3	3	
Pulmonary fibrosis, *n*	0	3	
Pulmonary embolism, *n*	1	1	
Atrial fibrillation, *n*	4	0	
Pneumothorax, *n*	2	0	
Bleeding, *n*	1	0	
Venous thrombosis, *n*	1	0	
Surgical infection, *n*	2	0	
Problems with defibrillator lead, *n*	7	0	
Malfunction of defibrillator generator, *n*	3	2	
Total no. of patients with adverse events	19	12	

a Some patients had more than one adverse event.

Comments

Methodological comments

- *Allocation to treatment groups*: random assignment of eligible patients to either the ICD group or the OPT group within 30 days of completing the qualifying electrophysiological study. The randomisation scheme included stratification according to centre and the interval between the most recent MI 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).[100] After March 1993 and once non-thoracotomy transvenous leads were approved 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 two 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 two-sided alternatives, was used with preset 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 the ICD group and the OPT group. Weekly data analysis 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 preset termination boundaries (efficacy, inefficacy or no difference in outcome) of the sequential design. Because of the slow rate of enrolment from 12 November 1995 (before first enrolled patient had reached the fifth year of the study), patient data were censored for analytical 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 the ITT principle. All analyses and potential covariates were prespecified. After termination of the trial, sequential analysis methods were used to calculate a *p*-value and HR (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. Preselected 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 compared with that in the OPT group (the HR). 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 HR, 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 mortality rate among ICD patients compared with a postulated 2-year mortality rate of 30% among the patients randomly assigned to OPT, with a two-sided significance level of 0.05. After the introduction of transvenous leads (1 September 1993), the power requirement of the trial was increased from 85% to 90% so 'as not to compromise the credibility of the study'.
- *Attrition/dropout*: numbers lost to follow-up reported (ICD $n = 1$; OPT $n = 2$). Percentage of patients who completed the 1838 scheduled follow-up clinic visits was 92% for the ICD group and 86% for the OPT group. There were 16crossovers, 11 in the OPT group [adverse drug reaction $n = 2$, unexplained syncope $n = 2$, investigator concern about episodes of ventricular tachyarrhythmia $n = 6$ and aborted cardiac arrest (VF) $n = 1$] and five in the ICD group (high defibrillation threshold $n = 1$ and patient 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 CHD and left ventricular dysfunction, spontaneous asymptomatic unsustained VT and inducible and non-suppressible ventricular tachyarrhythmia on electrophysiological testing.
- *Outcome measures*: appear appropriate although unclear if all ITT (cardiac medication).
- *Intercentre variability*: not reported. However, an evaluation of the consistency of the beneficial effect of ICDs in eachof the two centres with the highest enrolment ($n = 42$ 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 that the reduction in mortality with ICDs is 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 Corporation or any other defibrillator-manufacturing company before study participation and to abide by the conflict of interest standards (reference cited).
- *Other*: study officially stopped when the efficacy boundary of the sequential design was crossed (when 51 deaths were reported).

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	No details of randomisation procedure in either trial paper[99] or protocol.[100] Patients were 'randomly assigned' by clinical centre and chronology of the interval after a previous MI[100]
Allocation concealment	Low	Random assignment provided to centres by telephone before receiving hard copy[100]
Performance bias		
Blinding of participants and personnel	High	Unblinded trial
Detection bias		
Blinding of outcome assessment	Low	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.[99,100] Mortality unlikely to be influenced by lack of blinding
Attrition bias		
Incomplete outcome data addressed	Low	Analyses 'followed the ITT principle'. For the purpose of analysis, patients were not withdrawn from the trial and every effort was made to ascertain the occurrence or non-occurrence of the primary end point.[100] Although not a primary outcome, it is unclear how missing data for type of medication ($n = 10$) were dealt with in the analysis
Reporting bias		
Selective reporting	Low	Described outcomes reported. Protocol published[100]
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Multicenter Automatic Defibrillator Implantation Trial (MADIT) II

Reference and design	Intervention and comparator	Participants	Outcome measures
Moss *et al.* 1999[102] and 2002,[101] Greenberg *et al.* 2004,[103] Noyes *et al.* 2007[104] *Study design*: RCT *Countries*: USA and Europe *No. of centres:* 76 (USA 71, Europe 5) *Funding*: research grant from Guidant Corporation, St Paul, MN, to the University of Rochester School of Medicine and Dentistry, NY	*Intervention*: ICD + conventional medial therapy. Transvenous defibrillator systems (Guidant Corporation) and standard defibrillator implant techniques were used. ICD programming and prescribing medications were at the discretion of the patients' physicians *Comparator*: conventional medical therapy (OPT). The appropriate use of beta-blockers, ACE inhibitors and lipid-lowering drugs was strongly encouraged in both study groups *Other interventions used*: none reported	*Indication for treatment*: high-risk cardiac patients with previous MI and advanced left ventricular dysfunction *No. of randomised participants:* 1232; ICD: 742, OPT: 490 Crossovers: 54; ICD: 32 [no ICD fitted: 21 (2.8%); ICD removed: 11 (1.5%) (nine heart transplants)]; deactivated ICD: 12 (usually because of terminal illness); OPT: 22 (4.5%) ICD fitted Loss to follow-up: ICD: 2, OPT: 1 *Inclusion criteria*: age > 21 years, LVEF ≤ 0.30 in last 3 months (assessed by angiography, radionuclide scanning or ECG), MI > 1 month before study entry (documented by an abnormal Q wave on ECG, elevated cardiac enzyme levels on laboratory testing during hospitalisation for suspected MI, 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 January 1998 (discontinued as majority of cases had such arrhythmias) *Exclusion criteria*: indication approved by the FDA for an ICD (and patients who met the MADIT I criteria for an ICD[102]), NYHA class IV at enrolment, undergone coronary revascularisation within the last 3 months, MI within the past month (evidenced by measurement of cardiac enzyme levels), advanced cerebrovascular disease, women of childbearing age not using medically prescribed	*Primary outcome*: all-cause mortality *Secondary outcomes*: adverse events, HRQoL, economic outcomes, incidence of SCD, incidence of cardiac death from progressive left ventricular failure *Method of assessing outcomes*: patients followed up 1 month post randomisation and at 3-monthly intervals. Causes of death were assessed using a modified version of the Hinkle–Thaler system (see *General comments*) *Cause of death definitions*:[103] SCD (modified Hinkle–Thaler system): (1) Died suddenly and unexpectedly within 1 hour of cardiac symptoms in the absence of progressive cardiac deterioration; (2) died unexpectedly in bed during sleep; (3) died unexpectedly within 24 hours of last being seen alive. SCD subclassified into those with and those without symptoms of severe left ventricular 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 within 1 hour of symptom onset – primary (without preceding symptoms) or secondary

Reference and design	Intervention and comparator	Participants	Outcome measures
		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	(complaint of chest pain during the hour before 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 contributed to, but was not the dominant feature of, the mortality event *HRQoL*:[104] HUI3 self-administered during face-to-face study visits at baseline and 3, 12, 24 and 36 months. Patients could complete the HUI3 at home and mail it back. HUI3 has eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain discomfort; –0.0371 = worse possible state, 0 = death, 1 = best possible health state) *Length of follow-up*: average 20 months (range 6 days to 53 months); HUI3: up to 36 months[104] *Recruitment*: 11 July 1997–20 November 2001

Participant characteristics

Characteristic	ICD ($n = 742$)	OPT ($n = 490$)	p-value
Age (years), mean (SD)	64 (10)	65 (10)	NR
Sex, % male/female	84/16	85/15	NR
Ethnicity	NR	NR	
Diagnosis	NR	NR	
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	NR	NR	
Blood urea nitrogen > 25 mg/dl (8.92 mmol/l), %	29	32	NR
Atrial fibrillation, *n*	9	8	NR
QRS interval ≥ 120 milliseconds, *n*	50	51	NR
Non-specific conduction defect, *n*	22	26	NR
RBBB, *n*	9	7	NR
LBBB, *n*	19	18	NR
Medication at last contact, %[b]			
Amiodarone	13	10	NR
ACE 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 months between most recent MI and enrolment, %	88	87	NR
Previous treatment, %			
Hypertension	53	53	NR
CABG surgery	58	56	NR
Coronary angioplasty	45	42	NR
Diabetes, %	33	38	NR
Current or former cigarette smoker, %	80	82	NR

NR, not reported; RBBB, right bundle branch block.

a Values reflect the highest NYHA functional class recorded in the 3 months before 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 group and 17 months in the OPT group.

Baseline characteristics by subgroup[103]

Characteristic	ICD		OPT		*p*-value
	Alive (*n* = 637)	Dead (*n* = 105)	Alive (*n* = 393)	Dead (*n* = 97)	
Age (years), mean (SD)	64 (11)	69 (9)[a]	64 (10)	68 (10)[a]	
Sex, % male	84	82	86	84	
NYHA functional class, %[b]					
I	36	27[a]	41	29[a]	
II	37	27[a]	36	27[a]	
III	27	46[a]	23	44[a]	
LVEF (%), mean (SD)	23 (5)	22 (6)[a]	24 (5)	23 (6)[a]	
Blood urea nitrogen > 25 mg/dl (8.92 mmol/l), %	25	51[a]	28	49[a]	
Atrial fibrillation, *n*	8	12	7	16[a]	
QRS interval ≥ 12 seconds, *n*	49	57	49	59	
RBBB, *n*	9	7	7	8	
LBBB, *n*	19	28	16	27	
Previous treatment, %					
Hypertension	53	54	53	55	
CABG surgery	58	59	56	56	
Coronary angioplasty	47	36	45	31	
Cardiac history, %					
Interval of > 6 month between most recent MI and enrolment, %	88	87	87	89	
Diabetes, %	32	34	36	43	
Cardiac morbidity after enrolment					
Hospitalisation for HF, *n*	20	60[a]	15	41[a]	
MI, *n*	4	20[a]	4	15[a]	
Coronary revascularisation, *n*	5	6	4	6	

RBBB, right bundle branch block.
a $p < 0.01$ for comparison between alive and dead within each treatment arm.
b Values reflect the highest NYHA functional class recorded in the 3 months before enrolment; limited to NYHA class I, II or III at enrolment.

Baseline health-related quality of life[104]

HRQoL measure	ICD ($n = 658$)	OPT ($n = 431$)	p-value
HUI3 score, mean	0.637	0.646	> 0.10
SF-12 PCS, mean	36.293	36.444	> 0.10
SF-12 MCS, mean	50.505	50.419	> 0.10
Hospitalised at baseline (%), mean	14.7	10.9	> 0.10

Comment
- All other baseline scores for these subgroups were similar to those of the main patient group above. HRQoL was not measured in European study centres ($n = 109$).

Results

Outcome	ICD ($n = 742$)	OPT ($n = 490$)	HR (95% CI), p-value
Primary outcome: mortality, no. of deaths (%)	105 (14.2)	97 (19.8)	0.69 (0.51 to 0.93), 0.016[a] 31% reduction in risk of death at any interval for ICD compared with OPT
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalisations	NR	NR	
Change in NYHA class	NR	NR	
Change in LVEF	NR	NR	
Exercise capacity outcomes (e.g. 6-minute walk distance, total exercise time, peak VO_2)	NR	NR	

NR, not reported.
a Adjusted for stopping rules.

Comments
- Kaplan–Meier estimates of survival were reported for years 1–4 and difference in survival between the groups was significant (nominal $p = 0.007$). The two survival curves began to diverge at around 9 months. Survival curves showed reductions in the rate of death with ICD use of 12% (95% CI to –27% to 40%) at 1 year, 28% (95% CI 4% to 46%) at 2 years and 28% (95% CI 5% to 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, NYHA class or QRS interval (presented in figure).
- There were also no significant differences in the effect of ICDs on survival in subgroup analyses classified according to the presence or absence of hypertension, diabetes, LBBB or atrial fibrillation; the interval since the most recent MI (≤ 6 months vs. > 6 months); the type of defibrillator implanted (single chamber vs. dual chamber); or the blood urea nitrogen level (≤ 25 mg/dl vs. > 25 mg/dl) (not presented in figure).

Subgroup analyses[103]

Outcome	ICD ($n = 105$)	OPT ($n = 97$)	p-value
Cause of death by treatment group (modified Hinkle–Thaler scheme), *n* (%)			
Cardiac death			
SCD	28 (27)	49 (51)	$p < 0.01$
Without severe left ventricular dysfunction	18	34	
With severe left ventricular dysfunction	10	15	
Non-SCD	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, % (*n*/*N*)			
Cardiac death rate	10.6 (79/742)	16.3 (80/490)	$p < 0.01$
SCD rate	3.8 (28/742)	10.0 (49/490)	
Non-SCD 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, *n* (%)			
SCD	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, % (*n*/*N*)			
Cardiac death	9.8 (73/742)	14.5 (71/490)	$p < 0.01$
SCD	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 rate out of hospital[a]	3.8 (28/742)	9.6 (47/490)	$p < 0.01$
Nominal death rate in hospital	5.7 (42/742)	4.5 (22/490)	

a ICD vs. OPT; cardiac deaths include only SCD and non-SCD according to the Hinkle–Thaler classification. Also reported are location and number of SCDs and non-SCDs, as well as chronology of cardiac death by treatment group (not extracted).

Comments

- Data are presented as the percentage of SCDs and non-SCDs 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 percentage.
- SCD: 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, $p < 0.01$; nominal death rate, non-SCD: higher for ICD than OPT but not significant (*p*-value not reported).
- Kaplan–Meier: HR for SCD 0.33 (95% CI 0.20 to 0.53), $p < 0.0001$; HR for non-SCD $p = 0.32$ (cumulative Kaplan–Meier curves of SCD rates reported years 0–4).

Health-related quality of life

	HUI3 scores while alive							
	ICD ($n = 658$)				OPT ($n = 431$)			
	0	Year 1	Year 2	Year 3	0	Year 1	Year 2	Year 3
Proportion alive		0.93	0.846	0.767		0.903	0.792	0.667
Mean score	0.637	0.627	0.622	0.601	0.646	0.659	0.667	0.678
Mean annual change[a]		–0.019	–0.027[b]	–0.019[c]		–0.012	–0.011	–0.013
Overall mean score including death[d]	0.637	0.584	0.526	0.461	0.646	0.595	0.529	0.452

a Equals (difference from baseline)/year.
b $p < 0.05$.
c $p < 0.10$.
d Mean HRQoL score (among n patients) after setting score for death to 0.

Adverse effects of treatment

Adverse effect	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 because of HF, 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 the week before SCD,[103] (%)	($n = 28$)	($n = 49$)	
Syncope	4	4	
Angina pectoris	4	4	
MI	4	10	
Ventricular arrhythmia	25	10	
CHF	43	16	

Comments

Methodological comments

- *Allocation to treatment groups*: patients were randomly assigned by the co-ordinating centre in a 3 : 2 ratio to receive an ICD (60.2%) or OPT (39.8%) stratified by clinical centre.
- *Blinding*: none reported. Authors state that information will be reported periodically to the independent safety monitoring subcommittee but kept confidential from investigators, executive committee and sponsors.
- *Comparability of treatment groups*: authors state that baseline characteristics and prevalence of the use of various cardiac mediations at the time of the last follow-up visit were similar between the two groups but no *p*-values are reported.
- *Method of data analysis*: analysis was performed according to the ITT principle. A triangular sequential design modified for two-sided alternatives and corrected for the lag in obtaining data accrued but not reported before the termination of the trial, for weekly monitoring, with preset boundaries to permit termination of the trial if ICD was found to be superior to, inferior to or equal to OPT was used. Secondary analyses were performed with the use of the Cox proportional hazards regression model. Survival curves were determined according to the Kaplan–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 two-tailed. Analyses used version 2.0 of the trial database, released on 16 January 2002. The trial was stopped on 20 November 2001 after analysis revealed that the difference in mortality between both groups had reached the prespecified efficacy boundary ($p = 0.027$). Subgroups were prespecified. Mortality events[103] were based on version 3.0 of the database (released 26 July 2002), chi-squared statistics were used for categorical data, *t*-test were used for continuous variables (independent samples), the Kaplan–Meier method was used for cumulative survival curves and the log-rank method was used for statistical comparison of cumulative mortality. The Cox proportional hazards regression model was used to calculate the risk of SCD and non-SCD in the total population and in subgroups stratified by relevant baseline characteristics for patients randomised to ICD compared with OPT. Missing HUI3 scores[104] were imputed using a multivariate fixed-effects model, regressing the difference between baseline score and a score for each subsequent visit on time, treatment, sex, age, death during the trial, death within 6 months of the HRQoL assessment, sudden death within 6 months of the HRQoL assessment, presence of diabetes, use of diuretics and having NYHA class II–IV symptoms.
- *Sample size/power calculation*: the 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 two-sided significance level of 0.05. For proportional hazards modelling, power was maintained for a true HR of 0.63 after allowance for crossover. Originally it was estimated that 1200 patients (720 ICDs and 480 OPT) were needed. On 4 May 2001, the executive committee increased the enrolment goal to 1500 patients so that enrolment would be ongoing while data on outcomes were still accruing.
- *Attrition/dropout*: the percentage of patients who completed the 8749 scheduled follow-up clinic visits was 97% for the ICD group and 94% for the OPT group [authors state that the status of three patients (two ICD, one OPT) at the termination of the trial is unknown]. Reasons for dropout not reported. HRQoL assessed in the 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-quality data. In total, 8.5% of the HRQoL data were missing and summary reasons were provided.

General comments

- *Generalisability*: limited to high-risk cardiac patients with a previous MI and advanced left ventricular dysfunction.
- *Outcome measures*: appear appropriate.
- *Intercentre variability*: not reported.
- *Conflict of interests*: supported by a research grant from Guidant Corporation, St Paul, MN. Drs Cannom, Daubert and Higgins have given lectures sponsored by the grant provider (Guidant Corporation). Authors state that all investigators agreed to abide by the conflict-of-interest guidelines and that investigators had full access to the data and performed the analysis with no limitations imposed by the sponsor.
- *Other:* ICD patients were not responsible for the incurred costs of the ICD, implantation or hospitalisation for the procedure.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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	No blinding reported
Detection bias		
Blinding of outcome assessment		
Mortality	Low	No blinding reported. Data were independently reviewed but the committee was not blinded.[103] Mortality unlikely to be influenced by lack of blinding
QoL	High	
Attrition bias		
Incomplete outcome data addressed	Low	Analysis was performed according to the ITT principle. Missing HUI3 scores were imputed using a multivariate fixed-effects model (see *Methodological comments*)
Reporting bias		
Selective reporting	Unclear	Apart from the primary end point, the protocol paper specifies only four secondary objectives (association of induced VT with ICD discharge rate; patients at risk of increased mortality according to prespecified Holter-recorded electrocardiological parameters at baseline; cost-effectiveness of ICDs; QoL)
Other bias		
Other sources of bias	Low	No costs in relation to ICDs were incurred by patients

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

Reference and design	Intervention and comparator	Participants	Outcome measures
Bardy *et al.* 2005,[105] Packer *et al.* 2009,[108] Michell *et al.* 2008,[106] Mark *et al.* 2008[107] *Study design*: RCT *Countries*: USA (99%[107]), Canada and New Zealand[106] *No. of centres:* 148[106] *Funding*: grants from the National Heart, Lung, and Blood Institute, the National Institutes of Health and Medtronic, Wyeth-Ayerst Laboratories and Knoll Pharmaceuticals	*Group 1*: ICDs. Single chamber ICD (Medtronic, model 7223) programmed to shock only mode (to treat only rapid 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 800 mg daily for 1 week and then 400 mg daily for 3 weeks. Then, patients > 200 lb (90.9 kg) received 400 mg daily, patients 150–200 lb (68.2–90.9 kg) received 300 mg daily and patients < 150 lb (68.2 kg) received 200 mg 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.[108] If clinically reasonable, all patients were required to receive treatment with a beta-blocker and an ACE inhibitor. When appropriate, participants received aldosterone, aspirin and statins[105]	*Indication for treatment*: Broad population of patients with mild to moderate HF *No. of randomised participants:* 2521; ICD: 829, amiodarone: 845, placebo:847 *Inclusion criteria*: NYHA class II or III chronic stable CHF from ischaemic or non-ischaemic causes, LVEF ≤ 35%, ≥ 18 years. Ischaemic CHF defined as LVSD associated with ≥ 75% narrowing of at least one of three major coronary arteries (marked stenosis) or a documented history of MI. Non-ischaemic CHF defined as LVSD without marked stenosis *Exclusion criteria*: None stated	*Primary outcomes*: death from any cause. For the QoL study, the DASI and the SF-36 MHI-5 *Secondary outcomes*: other scales from the SF-36, number of 'bed-days' and 'disability-days', MLWHFQ, 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 non-vascular events (e.g. serious lung, liver, kidney or other organ failure, cancer and sepsis)[108] QoL:[107] measured by structured interviews at baseline (before randomisation) and at months 3, 12 and 30 (or at the end of study follow-up). Interviews at the time of scheduled clinic visit or by telephone if visit was missed. A short proxy form was used if patients were too ill, had a 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 of ≥ 4 points is considered clinically significant). The 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

Reference and design	Intervention and comparator	Participants	Outcome measures
			(5 points in this study). Other SF-36 scales were scored the same way 'Bed-days' were defined as the number of days spent in bed all or most of the day in the last 42 days. 'Disability-days' were defined as the number of days (excluding bed-days) that the patient cut down usual activities for health reasons MLWHFQ was scored from 0 to 105 (higher scores indicate worse function, clinically significant difference approximately 5 points) Health status utility [0 (dead)–1 (excellent)] was assessed using the time trade-off technique Global health was rated on a scale of 0 (dead)–100 (excellent health) with a 5-point difference (one-quarter of 1 SD) approximating clinical significance *Length of follow-up*: to 31 October 2003. Median follow-up for surviving patients 45.5 (range 24–72.6) months *Recruitment*: September 1997–July 2001

bpm, beats per minute.

Participant characteristics

Characteristic	ICD ($n = 829$)	Amiodarone ($n = 845$)	Placebo ($n = 847$)	p-value
Age (years), median (IQR)	60.1 (51.9 to 69.2)	60.4 (51.7 to 68.3)	59.7 (51.2 to 67.8)	
Sex, male, *n* (%)[a]	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 (bpm), median (IQR)	74 (65 to 84)	72 (64 to 82)	73 (64 to 84)	
NSVT,[b] *n* (%)	210 (25)	193 (23)	180 (21)	
Syncope, *n* (%)	52 (6)	54 (6)	56 (7)	
Systolic blood pressure (mmHg), median (IQR)	118 (104–131)	118 (106–130)	120 (108–132)	
Diastolic blood pressure (mmHg), median (IQR)	70 (61–80)	70 (62–80)	70 (62–80)	
Medication use at enrolment, *n* (%)				
ACE inhibitor	684 (83)	731 (87)	718 (85)	
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)	
Acetylsalicylic acid (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)	
Hypercholesterolaemia, *n* (%)[c]	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)	

bpm, beats per minute.
a Calculated by reviewer.
b NSVT defined as three or more consecutive ventricular beats at a heart rate > 100 bpm.
c Hypercholesterolaemia defined as low-density lipoprotein cholesterol at enrolment of > 130 mg/dl after an overnight fast.

Comments

- Baseline characteristics of the electrophysiological study, weight, serum sodium and serum creatinine, were reported but not extracted. Groups were well balanced.
- Overall, 70% of the population had NYHA class II CHF and 30% had class III CHF.
- Selected baseline characteristics are reported for the participants in the QoL study[107] (ICD $n = 816$, amiodarone $n = 830$, placebo $n = 833$) but have not been extracted.
- Baseline characteristics are reported by race[106] but have not been extracted. Significant differences in demographic and clinical data were found between different racial groups.

Results

Outcome	ICD ($n = 829$)	Amiodarone ($n = 845$)	Placebo ($n = 847$)	HR (95% CI), 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 estimate for death from any cause, 5-year event rate	0.289	0.340	0.361	
Cardiac deaths, *n*/no. of deaths (%)[108]	122/182 (67)	162/240 (68)	167/244 (68)	HR amiodarone vs. placebo 1.05 (0.85 to 1.31), NS; HR ICD vs. placebo 0.76 (0.60 to 0.95), 0.018
Tachyarrhythmic	37/182 (20)	75/240 (31)	95/244 (39)	HR amiodarone vs. placebo 0.84 (0.62 to 1.13), 0.25; HR ICD vs. placebo 0.40 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 (0.81 to 1.60), NS; HR ICD vs. placebo 1.14 (0.82 to 1.60), NS
Non-arrhythmic, 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)	
Non-cardiac deaths, *n*/no. of deaths (%)[108]	48/182 (26)	54/240 (23)	53/244 (22)	HR amiodarone vs. placebo 1.10 (0.80 to 1.50), NS; HR ICD vs. placebo 0.80 (0.57 to 1.12), NS
Vascular	11/182 (6)	10/240 (4)	12/244 (5)	
Non-vascular	37/182 (20)	44/240 (18)	41/244 (17)	
Unknown deaths, *n*/no. of deaths (%)[108]	12/182 (7)	24/240 (10)	24/244 (10)	NS
Medication use at last follow-up, *n* (%)	($n = 822$)	($n = 840$)	($n = 838$)	
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)	
Acetylsalicylic acid (aspirin)	449 (55)	474 (56)	451 (54)	
Warfarin	279 (34)	272 (32)	300 (36)	
Statin	395 (48)	405 (48)	387 (46)	

Outcome	ICD ($n = 829$)	Amiodarone ($n = 845$)	Placebo ($n = 847$)	HR (95% CI), p-value
ICD shocks, *n/N* (%)				
Received for any cause, *n/N* (%)	259/829 (31)			
Received for rapid VT or VF, *n/N* (%)	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			

NS, not significant.

Comments

- As indicated by the HR for the mortality of ICD therapy compared with placebo, the RRR of ICD therapy was 23%. The absolute reduction at 5 years was 7.2 percentage points.
- Kaplan–Meier curves for mortality from any cause are presented but not extracted.[105] Curves are also presented for classifications of death but are not extracted.[108]

Adverse effects of treatment

Adverse effect	ICD ($n = 829$)	Amiodarone ($n = 845$)	Placebo ($n = 847$)	p-value
Implantation unsuccessful, *n* (%)	1 (< 1)			
ICD removed during follow-up, *n* (%)	32 (4)			
Clinically significant ICD complications,[a] %				
At the time of implantation	5			
Later in the course of follow-up	9			
At time of last follow-up, %				
Increased tremor		4 (amiodarone vs. placebo)		0.02
Increased hypothyroidism		6 (amiodarone vs. placebo)		< 0.001

a Defined as clinical events requiring surgical correction, hospitalisation or new and otherwise unanticipated drug therapy.

Prespecified subgroup analyses[105,106,108]

Outcome	ICD ($n = 829$)	Amiodarone ($n = 845$)	Placebo ($n = 847$)	HR (95% CI), p-value
Mortality from any cause – ischaemic CHF[105]				HR amiodarone vs. placebo 1.05 (97.5% CI 0.81 to 1.36), 0.66; HR ICD vs. placebo 0.79 (97.5% CI 0.60 to 1.04), 0.05
Kaplan–Meier estimates of mortality from any cause – 5-year event rate ischaemic CHF[105]	0.359 ($n = 431$)	0.417 ($n = 426$)	0.432 ($n = 453$)	
Cause of death, participants with ischaemic CHF[108]				
Cardiac				HR amiodarone vs. placebo 0.96 (0.73 to 1.26); HR ICD vs. placebo 0.80 (0.60 to 1.05)
Sudden tachyarrhythmic				HR amiodarone vs. placebo 0.70 (0.48 to 1.03); HR ICD vs. placebo 0.43 (0.27 to 0.67)
HF				HR amiodarone vs. placebo 1.17 (0.78 to 1.77); HR ICD vs. placebo 1.11 (0.74 to 1.67)
Non-cardiac				HR amiodarone vs. placebo 1.21 (0.88 to 1.94); HR ICD vs. placebo 0.79 (0.50 to 1.22)
Mortality from any cause – non-ischaemic CHF[105]				HR amiodarone vs. placebo 1.07 (97.5% CI 0.76 to 1.51), 0.65; HR ICD vs. placebo 0.73 (97.5% CI 0.50 to 1.07), 0.06
Kaplan–Meier estimates of mortality from any cause – 5-year event rate non-ischaemic CHF[105]	0.214 ($n = 398$)	0.258 ($n = 419$)	0.279 ($n = 394$)	
Cause of death, participants with non-ischaemic CHF[108]				
Cardiac				HR amiodarone vs. placebo 1.23 (0.85 to 1.77); HR ICD vs. placebo 0.68 (0.44 to 1.03)
Sudden tachyarrhythmic				HR amiodarone vs. placebo 1.13 (0.68 to 1.85); HR ICD vs. placebo 0.34 (0.17 to 0.70)
HF				HR amiodarone vs. placebo 1.06 (0.58 to 1.96) HR ICD vs. placebo 1.21 (0.67 to 2.18)
Non-cardiac				HR amiodarone vs. placebo 0.81 (0.48 to 1.36); HR ICD vs. placebo 0.81 (0.48 to 1.37)
Mortality from any cause – NYHA II[105]				HR amiodarone vs. placebo 0.85 (97.5% CI 0.65 to 1.11), 0.17; HR ICD vs. placebo 0.54 (97.5% CI 0.40 to 0.74), < 0.001
Kaplan–Meier estimates of mortality from any cause – 5-year event rate NYHA II[105]	0.201 ($n = 566$)	0.264 ($n = 601$)	0.320 ($n = 594$)	

Outcome	ICD ($n = 829$)	Amiodarone ($n = 845$)	Placebo ($n = 847$)	HR (95% CI), p-value
Cause of death, participants with NYHA class II CHF[108]				
Cardiac				HR amiodarone vs. placebo 0.88 (0.66 to 1.17); HR ICD vs. placebo 0.50 (0.36 to 0.70)
Sudden tachyarrhythmic				HR amiodarone vs. placebo 0.68 (0.47 to 0.99); HR ICD vs. placebo 0.26 (0.15 to 0.44)
HF				HR amiodarone vs. placebo 0.93 (0.56 to 1.54); HR ICD vs. placebo 0.93 (0.56 to 1.54)
Non-cardiac				HR amiodarone vs. placebo 0.79 (0.52 to 1.20); HR ICD vs. placebo 0.63 (0.40 to 0.99)
Mortality from any cause – NYHA III[105]				HR amiodarone vs. placebo 1.44 (97.5% CI 1.05 to 1.97), 0.010; HR ICD vs. placebo 1.16 (97.5% CI 0.84 to 1.61), 0.30
Kaplan–Meier estimates of mortality from any cause – 5-year event rate NYHA III[105]	0.484 ($n = 263$)	0.528 ($n = 244$)	0.456 ($n = 253$)	
Cause of death, participants with NYHA class III CHF[108]				
Cardiac				HR amiodarone vs. placebo 1.33 (95% CI 0.95 to 1.86); HR ICD vs. placebo 1.17 (95% CI 0.84 to 1.64)
Sudden tachyarrhythmic				HR amiodarone vs. placebo 1.22 (95% CI 0.73 to 2.03); HR ICD vs. placebo 0.73 (95% CI 0.41 to 1.29)
HF				HR amiodarone vs. placebo 1.34 (95% CI 0.84 to 2.11); HR ICD vs. placebo 1.34 (95% CI 0.86 to 2.09)
Non-cardiac				HR amiodarone vs. placebo 1.68 (95% CI 1.03 to 2.73); HR ICD vs. placebo 1.10 (95% CI 0.66 to 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 1.44). For patients with NYHA class II CHF, no excess risk of death was associated with amiodarone therapy compared with placebo (HR 0.85).
- The interaction between ICD therapy and NYHA class was significant ($p < 0.001$). Among patients with NYHA class II CHF there was a 46% relative reduction in the risk of death (HR 0.54) for those in the ICD group compared with the placebo group. 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 with the placebo (HR 1.16).
- Kaplan–Meier plots are presented but were not extracted.
- Other subgroup analyses [sex, age, race (white vs. non-white; see next section for white vs. African American), LVEF, QRS duration, 6-minute walk distance, use of beta-blockers, diabetes] are presented but were not data extracted as not specified a priori.
- Packer *et al.*,[108] reporting on the 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 amiodarone therapy and HF classes with respect to cardiac mortality ($p = 0.064$), sudden death ($p = 0.073$) or HF mortality ($p = 0.30$).
- For type of HF (ischaemic/non-ischaemic), Packer *et al.*[108] 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 between 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[106]

	ICD		Amiodarone		Placebo	
Outcome	AA 36%	White 33%	AA 30%	White 34%	AA 34%	White 33%
Risk of death	HR ICD vs. placebo 0.65 (95% CI 0.43 to 0.99), p = not reported	HR ICD vs. placebo 0.73 (95% CI 0.58 to 0.90), p = not reported	HR amiodarone vs. placebo 1.08 (95% CI 0.71 to 1.64), p = not reported	HR amiodarone vs. placebo 1.11 (95% CI 0.90 to 1.37), p = not reported		
ICD discharges	No significant difference observed between white and AA participants, HR 1.10 (95% CI 0.80 to 1.51), p = 0.56					

AA, African American.

Quality-of-life study[107]

Outcome	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, mean score (SD)				
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)

Outcome	ICD ($n = 816$)	Amiodarone ($n = 830$)	Placebo ($n = 833$)	Difference (95% CI), p-value
MLWHFQ, 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[107]				
3 months	75		70	0.002
12 months	75		70	0.05
30 months	70		70	0.18

NR, not reported.

Comments

- Median (IQR) scores for DASI reported but not extracted. This also showed no significant difference between the ICD group and the placebo group at baseline ($p = 0.76$) and at months 3, 12 and 30 ($p > 0.10$). There were also no significant differences at any point between the amiodarone group and the placebo group.
- Median (IQR) scores for MHI-5 also reported but not extracted. This also showed no significant difference between the ICD group and the placebo group at baseline ($p = 0.17$) score was better in the ICD group than in the placebo group at 3 months (median scores 80 and 76 respectively, $p = 0.01$) and 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 group and the placebo group.
- 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 a significantly better score 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 patients in the placebo group on the SF-36 pain index at all four time points.
- Baseline (for the whole sample) but not follow-up data on number of bed-days are reported. Authors state that an effect of ICD therapy compared with placebo could not be detected for number of bed-days, or disability-days, or for the proportion of patients who were able to drive a car, manage their finances or maintain employment during the follow-up period.
- Authors state that there was a significant improvement in the ICD group compared with 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 are presented (baseline utility measure averaged 0.80 at baseline in all three groups).
- Results are presented for an analysis accounting for the improved survival in participants in the ICD group but these have not been extracted. Authors state that these results were not materially different from the unadjusted comparisons, which have been extracted.

Subgroup analyses: quality-of-life study[107]

Outcome	ICD ($n = 816$)		
	Received shock[a] ($n = 49$)	No shock	*p*-value
SF-36 score, mean change[b]			
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 49 participants received a shock up to 1 month before a scheduled QoL assessment.
b Changes in scores for patients who had received a shock are calculated as the value after the shock was delivered minus the most recent value before the shock. Changes in scores for the non-shock group are calculated as the QoL value at 3 months minus the value at baseline. Authors state that the results were similar when other follow-up time points were used to calculate the change in scores. A positive change indicates better function.

Comments

- Authors state that the pattern was the same for the 66 participants who had received a shock up to 2 months before a scheduled QoL assessment, but with smaller differences.
- Authors state that a comparison between 100 surviving patients who received an ICD shock at any time in the first year and 638 participants who did not receive a shock showed no significant differences. Also, the number of ICD discharges (above a range of two to five) did not have a significant effect on subsequent QoL. Further details not reported.

Comments

Methodological comments

- *Allocation to treatment groups*: patients assigned to amiodarone or placebo began therapy as outpatients immediately after randomisation. ICD group patients received the device a median of 3 days after randomisation (IQR 2-5 days). Permuted-block randomisation was carried out, stratified by clinical site, cause of CHD (ischaemic vs. non-ischaemic) 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 tablets that appeared identical.[105] The events committee that adjudicated deaths was blinded to treatment assignment (a nurse removed all information identifying randomised therapy assignment from reports).[108]
- *Comparability of treatment groups*: authors state that there were no significant differences between the groups at baseline. By the last follow-up visit there was a difference in use of beta-blockers ($p < 0.001$). The median dose of amiodarone and placebo was 300 mg/day 3 months after randomisation and remained so throughout the study. QoL study:[107] 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 according to the ITT principle. All statistical tests two-tailed. Cumulative mortality rates calculated using the Kaplan–Meier method. Event (or censoring) times measured from time of randomisation (time zero). Differences in mortality rates assessed using the log-rank test, with adjustment for NYHA class and cause of CHF. RRs expressed as HRs with 97.5% CIs (consistent with an alpha level of 0.025) are derived from the Cox proportional hazards model (however, 95% CIs are reported by Parker *et al.*[108]). Cox model also used to test the significance of interactions between NYHA class and treatment, and between cause of CHF and treatment. Six interim analyses were performed and reviewed by the independent data and safety monitoring board using two-sided, symmetrical 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. QoL study:[107] continuous data described with means (SD) and/or medians (25–75 percentiles). Categorical variables described with percentages. Pearson's chi-squared test was used for categorical variable comparisons and the Wilcoxon rank-sum test was used for continuous variables. The Wilcoxon rank-sum test for changes in scores from the most recent QoL measurements before a shock occurred was used to compare patients who received a shock within the month preceding a QoL assessment with those who did not. The analysis was repeated with 2- and 12-month time frames. To account for potential bias as a result of the significant difference in mortality between the groups, an estimator for the survival average causal effect was applied in a sensitivity analysis. All reported *p*-values were two-sided and no adjustments were made for multiple testing.
- *Sample size/power calculation*: based on the assumption that the placebo group would have an annual mortality rate of 10%. Powered at 90% to detect a 25% reduction in death from any cause with amiodarone or ICD therapy compared with placebo on the basis of an alpha level for each comparison of 0.025.
- *Attrition/dropout*: vital status known for all 2521 patients at the time of the last scheduled follow-up visit. The non-compliance rate for study drug therapy (discontinuation of placebo or amiodarone for any period) was 27% (458 patients) – 22% of the placebo group (189/847 patients) and 32% of the amiodarone group (269/845 patients). Crossovers: 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%) patients received open-label amiodarone during some part of the follow-up and 17/829 (2%) patients assigned to ICD therapy declined to undergo implantation. Crossover 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:[107] 98% completed the baseline QoL questionnaires. At each

follow-up 93–95% of eligible patients were included; overall, 95% of the questionnaires were collected. A total of 1.2% of patients declined to complete the questionnaires, 1.4% of the forms were judged incomplete and in 69/6268 (1.1%) 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 HF and no exclusions stated. However, the majority of the participants were American and the racial mix of participants differs to that likely in the UK.
- *Outcome measures*: appear appropriate.
- *Intercentre variability*: for the QoL study specific training was provided at each site to ensure standardisation of data collection.[107] No other details provided.
- *Conflict of interests*: authors state that companies provided study drugs and ICDs free of charge and provided additional clinical and research funding. However, neither company had any role in the design, analysis or interpretation of the study.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	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	No blinding of ICD arm. QoL: risk of bias between ICD and non-ICD groups because of knowledge of intervention received
Detection bias		
Blinding of outcome assessment		
Mortality	Low	Events committee who adjudicated deaths was blinded to treatment group
QoL	High	QoL data obtained by structured interview; risk of bias between ICD and non-ICD groups because of knowledge of intervention received
Attrition bias		
Incomplete outcome data addressed		
Mortality	Low	ITT analysis and vital status known for all patients at time of last visit
QoL	Unclear	Some explanation of missing data but not by treatment group
Reporting bias		
Selective reporting	Low	Protocol not available but papers appear to report all of the expected and stated outcomes
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Appendix 8 Data extraction: people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony

Cardiac Resynchronization – Heart Failure (CARE-HF) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Cleland *et al.* 2001,[110] 2005,[109] 2006,[111] 2008[112] and 2009,[113] Gras *et al.* 2007,[36] Gervais *et al.* 2009,[114] Ghio *et al.* 2009[115] *Study design*: RCT *Countries*: European countries including the UK, France, Germany, Switzerland and Italy[109] *No. of centres:* 82[109] *Funding*: supported by a grant from Medtronic	Intervention: CRT-P + medical therapy (standard pharmacological therapy). CRT (Medtronic InSync or InSync III device) provided atrial-based, biventricular stimulation. Standard right ventricular and Attain (Medtronic) left ventricular leads. Back-up atrial pacing set at 60 bpm, interventricular delay set at zero, atrioventricular delay echocardiographically optimised[109] Comparator: medical therapy (standard pharmacological therapy) only[109] Other interventions used: none reported. Standard medications adjusted if needed at follow-up visits	*Indication for treatment*: NYHA class III or IV from LVSD and cardiac dyssynchrony receiving standard pharmacological therapy[109] *No. of randomised participants:* 813; CRT-P + medical therapy: 409, medical therapy alone: 404[109] *Inclusion criteria*: NYHA class III or IV despite standard pharmacological therapy, LVEF ≤ 35%, LVEDD ≥ 30 mm (indexed to height), QRS interval ≥ 120 milliseconds (patients with QRS interval of 120–149 milliseconds required to meet two of three additional criteria for dyssynchrony: aortic pre-ejection delay > 140 milliseconds, interventricular mechanical delay > 40 milliseconds, delayed activation of posterolateral left ventricular wall), age ≥ 18 years, HF for ≥ 6 weeks[109] *Exclusion criteria*: major cardiovascular event in previous 6 weeks, conventional indications for a pacemaker or an ICD, HF requiring continuous intravenous therapy, atrial arrhythmias[109]	*Primary outcomes*: composite of death from any cause or an unplanned hospitalisation for a major cardiovascular event (only first hospitalisation counted).[109] For extension phase, death from any cause[111] *Secondary outcomes*: death from any cause, composite of death from any cause and unplanned hospitalisation for HF, 90-day NYHA class, 90-day QoL.[109] For extension phase, mode of death[111] *Method of assessing outcomes*: assessment at baseline and 1, 3, 6, 9, 12 and 18 months, then at 6-month intervals. For QoL,[113] assessment at baseline and 3 months, then disease-specific instrument only at 18 months and study end QoL: patient assessed using the disease-specific MLWHFQ (score range 0–105, higher score indicates lower QoL) and the generic EQ-5D (score range –0.594 to 1.0, lower score indicates lower QoL, negative scores considered worse than death) *Length of follow-up*: mean 29.4 months (range 18.0–44.7 months).[109] For QoL,[113] median 29.6 months (IQR 23.6–34.6 months). After 8-month extension phase, mean 37.4 months (range 26.1–52.6 months), median 37.6 months (IQR 31.5–42.5 months)[111] *Recruitment*: January 2001–March 2003[109]

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter.

Participant characteristics[109]

Characteristic	CRT-P + medical therapy ($n = 409$)	Medical therapy ($n = 404$)	*p*-value
Age (years), median (range)	67 (60–73)	66 (59–72)	
Sex, male, *n* (%)	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 (milliseconds), 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 (milliseconds), median (range)	49 (32–67)	50 (30–66)	
Mitral regurgitation area (cm^2), median (range)	0.21 (0.12–0.33)	0.23 (0.11–0.34)	
Use of ACE inhibitor or ARB, *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 (mmHg), median (range)	110 (100–125)	110 (100–125)	
Diastolic blood pressure (mmHg), 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/minute/1.73 m^2), median (range)	60 (46–73)	61 (46–73)	

bpm, beats per minute; NR, not reported.

Comments

- Beta-blockers were taken at some time during the study by 85% of the medical therapy group and 84% of the CRT-P group.
- Information on associations between baseline EQ-5D score and baseline patient characteristics is reported but has not been data extracted.[113]
- Baseline characteristics for the 735 participants who had an analysable echocardiographic examination at baseline are presented in another paper[115] on left ventricular reverse modelling outcomes but have not been data extracted. The clinical characteristics of these participants are described as similar to those of the whole study population.

Results

Outcome[109]	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, *n*[111]	19	34	
Deaths in main study + deaths in extension phase, *n/N* (%)	101/409 (24.7), 7.9% per annum	154/404 (38.1), 12.2% per annum	HR 0.60 (0.47 to 0.77), < 0.0001
Principal cause of death, *n/N* deaths (%)			
Cardiovascular	167/202 (83)		
Non-cardiovascular	34/202 (17)		
Not classifiable	1/202 (0.5)		
Death attributed to worsening HF, *n/N* deaths (%)	33/82 (40)	56/120 (47)	
Deaths from HF in main study + extension phase, *n*[111]	38 (3.0% per annum)	64 (5.1% per annum)	HR 0.55 (0.37 to 0.82), 0.003
Death classified as sudden, *n/N* deaths (%)	29/82 (35)	38/120 (32)	
Sudden deaths in the extension phase, *n/N* deaths[111]	3/19	16/34	
Sudden deaths in main study + extension phase, *n*[111]	32 (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[111]	23.6	35.1	
Death from any cause or unplanned hospitalisation with worsening HF, *n/N* (%)	118/409 (29)	191/404 (47)	HR 0.54 (0.43 to 0.68), < 0.001
Unplanned hospitalisation with worsening HF, *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, *n*	12	15	
Heart transplantations, *n*[b]			
Emergency	1	3	
Elective	9	6	

Outcome[109]	CRT-P + medical therapy ($n = 409$)	Medical therapy ($n = 404$)	HR or difference in means (95% CI), *p*-value
MLWHFQ score, mean (SD) at 90 days[c]	31 (22)	40 (22)	Difference in means –10 (–8 to –12), < 0.001
EQ-5D score, mean (SD) at 90 days[c]	0.70 (0.28)	0.63 (0.29)	Difference in means 0.08 (0.04 to 0.12), < 0.001
NYHA class, mean (SD) at 90 days	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, *n*			
Class I	105	39	
Class II	150	112	
Class III or IV	80	152	
	Difference in means[d] (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 (mmHg)			
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 (mmHg)			
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 (ms)[e]			
At 3 months	–21 (–25 to –18)		< 0.001
At 18 months	–21 (–25 to –17)		< 0.001
Left ventricular end-systolic volume 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 (cm^2)			
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

Outcome[109]	CRT-P + medical therapy ($n = 409$)		Medical therapy ($n = 404$)		HR or difference in means (95% CI), p-value
	IHD ($n = 168$)	Non-IHD ($n = 197$)	IHD ($n = 135$)	Non-IHD ($n = 235$)	p-value
LEVF					
Baseline (%), median (IQR)[115]	25 (22 to 29)	24 (21 to 29)	26 (22 to 30)	24 (21 to 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

bpm, beats per minute; IHD, ischaemic heart disease.

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 compared with the medical therapy group.

d Differences were not adjusted for the higher mortality rate in the medical therapy group. A plus sign indicates that the CRT-P value is greater than the medical therapy group-value; a minus sign indicates that the CRT-P value is smaller than the medical therapy group value.

e Similar but not identical data also presented by Ghio *et al*.[115]

f Values estimated from figure by reviewer using digitising software.[115] Not stated, but error bars presumed to show SDs.

Comments

- Authors state that 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, as these values differ from those in the table above, they 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 was the primary event in 309 patients.
- 12 CRT-P patients and 10 OPT patients had unplanned hospitalisations for a major cardiovascular event that occurred within 10 days of 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 HF and time to death from sudden death but these have not been data extracted.
- The 72 CRT-P participants with unplanned hospitalisations with worsening HF had 122 hospitalisations in total, whereas the 133 participants with unplanned hospitalisations in the medical therapy group had 252 hospitalisations in total.
- Outcomes from a multivariable analysis[112] of 15 baseline variables and eight 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[114] of electrocardiographic measures, which assessed whether a surface ECG can predict outcomes, have not been data extracted.
- Ejection fraction outcomes for subgroups with or without ischaemic heart disease but not for subgroups with restrictive/non-restrictive left ventricular filling or measures of right ventricular dysfunction have been extracted from the left ventricular reverse remodelling paper.[115] Other outcomes (end-diastolic and end-systolic volumes, severity of mitral regurgitation, predictors of long-term response) have not been extracted.

Quality-of-life results[113]

Outcome	CRT-P + medical therapy ($n = 409$)	Medical therapy ($n = 404$)	MD (95% CI), p-value
Mean QALYs (95% CI)			
3 months	0.16 (0.15 to 0.16)	0.15 (0.14 to 0.15)	0.01 (0.001 to 0.018), 0.285
18 months	0.95 (0.91 to 0.99)	0.82 (0.78 to 0.86)	0.13 (0.07 to 0.018), < 0.0001
End of study	1.45 (1.38 to 1.53)	1.22 (1.15 to 1.29)	0.23 (0.13 to 0.33), < 0.0001
Mean life-years (95% CI)			
3 months	0.241 (0.238 to 0.244)	0.241 (0.238 to 0.244)	0.0003 (–0.004 to 0.0045), 0.90
18 months	1.37 (1.34 to 1.40)	1.33 (1.29 to 1.37)	0.04 (–0.01 to 0.09), 0.13
End of study	2.07 (1.99 to 2.15)	1.96 (1.88 to 2.05)	0.10 (–0.01 to 0.22), 0.07[a]
EQ-5D score (95% CI)			
Baseline	0.60 (0.58 to 0.63)	0.60 (0.57 to 0.63)	–
3 months	0.69 (0.66 to 0.72)	0.61 (0.59 to 0.64)	0.08 (0.04 to 0.11), < 0.0001
18 months	0.61 (0.58 to 0.64)	0.51 (0.48 to 0.54)	0.10 (0.06 to 0.15), < 0.0001
End of study	0.56 (0.52 to 0.59)	0.43 (0.39 to 0.46)	0.13 (0.08 to 0.18), < 0.0001[b]
MLWHFQ score (95% CI)			
Baseline	44.6 (42.5 to 46.7)	43.7 (41.5 to 45.8)	–
3 months	30.1 (27.9 to 32.3)	38.9 (36.6 to 41.2)	–10.6 (–8.1 to –13.1), < 0.0001[c]
18 months	28.4 (26.2 to 30.5)	36.0 (33.5 to 38.5)	–10.7 (–7.6 to –13.8), < 0.0001[c]
End of study	27.2 (24.9 to 29.5)	35.1 (32.6 to 37.6)	–10.1 (–6.8 to –13.3), < 0.0001[c]
Mean [median (IQR)] days in hospital by 3 months	7.5 [4 (2–8)]	3.4 [0 (0–1)]	
Days in hospital after 3 months	222	384	
Mean [median (IQR)] days in hospital overall during entire study (median 29.6 months)	20.7 [9 (4–26)]	22.4 [9 (0–31)]	

a 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 earlier.
b Decline in EQ-5D score despite a maintained effect on the MLWHFQ is because death has a health use of zero on the EQ-5D and is not included in the MLWHFQ.
c MLWHFQ scores include the last value carried forward for missing items. Patients who died are not included. Difference between groups accounts for baseline NYHA class and MLWHFQ score.

Comments

- Baseline EQ-5D score (mean 0.60, 95% CI 0.58 to 0.62) is lower than that of representative age-matched general population (mean 0.78, 95% CI 0.76 to 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 are presented for the proportion of patients with improved, the same or worse EQ-5D scores but these have not been extracted (incomplete data: 320/409 in CRT group, 315/404 in medical therapy group). Data are presented in a figure for the proportion of patients with a deterioration in, an improvement in or the same MLWHFQ score but these have not been extracted.
- A figure showing that by 3 months CRT reduced the proportion of patients reporting problems in all EQ-5D dimensions has not been data extracted.
- Subgroup analyses (predefined) showing that there was little heterogeneity in the effect of CRT on QALYs are reported but not extracted.
- In first 3 months the CRT group spent more days in hospital as a result of device implantation but overall spent fewer days because of the small number of unplanned hospitalisations for major cardiovascular events.
- There are minor differences between the QoL results reported in the main trial publication[109] and those reported in this table.[113] The reasons for these minor differences are not clear.

Adverse effects of treatment[109]

Adverse effect	CRT-P + medical therapy ($n = 409$)	Medical therapy ($n = 404$)	p-value
Device-related deaths, *n*	1 (HF aggravated by lead displacement)	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 HF, *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 neurological events was similar in the two groups; numerical data not presented.
- More detailed reporting of adverse events in the paper by Gras *et al.*[36] 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; however; some of these data do not appear to match those data reported in this table from the main paper[109] and thus they have not been extracted.

Subgroup analyses[109]

Subgroup	Patients with event/total no. of patients	HR (95% CI)
Overall with primary end point	383/813	0.63 (0.51 to 0.77)
Age (years)[a]		
< 66.4	163/406	0.55 (0.40 to 0.75)
≥ 66.4	220/407	0.68 (0.52 to 0.89)
Sex		
Male	290/597	0.62 (0.49 to 0.79)
Female	93/215	0.64 (0.42 to 0.97)
NYHA class		
III	349/763	0.64 (0.52 to 0.80)
IV	34/50	0.50 (0.25 to 1.01)
Dilated cardiomyopathy		
No	238/443	0.68 (0.53 to 0.88)
Yes	145/370	0.51 (0.36 to 0.73)
Systolic blood pressure (mmHg)[a]		
< 117	208/401	0.60 (0.46 to 0.80)
≥ 117 mmHg	170/402	0.66 (0.48 to 0.89)
N-terminal pro-brain natriuretic peptide (pg/ml)		
< 214.5	122/366	0.53 (0.36 to 0.76)
≥ 214.5	224/366	0.70 (0.54 to 0.91)
Ejection fraction (%)[a]		
< 24.7	205/372	0.65 (0.49 to 0.86)
≥ 24.7	152/373	0.62 (0.44 to 0.85)
Left ventricular end-systolic volume index (ml/m^2)[a]		
< 119.2	156/366	0.71 (0.52 to 0.98)
≥ 119.2	193/366	0.54 (0.40 to 0.73)
QRS interval (milliseconds)		
< 160	152/290	0.74 (0.54 to 1.02)
≥ 160	222/505	0.60 (0.46 to 0.79)
Interventricular mechanical delay (milliseconds)[a]		
< 49.2	199/367	0.77 (0.58 to 1.02)
≥ 49.2	147/368	0.50 (0.36 to 0.70)
Mitral regurgitation area (cm^2)[a]		
< 0.218	114/302	0.86 (0.60 to 1.25)
≥ 0.218	175/303	0.56 (0.41 to 0.75)
Glomerular filtration rate (ml/minute/1.73 m^2)[a]		
< 60.3	196/369	0.67 (0.50 to 0.89)
≥ 60.3	142/370	0.57 (0.40 to 0.80)

Subgroup	Patients with event/total no. of patients	HR (95% CI)
Beta-blockers		
No	131/227	0.72 (0.51 to 1.02)
Yes	252/586	0.59 (0.46 to 0.76)
Spironolactone		
No	166/356	0.58 (0.43 to 0.79)
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)
≥ 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)
Yes	165/346	0.59 (0.43 to 0.81)

a Divided according to the median value in the study population.

Comments

- All analyses were stratified according to NYHA class, except for the subgroup analysis of NYHA class.
- For some data many patients had results at the median value and this led to some inequalities in the sizes of the subgroups (e.g. QRS interval).
- There were missing baseline data for sex, systolic blood pressure, N-terminal pro-brain natriuretic peptide level, 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 a major cardiovascular event).[111] 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.

Comments

Methodological comments

- *Allocation to treatment groups*: randomisation stratified by NYHA class and carried out by an independent clinical research organisation (Quintiles, Dublin) using a minimisation procedure.[109]
- *Blinding*: not blinded;[109] however, members of the end points committee (who classified all hospitalisations and some adverse events) were not aware of patients' treatment assignments. Procedure- or device-related adverse events classified by an unblinded independent expert.[109]
- *Comparability of treatment groups*: baseline characteristics similar.
- *Method of data analysis*: all prespecified analyses carried out according to the ITT principle. Time to event calculated using Kaplan–Meier method and analysed with Cox proportional hazard models (baseline NYHA as a covariate). Continuous data (including QoL[113] and ECG outcomes[115]) analysed using mixed models that included baseline variables as patient-level covariates and study centres as random effects. Dichotomous outcomes analysed using non-linear mixed models with NYHA class as a patient-level covariate and study centres as random effects. Adverse event rates compared using Fisher's exact test. Two planned interim analyses were conducted by the data and safety monitoring board with the use of non-symmetrical stopping rules.[109] Missing QoL scores were imputed using EQ-5D and MLWHFQ scores, sex, NYHA class, interventricular mechanical delay and mitral regurgitation at baseline. A score of zero was assigned at the time of patient death or time of heart transplantation.[113] QALYs 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 and 18 months and the end of the study.[113]
- *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 ($\alpha = 0.025$, 300 events predicted).[109]
- *Attrition/dropout*: 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 four cases the patient or the investigator decided not to proceed with implantation. A CRT-P device was implanted and activated in 390 (95%) patients [six patients had an unplanned hospitalisation for cardiovascular reasons (reached primary end point) before the device was activated], and eight patients received 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 five patients implantation was unsuccessful. In 19 patients (5%) the device was activated before the primary end point was reached; eight subsequently reached the primary end point (six died). Among the 31 patients who reached the primary end point before the device was activated, seven subsequently died.[109] At the end of the extension phase the survival of one participant in the medical therapy group was unknown.[111] During the extension phase four 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.[111] In the paper reporting left ventricular reverse modelling outcomes,[115] baseline ECGs were not analysable for 78 (10%) participants. Reasons for this were baseline data not received by the core ECG laboratory ($n = 36$), damaged video tape ($n = 4$) and poor-quality examination ($n = 38$).
- *Other*: the extension phase was declared before study closure and without knowledge of the results.[111]

General comments

- *Generalisability*: included patients with LVSD and cardiac dyssynchrony who have moderate or severe HF and who are in sinus rhythm.
- *Outcome measures*: appear appropriate.
- *Intercentre variability*: not commented on but data analysis included study centres as random effects as noted in the method of data analysis, which presumably took this into account.[109]
- *Conflict of interests*: all of the authors had conflicts of interest, which are stated at the end of the report.[109] 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 randomised controlled trials[65]

	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Low	Randomisation used a minimisation procedure
Allocation concealment	Low	Allocation by independent organisation
Performance bias		
Blinding of participants and personnel	High	Unblinded trial
Detection bias		
Blinding of outcome assessment		
Mortality and hospitalisation	Low	End points committee not aware of patients' treatment assignments
ECG outcomes	High	Unblinded trial. No indication that core laboratory quantifying these data were unaware of treatment assignment
Adverse events	Unclear	Some adverse events (not specified which) were classified by the end points committee who were unaware of patients' treatment assignments but other procedure- or device-related adverse events were classified by an unblinded independent expert
Attrition bias		
Incomplete outcome data addressed		
Mortality, hospitalisation, ECG outcomes	Low	Analyses according to the ITT principle. Crossovers reported
QoL	Unclear	Missing QoL scores imputed but amount of missing data not reported
Left ventricular reverse remodelling outcomes	Unclear	Not all participants were included because not all had a readable baseline ECG (10% missing). Authors state that clinical characteristics of groups were similar to those of the total trial population. Reasons for missing data not reported for each group, only overall, so not clear if reasons for missing data are similar between groups
Reporting bias		
Selective reporting	Low	Rationale, design and end points paper available.[110] Primary and secondary outcomes appear to have been reported as planned. Separate papers report outcomes[109,111,113,115]
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Bristow *et al.* 2000[117] and 2004,[116] Carson *et al.* 2005,[119] US FDA 2004[118] Anand *et al.* 2009[120] *Study design*: RCT *Country*: USA *No. of centres:* 128 *Funding*: Guidant Corporation, St Paul, MN	*Intervention*: OPT and either CRT-P (Guidant model 1241 Contak TR) or CRT-D (Guidant model 1823 Contak CD) *Comparator*: OPT – loop diuretics, ACE inhibitors, spironolactone and beta-blockers (unless not tolerated). Also permitted: booster diuretics, ARBs, digoxin, alternative vasodilators, calcium channel blockers *Other interventions used*: none reported	*Indication for treatment*: advanced chronic HF and intraventricular conduction delays *No. of randomised participants:* 1520; CRT-P: 617, CRT-D: 595, OPT: 308 *Inclusion criteria*: NYHA class III or IV, QRS duration ≥ 120 milliseconds, PR interval > 150 milliseconds, LVEF ≤ 35%, OPT, LVEDD ≥ 60 mm, age ≥ 18 years, sinus rhythm *Exclusion criteria*: 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 heart disease, progressive or unstable angina, pregnancy, hypertrophic obstructive cardiomyopathy, amyloid disease, tricuspid prosthesis, hospitalisation for HF > 4 hours in previous month[117]	*Primary outcomes:* all-cause mortality and all-cause hospitalisation (composite end point) *Secondary outcomes*: cardiac morbidity, all-cause mortality, cardiac hospitalisation, 6-minute walk distance, NYHA class before and after treatment, adverse events, HRQoL (MLWHFQ) *Method of assessing outcomes:* first events for hospitalisation related to cardiovascular causes or HF, use of outpatient intravenous medication and cause of death adjudicated by end points committee. Clinical evaluations at baseline, 1 week and 1 month, then 3-monthly[117] *Length of follow-up, median*: primary end point: 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*: January 2000–December 2002

LVEDD, left ventricular end-diastolic diameter.

Participant characteristics (pre randomisation/implant)

Characteristic	CRT-P ($n = 617$)	CRT-D ($n = 595$)	OPT ($n = 308$)	*p*-value
Age (years), median	67	66	68	
Sex, % male	67	67	69	
Ethnicity	NR	NR	NR	
Severity of HF, %				
NYHA class III	87	86	82	
NYHA class IV[a]	13	14	18	
QRS interval (ms), median	160	160	158	
LVEF, median	0.20	0.22	0.22	
LVEDD (mm), median	68	67	67	
Heart rate (bpm), median	72	72	72	
Blood pressure (mmHg), median				
Systolic	110	112	112	
Diastolic	68	68	64	
Ischaemic cardiomyopathy, %	54	55	59	
Pharmacological therapy, %				
Beta-blocker	68	68	66	
Spironolactone	53	55	55	
ACE inhibitor	70	69	69	
ACE inhibitor or ARB	89	90	89	
Loop diuretic	94	97	94	
Left branch bundle block, %	69	73	70	
Right branch bundle block, %	12	10	9	
Duration of HF (years), median	3.7	3.5	3.6	
6-minute walk distance (m), median	274	258	244	
Diabetes, %	39	41	45	

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter; NR, not reported.
a Calculated by reviewer.

Comments

- Authors state that there are no clinically significant differences between the groups.

Results

Outcome	CRT-P ($n = 617$)	CRT-D ($n = 595$)	OPT ($n = 308$)	HR (95% CI), p-value: OPT vs. CRT-P; OPT vs. CRT-D
Composite end point (all-cause mortality or hospitalisation) (primary end point)[a]				
Events during study, *n*	414	390	216	
12-month event rate, %	56	56	68	0.81 (0.69 to 0.96), 0.014; 0.80 (0.68 to 0.95), 0.010
All-cause mortality[a]				
Events during study, *n/N* (%)	131/617 (21.2)	105/595 (17.6)	77/308 (25.0)	
12-month event rate, %	15	12	19	0.76 (0.58 to 1.01), 0.059; 0.64 (0.48 to 0.86), 0.003
Death or hospitalisation from cardiovascular causes[a]				
Events during study, *n*	338	312	188	
12-month event rate, %	45	44	60	0.75 (0.63 to 0.90), 0.002; 0.72 (0.60 to 0.86), < 0.001
Death or hospitalisation from HF[a]				
Events during study, *n*	237	212	145	
12-month event rate, %	31	29	45	0.66 (0.53 to 0.87), 0.002; 0.60 (0.49 to 0.75), < 0.001
Cause of death,[119] *n* (% of patients) [% of deaths]				
Cardiac[b]	109 (17.1) [83.2]	76 (12.8) [72.4]	54 (18.8) [75.3]	$p = 0.334$; $p = 0.006$
SCD[b]	48 (7.8) [36.6]	17 (2.9) [16.2]	18 (5.8) [23.4]	1.21 (0.70 to 2.07), 0.485; 0.44 (0.23 to 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 to 1.09), 0.112; 0.73 (0.47 to 1.11), 0.143
Ischaemic	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]	
Other	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]	$p = 0.122$; $p = 0.717$
Unknown	3 (0.5) [2.3]	5 (0.8) [4.8]	8 (2.6) [10.4]	
[c,d]Hospital admissions[120]				
Patients hospitalised at least once, *n/N* (%)				
All hospital admissions	388/617 (63)	372/595 (63)	199/308 (65)	$p = 0.02$;[e] $p = 0.03$[e]
Cardiac	301/617 (49)	284/595 (48)	164/308 (53)	$p < 0.01$;[e] $p < 0.01$[e]
HF	179/617 (29)	166/595 (28)	112/308 (36)	$p < 0.01$;[e] $p < 0.01$[e]
Non-cardiac	222/617 (36)	207/595 (35)	84/308 (27)	

Outcome	CRT-P ($n = 617$)	CRT-D ($n = 595$)	OPT ($n = 308$)	HR (95% CI), p-value: OPT vs. CRT-P; OPT vs. CRT-D
No. of admissions (% of total admissions), no. of average admissions per patient-year of follow-up				
All hospital admissions	993 (NA), 1.25	919 (NA), 1.20	516 (NA), 1.59	
Cardiac	628 (63), 0.79	580 (63), 0.76	338 (75), 1.20	
HF	329 (33), 0.41	333 (36), 0.43	235 (46), 0.73	
Non-cardiac	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)	
HF	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)	NS
Cardiac procedure, number of hospital admissions per patient-year[f]	0.13	0.09	0.24	$p < 0.01$
CRT implants, *n/N* (% of procedures)			33/78 (42)	
Electrophysiological studies, *n/N* (% of procedures)			13/78 (17)	
Pacer/ICD implants, *n/N* (% of procedures)	13/101 (13)		10/78 (13)	
Heart transplants, *n/N* (% of procedures)			5/78 (6)	
Other, *n/N* (% of procedures)			15/78 (19)	
Lead revision, *n/N* (% of procedures)	42/101 (42)	36/69 (52)		
Increase in 6-minute walk distance (m), mean change (SD)				
3 months	($n = 422$) 33 (99)	($n = 420$) 44 (109)	($n = 170$) 9 (84)	$p < 0.001$; $p < 0.001$
6 months	($n = 373$) 40 (96)	($n = 378$) 46 (98)	($n = 142$) 1 (93)	$p < 0.001$; $p < 0.001$
Increase in QoL (%),[g] mean change (SD)				
3 months	($n = 510$) –24 (27)	($n = 514$) –24 (28)	($n = 243$) –9 (21)	$p < 0.001$; $p < 0.001$
6 months	($n = 460$) –25 (26)	($n = 478$) –26 (28)	($n = 207$) –12 (23)	$p < 0.001$; $p < 0.001$
Proportion of patients with improvement in NYHA class symptoms, %				
3 months	($n = 551$) 58	($n = 543$) 55	($n = 242$) 24	$p < 0.001$; $p < 0.001$
6 months	($n = 489$) 61	($n = 497$) 57	($n = 199$) 38	$p < 0.001$; $p < 0.001$

Outcome	CRT-P ($n = 617$)	CRT-D ($n = 595$)	OPT ($n = 308$)	HR (95% CI), p-value: OPT vs. CRT-P; OPT vs. CRT-D
Duration of procedure (minutes), median (patients randomised after 1 July 2001)	(n = NR) 164	(n = NR) 176		

NA, not applicable; NR, not reported; NS, not significant.
a Kaplan–Meier curves presented.
b Kaplan–Meier curves of time to first event presented but not extracted.
c Total follow-up time for hospital admissions: OPT 324 years, CRT-P 793 years, CRT-D 768 years.
d Predictors of hospitalisation reported but not data extracted.
e Analysis adjusted for multiple hospital admissions, follow-up time and competing risk of death.
f Authors state that after hospitalisations for HF, cardiac procedures were the next most common cause for hospitalisation. Selected procedures are reported in the paper. Hospitalisation curves presented. Authors state that no significant differences were found in any of the end-points for CRT-P vs. CRT-D.
g 21 questions rated on a 6-point scale, total score 105; higher score indicates poorer QoL.

Comments

- Subgroup analyses presented according to baseline characteristics – not data extracted.
- Median changes in systolic blood pressure from baseline to 3, 6 and 12 months were significantly better in the CRT-P and CRT-D groups than in the OPT group. There were no significant changes in diastolic blood pressure in any group (data presented in figure, not data extracted).

Adverse effects of treatment

Adverse effect	CRT-P ($n = 617$)	CRT-D ($n = 595$)	OPT ($n = 308$)	p-value: CRT-P vs. OPT; CRT-D vs. OPT
Unsuccessful implantation, n/N (%)	78/617 (13)	54/595 (9)		
Deaths from procedural complications, n/N (%)	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, %[a]	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 the primary end point	2	2	13	

a CRT-P vs. CRT-D, $p = 0.042$.

Comment

- More detailed adverse event reporting for CRT-D is available in the FDA report.[118]

Comments

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 were carried out according to the ITT principle. Efficacy analyses were based on time to first event (unless otherwise stated), differences were determined using the log-rank statistic and time to event used the Kaplan–Meier method. Nominal *p*-values and *p*-values adjusted for sequential monitoring were reported. HRs were unadjusted for covariates, Wald chi-squared statistic used for subgroups. Baseline differences were evaluated using the Wilcoxon rank-sum test for continuous and ordered data and Pearson's chi-squared 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 the CRT-P group and 0.03 in the CRT-D group, each compared with OPT. With a target of 1000 primary events, the trial had statistical power of > 90% for the primary end point and 80% for the secondary end point. The trial was stopped early when pre-established boundaries had been crossed; 1520 participants had been randomised and 1000 primary end points already or almost met.
- *Attrition/dropout*: substantial withdrawals from the OPT group (see *Adverse effects of treatment*) to receive commercially available implants, because of arrhythmia or HF. Patients contacted to consent to collection of data for the duration of the study; data censored if this information could not be obtained. Status for the primary end point through to the end of the study known for 91% of the OPT group and 99% of the other groups; data on mortality complete for 96% of the OPT group and 99% of the other groups.

General comments

- *Generalisability*: people with advanced HF and increased QRS interval.
- *Outcome measures*: authors state that the composite end point based on both mortality and hospitalisation was chosen to avoid the analytical difficulty encountered with competing risk: death precludes subsequent hospitalisation for chronic HF decompensation.[117] Demonstration of a favourable hospitalisation outcome may be offset by the inability to survive, and benefit of survival may be offset by incremental chronic HF morbidity requiring recurrent hospitalisations.
- *Intercentre variability*: not reported.
- *Conflict of interests*: authors state that sponsor had no role in data analysis.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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	No blinding
Detection bias		
Blinding of outcome assessment	Low	Steering committee and end points committee unaware of assignment. Outcomes objective and unlikely to be influenced
Attrition bias		
Incomplete outcome data addressed	Low	ITT analysis. Data censored for people who withdrew and for whom data could not be obtained
Reporting bias		
Selective reporting	Low	Protocol published; no evidence of missing outcomes
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Multicenter InSync Randomized Clinical Evaluation (MIRACLE)

Reference and design	Intervention and comparator	Participants	Outcome measures
Abraham *et al.* 2000[122] and 2002,[121] St John Sutton *et al.* 2003,[124] US FDA 2001[123] *Study design*: RCT *Countries*: USA and Canada *No. of centres:* 45 *Funding*: Medtronic, Inc., Minneapolis, MN	*Intervention*: optimal medical therapy and CRT-P on: VDD[a] 30, InSync model 8040 (Medtronic), three pacing leads *Comparator*: optimal medical therapy and CRT-P off: VDI 30 (ventrical paced, atrial and ventricular sensed, no response to sensing), InSync model 8040 (Medtronic Inc.) *Other interventions used*: medication for HF for both groups kept constant	*Indication for treatment*: moderate to severe HF and a prolonged QRS interval *No. of randomised participants:* 453; CRT-P on: 228, OPT: 225 *Inclusion criteria*: HF due to ischaemic or non-ischaemic cardiomyopathy for > 1 month, NYHA class III or IV, LVEF ≤ 35%, LVEDD ≥ 55 mm, QRS interval ≥ 130 milliseconds, age ≥ 18 years, 6-minute walk distance ≤ 450 m, optimal medical therapy[121,122] *Exclusion criteria*: pacemaker or ICD, indication for or contraindication to cardiac pacing, cardiac or cerebral ischaemic event within ≤ 3 months, atrial fibrillation within ≤ 1 month, severe primary pulmonary disease, systolic blood pressure > 170 mmHg or < 80 mmHg, heart rate > 140 bpm, serum creatinine > 3.0 mg/dl, serum aminotransferase more than three times the upper limit of normal, unstable angina, acute MI or coronary surgery within ≤ 3 months, life expectancy < 6 months[121,122]	*Primary outcomes*: NYHA class, QoL, 6-minute walk distance *Secondary outcomes*: all-cause mortality, HF hospitalisations, exercise capacity (peak oxygen consumption, time on treadmill), LVEF, LVEDD, QRS duration, severity of mitral regurgitation, clinical composite response (improved, worsened or unchanged), an analysis of death or worsening HF (as safety variables), number of days spent in hospital *Method of assessing outcomes*: questionnaires at baseline and at 1, 3 and 6 months. Clinical events review committee adjudicated adverse events/end points[122] *Length of follow-up*: 6 months *Recruitment*: November 1998–December 2000

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter.
a The pacemaker senses atrial and ventricular activity, but paces only in the ventricle.

Participant characteristics (pre randomisation and ≤ 7 days pre implantation)

Characteristic	CRT-P ($n = 228$)	OPT ($n = 225$)
Age (years), mean (SD)	63.9 (10.7)	64.7 (11.2)
Sex, % male	68	68
Ethnicity, % white	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 (milliseconds), mean (SD)	167 (21)	165 (20)
Heart rate (bpm), mean (SD)	73 (13)	75 (13)
LVEDD (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)
MLWHFQ score,[a] mean (SD)	59 (20)	59 (21)
Total exercise time (seconds), mean (SD)	484 (209)	462 (217)
Peak oxygen consumption (ml/kg bodyweight/minute), mean (SD)	14.0 (3.5)	13.7 (3.8)
Systolic blood pressure (mmHg), mean (SD)	114 (18)	115 (18)
Diastolic blood pressure (mmHg), mean (SD)	69 (10)	68 (10)
Receiving digitalis, %	78	79
Receiving diuretic agents, %	94	93
Receiving ACE inhibitors or ARBs, %	93	90
Receiving beta-blockers, %	62	55

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter.
a Score range 0–105, higher score indicates more severe impairment.

Comment

- Groups were similar at baseline.

Results

Outcome (at 6 months)	CRT-P ($n = 228$)	OPT ($n = 225$)	HR (CI 95%), p-value
All-cause mortality, *n/N*	12/228	16/225	0.73 (0.34 to 1.54), 0.40
Hospitalisations for worsening HF			
People, *n/N*	18/228	34/225	0.50 (0.28 to 0.88), 0.02
Events, *n*	25	50	
Total no. of days	83	363	
Death or worsening HF requiring hospitalisation, *n/N*	28/228	44/225	0.60 (0.37 to 0.96), 0.03
Death or worsening HF requiring hospitalisation or intravenous treatment, *n/N*	36/228	55/225	0.61 (0.40 to 0.93), 0.02
Worsening HF leading to use of intravenous, *n/N*			
Diuretic agents	13/228	24/225	0.51 (0.26 to 1.00), 0.05
Vasodilators or positive inotropic agents	6/228	14/225	0.41 (0.16 to 1.08), 0.06
Medication for HF	16/228	35/225	0.43 (0.24 to 0.77), 0.004
Change in NYHA class (primary outcome), *n/N* (%)			$p < 0.001$
Improved by two or more classes	34/211 (16)	12/196 (6)	
Improved by one 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 minutes (m), median (95% CI) (primary outcome)	($n = 214$) +39 (26 to 54)	($n = 198$) +10 (0 to 25)	$p = 0.005$
Change in MLWHFQ score, median (95% CI) (primary outcome)	($n = 213$) –18 (–22 to –12)	($n = 193$) –9 (–12 to –5)	$p = 0.001$
Change in peak oxygen consumption (ml/kg/minute), median (95% CI)	($n = 158$) +1.1 (0.6 to 1.7)	($n = 145$) +0.2 (–0.2 to 0.8)	$p = 0.009$
Change in total exercise time (seconds), median (95% CI)	($n = 159$) +81 (62 to 119)	($n = 146$) +19 (–1 to 47)	$p = 0.001$
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)	$p < 0.001$
Change in LVEDD (mm), median (95% CI)	($n = 90$) –3.5 (–6 to –1)	($n = 98$) 0.0 (–1 to 2)	$p < 0.001$
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)	$p < 0.001$
Change in QRS duration (ms), median (95% CI)	($n = 206$) –20 (–20 to –12)	($n = 192$) 0 (–10 to 0)	$p < 0.001$

Outcome (at 6 months)	CRT-P ($n = 228$)	OPT ($n = 225$)	HR (CI 95%), p-value
Clinical composite HF score			$p < 0.001$
Improved, %	67	39	
Worsened, %	16	27	

LVEDD, left ventricular end-diastolic diameter.

Comment

- States that the magnitude of the effect on the 3 primary endpoints was not influenced by use of a beta-blocker, cause of HF, (ischaemic or non-ischaemic), 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

Adverse effect	CRT-P ($n = 228$)	OPT ($n = 225$)
Hospitalised for repositioning or replacement of left ventricular lead,[a] *n*	11	3
Hospitalisations not related to HF or function of left ventricular lead,[a] *n*	37	33
	All participants undergoing implantation ($n = 571$)	
Complete heart block requiring permanent cardiac pacing, *n/N*	2/571	
Death from progressive hypotension, *n/N*	1/571	
Asystole, resuscitated but died 1 month later, *n/N*	1/571	
Coronary sinus dissection, *n/N* (%)	23/571 (4)	
Cardiac vein or coronary sinus perforation (three of these recovered and continued in the study), *n/N* (%)	12/571 (2)	
	Participants who underwent successful implantation ($n = 528$)	
Left ventricular lead repositioned, *n/N*	20/528	
Left ventricular lead replaced, *n/N*	10/528	
Pacemaker-related infection requiring explantation, *n/N*	7/528	

a Median duration of procedure not data extracted.

Comments

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 HF and performing study evaluations were unaware of treatment assignments. An electrophysiologist who was not involved 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*: authors state that groups were similar with respect to all baseline characteristics.
- *Method of data analysis*: authors state that all end points were analysed according to the ITT principle. For continuous variables, comparisons of changes from baseline to 6 months between groups were evaluated using the Wilcoxon rank-sum test. The chi-squared test was used for categorical end points. Only patients with data at baseline and 6 months were included in these analyses, but results were similar if patients with incomplete data were included, using the last value carried forward. Cumulative survival curves for the risk of a major clinical event used the Kaplan–Meier method and were tested for significance using the log-rank statistic. Cox proportional hazards regression models were used to estimate HRs.
- *Sample size/power calculation*: sample size of 224 patients per group estimated on the basis of the assumption that the study would have 80% power (two-sided $\alpha = 0.0167$) to detect a difference in NYHA class of 0.75, in QoL of 13 points or in distance walked in 6 minutes of 50 m.
- *Attrition/dropout*: in total, 571 agreed to participate, with 528 successfully implanted and 43 not successfully implanted. Of those who were successfully implanted, two required cardiac pacing, two became clinically unstable, 71 were enrolled in the initial pilot phase and 453 were randomised to main study. OPT group: 24/225 did not complete the 6-month follow-up (16 died, two had a heart transplant, one had complications related to the device and five missed the 6-month visit). CRT-P group: 13/228 did not complete the 6-month follow-up (12 died and one had complications related to the device). No patient was lost to follow-up for the analysis of death or worsening HF. In total, 10/225 in the control group crossed over to the CRT-P group, seven because of worsening HF and three because of bradycardia.

General comments

- *Generalisability*: only those successfully implanted underwent randomisation. Generalisability limited to people with moderate to severe HF and a prolonged QRS interval.
- *Outcome measures*: clinical events review committee adjudicated with regard to adverse events/end points. QoL was assessed using a validated questionnaire.
- *Intercentre variability*: not reported.
- *Conflict of interests*: stated. some of the authors are consultants or investigators for, or employees of, Medtronic; one author was also on the advisory board of St Jude Medical. Authors state that investigators had full access to all data and performed analyses without restrictions or limitations from the sponsor.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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	Patients and physicians treating them for HF and performing study evaluations were unaware of treatment assignments
Detection bias		
Blinding of outcome assessment	Low	Patients and physicians treating them for HF and performing study evaluations were unaware of treatment assignments
Attrition bias		
Incomplete outcome data addressed		
Primary outcomes	Unclear	States ITT analysis used and attrition reported; also reports that analysis included last value carried forward analysis. However, numbers are low for NYHA class (primary outcome) without giving reasons why
Secondary outcomes	Unclear	Reasons for different sample sizes unclear
Reporting bias		
Selective reporting	High	SF-36 is included in the protocol paper[122] but results for this measure are not reported
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Multisite Stimulation in Cardiomyopathies (MUSTIC) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Cazeau *et al.* 2001[125] *Study design*: randomised crossover study *Countries*: Europe (France, Germany, Italy, Sweden, Switzerland, the UK) *No. of centres:* 15 *Funding*: ELA Recherche, Medtronic and the Swedish Heart and Lung Association and by a grant from the Swedish Medical Research Council	*Intervention*: CRT-P on: atrioventricular (active) pacing [Chorum 7336 MSP (ELA Medical), and InSync 8040 (Medtronic Inc.)] *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. OPT ($n = 67$): ACE inhibitors or equivalent 96%, diuretics 94%, digoxin 48%, amiodarone 31%, beta-blockers 28%, spirololactone 22%	*Indication for treatment*: severe HF and major intraventricular delay but without standard indications for a pacemaker *No. of enrolled participants:* 67 *No. of randomised participants:* 58; group 1 (CRT-P on, CRT-P off): 29, group 2 (CRT-P off, CRT-P on): 29 *Inclusion criteria*: severe HF because of idiopathic or ischaemic LVSD, NYHA class III for ≥ 1 month whilst on OPT, LVEF $< 35\%$, LVEDD > 60 mm; QRS interval > 150 milliseconds, in sinus rhythm, without a standard indication for a pacemaker *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 an ICD	*Primary outcome*: distance walked in 6 minutes *Secondary outcomes*: QoL, peak oxygen uptake, hospital admissions because of decompensated HF, patient preference, death *Method of assessing outcomes*: assessed at baseline (4 weeks before implantation), at randomisation (2 weeks after implantation) and at the end of each crossover phase. QoL measured using the MLWHFQ (total score 0–105, higher score indicates worse QoL). The 6-minute walk test was carried out according to Guyatt *et al.* and Lipkin *et al.* (references provided): two tests at each visit with an interval of at least 3 hours between them; the maximal difference between the two tests was 15% and the value recorded was the mean of the results of the two tests. Patient preference – at the end of the crossover phase patients were asked which 3-month period they preferred *Length of follow-up*: participants received the intervention and the comparator for 3 months each in random order *Recruitment*: March 1998–March 1999

LVEDD, left ventricular end-diastolic diameter.

Participant characteristics (at randomisation 2 weeks post implant)

Characteristic	Group 1 (CRT-P 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
Sex, male, *n*/*N*	19/29	24/29	0.13
Ethnicity	NR	NR	
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 VO_2 (ml/kg of body weight/minute), 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 (milliseconds), mean (SD)	172 (22)	175 (19)	0.48

NR, not reported.

Comment

- Baseline characteristics for $n = 67$ at baseline (4 weeks before implantation) are also presented but not extracted.

Results

Outcome	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 as a result of 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)[a]			
Group 1 (CRT-P on, CRT-P off) ($n = 22$)	384.1 (78.9)	336.1 (128.3)	
Group 2 (CRT-P off, CRT-P on) ($n = 24$)	412.9 (116.9)	316.2 (141.8)	
Both groups ($n = 46$)	399.2 (100.5)	325.7 (134.4)	$p < 0.001$
Peak VO_2 (ml/kg of body weight/minute), mean (SD)			
Group 1 (CRT-P on, CRT-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)	$p = 0.029$
QoL score, mean (SD)			
Group 1 (CRT-P on, CRT-P off) ($n = 23$)	33.3 (22)	42.6 (20.9)	
Group 2 (CRT-P off, CRT-P on) ($n = 22$)	25.7 (20.4)	44 (25)	
Both groups ($n = 45$)	29.6 (21.3)	43.2 (22.8)	$p < 0.001$
HF hospitalisations at 3 months (first crossover period only), *n/N*	3/29	9/29	$p < 0.05$
Patient preference after 6 months ($n = 48$),[b] *n/N* (%)	41/48 (85)	2/48 (4)	$p < 0.001$

a In the per-protocol analysis ($n = 23$), the mean distance walked (CRT-P on vs. CRT-P off) was 424 (SD 83) m vs. 375 (SD 83) m ($p < 0.04$).
b 48 patients completed both phases of the study. Patient preference: 5/48 (10%) patients had no preference; *p*-value reported in the abstract of the paper but not in the results section.

Adverse effects of treatment

Adverse effect	CRT-P on	CRT-P off	*p*-value
Uncorrectable loss of left ventricular pacing efficacy, *n*	2		
Severe decompensation leading to a premature switch to active pacing, *n*		1	
Decompensation attributed to rapidly progressive aortic stenosis, *n*	1		
Decompensation due to persistent atrial fibrillation, *n*		1	

Comments
- Implantation of a left ventricular lead was attempted in 64/67 patients with a 92% (59/64) success rate. The five failures were not randomised.
- A lateral position was reached in 80% of patients with a mean pacing threshold of 1.4 (SD 1.1) V.
- Early dislodgement occurred in eight patients and was successfully corrected in five.
- Overall, 88% of patients had a functional left ventricular lead at the end of the crossover phase.

Comments

Methodological comments

- *Allocation to treatment groups*: randomisation of order of treatment followed a block design with stratification according to study centre. Authors also state that patients were 'randomly assigned to and equally distributed between the two study groups.
- *Blinding*: described as single blind. Authors state that patients had no knowledge of the order of treatment but no details are provided.
- *Comparability of treatment groups*: similar.
- *Method of data analysis*: authors state that all analyses are based on the ITT principle; thus, all enrolled patients were included in the analysis but each efficacy end point could be assessed only in patients with no data missing after the completion of both crossover phases. Baseline characteristics were assessed using the chi-squared test for dichotomous variables and the Student's *t*-test or Wilcoxon non-parametric test for quantitative or categorical variables. Responses obtained for all criteria assessing clinical efficacy were compared using the Wilcoxon test and according to a two-period and two-treatment (two-by-two) crossover design. Period and carry-over 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. The stability of the results was assessed in a per-protocol analysis, which included only patients without any deviations from the protocol. The authors state that no significant carry-over and period effects were noted. Threshold of significance 0.05
- *Sample size/power calculation*: on the basis of previous reports of mortality rates in NYHA class III, a 10% mortality rate at 6 months was estimated. A 10% failure rate of left ventricular lead implantation and a 20% rate of premature termination because of loss of left ventricular pacing efficacy of unstable HF was expected. A 10% increase in the distance walked in 6 minutes with active pacing was estimated. The total target sample needed was estimated to be 22 patients for a study with a 95% confidence level and 95% power. For the MLWHFQ score, a predicted 10% reduction with active pacing necessitated a 30-patient sample. Considering mortality and dropouts, 40 patients were needed
- *Attrition/dropout*: three patients withdrew before implantation, two with unstable HF (one subsequently died) and one with a pre-existing indication for pacing. Implantation of a left ventricular lead was attempted in 64 patients. In six patients it was removed before randomisation, five because of failed implantation of the left ventricular lead and one because of sudden death while the device was inactive. A total of 10 patients did not complete two crossover periods: first crossover period: one withdrew consent at randomisation, two had uncorrectable loss of ventricular pacing efficacy, one switched from inactive to active pacing because of severe decompensation and one died suddenly after 26 days of active pacing; second crossover period: three had worsening HF (one had decompensation with active pacing, one had decompensation during inactive pacing), one died suddenly after switching to active pacing and one had lung cancer

General comments

- *Generalisability*: patients were randomised 2 weeks after implantation. Only patients who were successfully implanted were randomised.
- *Outcome measures*: appropriate but change in NYHA class not reported.
- *Intercentre variability*: not reported.
- *Conflict of interests*: part funded by ELA Recherche and Medtronic. Four authors are paid consultants of Medtronic or ELA Recherche and one author is an employee of ELA Recherche.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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	Authors state that participants had no knowledge of the order of treatments, but not clear how this was maintained. Personnel not blinded; 6-minute walk test and QoL outcomes may be influenced by lack of blinding
Detection bias		
Blinding of outcome assessment	High	States 'single blind' so assume only participants were blinded
Attrition bias		
Incomplete outcome data addressed	Low	Numbers and reasons reported
Reporting bias		
Selective reporting	High	Change in NYHA class assessed but data not reported
Other bias		
Other sources of bias	High	Use of block randomisation without blinding means that it may be possible to predict future assignments. Crossover design appears appropriate

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Appendix 9 Data extraction: people with both conditions

CONTAK-CD trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Higgins *et al.* 2003,[126] Lozano *et al.* 2000,[128] US FDA 2002,[129] Saxon *et al.* 1999[127] *Study design*: crossover RCT in phase I; parallel RCT in phase II Country: USA (see *General comments*, *Intercentre variability*) *No. of centres:* 47 *Funding*: Guidant Corporation, St Paul, MN	*Intervention*: CRT-D + OPT *Comparator*: ICD + OPT Devices were either Model 1822 Ventak CHF Automatic Implantable Cardioverter Defibrillator or Model 1283 Contak CD device (Guidant Corporation) Initially, the left ventricle 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 three-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 pharmacological therapy. OPT not defined *Other interventions used*: none stated	*Indication for treatment*: patients with symptomatic HF, intraventricular conduction delay and malignant ventricular tachyarrhythmias (VT/VF) requiring therapy from an ICD *No. of randomised participants:* 490; CRT-D: 245, ICD: 245 *Inclusion criteria*: NYHA class II–IV, LVEF ≤ 35%, QRS interval ≥ 120 milliseconds, conventional indications for an ICD (American College of Cardiology/American Heart Association guidelines),[126] age ≥ 18 years, symptomatic HF despite OPT (must include ACE inhibitors if tolerated)[127] *Exclusion criteria*: atrial tachyarrhythmias or conventional indications for a permanent pacemaker,[126] concomitant cardiac surgery, unable to undergo device implant, unable to comply with protocol and follow-up including exercise testing, life expectancy < 6 months because of other conditions, amyloid disease, hypertrophic obstructive cardiomyopathy, requires in-hospital continuous intravenous inotropes, use of pre-existing cardioversion/defibrillation leads other than those specified in the protocol, involved in other cardiovascular clinical investigations of active therapy or treatment[127]	*Primary outcome*: progression of HF, defined as a composite end point of all-cause mortality, hospitalisation for worsening HF, ventricular tachyarrhythmias requiring device therapy (initially the primary outcome was peak VO_2 but this was changed when the study design was changed) *Secondary outcomes*: VO_2, QoL, 6-minute walk distance, biventricular antitachycardia pacing efficacy, defibrillation therapy safety[127] *Method of assessing outcomes*: VO_2 assessed by cardiopulmonary exercise test.[127] QoL measured using the MLWHFQ. A Heart Failure Events Committee adjudicated all deaths and hospitalisations. Operative mortality was defined as death from any cause within 30 days of the implant procedure *Length of follow-up*: maximum of 6 months (but some patients, presumed to be all those in phase I, only 3 months) *Recruitment*: February 1998–December 2000

Participant characteristics

Participant characteristics	CRT-D ($n = 245$)	ICD ($n = 245$)	p-value
Age (years), mean (SD)[a]	66 (11)	66 (11)	
Sex, % male	85	83	
Ethnicity	NR	NR	
Aetiology ischaemic, %	67	71	
NYHA class, %			
II	32	33	
III	60	57	
IV	8	10	
LVEF (%), mean (SD)[a]	21 (7)	22 (7)	
QRS interval (milliseconds), mean (SD)[a]	160 (27)	156 (26)	
Intraventricular conduction delay, %			
LBBB	54	55	
Non-specific	32	33	
RBBB	14	12	
Diuretic, %	88	83	
ACE inhibitor/ARB, %	86	89	
Beta-blocker, %	48	46	
Digoxin, %	69	68	
Peak VO_2 (ml/kg/minute), mean (SD)[a]	13.8 (4.6)	13.5 (3.8)	
QoL score, mean (SD)[a]	44 (25)	40 (23)	
6-minute walk distance (m), mean (SD)[a]	316 (119)	320 (121)	
LVID in diastole (mm), mean (SD)[a]	71 (11)	70 (10)	
LVID in systole (mm), mean (SD)[a]	59 (11)	58 (11)	
Heart rate	NR	NR	
Cardiac history	NR	NR	
Previous treatment	NR	NR	
Comorbidities	NR	NR	

LVID, left ventricular internal diameter; NR, not reported; RBBB, right bundle branch block.
a Data are assumed to be mean (SD) although this is not specifically stated anywhere in the paper.

Comments

- Characteristics are reported for the 490 participants who were randomised at the time of implantation.
- During the 30-day post-implant recovery period, when investigators were permitted to adjust or initiate HF medications, many patients demonstrated a 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 30/162 (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 I of the study[128] have not been extracted. It is not clear whether some or all of these participants are included in the data from Higgins *et al.*[126] reported in this table.

Results

Outcome	CRT-D ($n = 245$)	ICD ($n = 245$)	p-value
Progression of HF, *n*/*N*	79/245	94/245	0.35
Mortality	11/245	16/245	
HF hospitalisations (at least one)	32/245	39/245	
At least one VT/VF event	36/245	39/245	
All-cause mortality,[a] *n*	109		
Death during the study treatment phase (detail by group below)	27		
Death during the long-term follow-up phase	70		
Cause of death, *n*/*N* (%)			
Pump failure	47/109 (43)		
Non-cardiac	21/109 (19)		
Arrhythmic	9/109 (8)		
Ischaemic	2/109 (2)		
Cardiac in nature but unknown aetiology	2/109 (2)		
Insufficient information for independent events committee to be able to adjudicate	28/109 (26)		
Deaths during the study treatment phase,[129] *n*/*N* (%)	11/245 (4.5)	16/245 (6.5)	
Cardiac, pump failure	4/245 (1.6)	9/245 (3.7)	
Cardiac, arrhythmic	1/245 (0.4)	0/245 (0)	
Cardiac, other	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)	
Total survival, %			
At 1 year	85		
At 2 years	74		
At 3 years	70		
Received appropriate treatment of ventricular tachyarrhythmias, *n*/*N* (%)	36/245 (15)	39/245 (16)	
VT alone	25/245 (10)	27/245 (11)	
VF alone	7/245 (3)	6/245 (2)	
VT and VF	4/245 (2)	6/245 (2)	
VT/VF episodes during therapy evaluation phase (excluding those with no episodes), median	2.5	2	
QoL score, mean change (SE)[b]	–7 (2) ($n = 234$)	5 (2) ($n = 225$)	0.39
Change in NYHA class, %	($n = 109$)	($n = 116$)	
Improved by two classes	11	2	
Improved by one class	25	30	0.10[c]
No change	51	51	
Worsened	13	17	

Outcome	CRT-D ($n = 245$)	ICD ($n = 245$)	p-value
LVEF (%), mean change (SE)[b]	5.1 (0.7) ($n = 222$)	2.8 (0.7) ($n = 216$)	0.020
LVID in diastole (mm), mean change (SE)[b]	–3.4 (0.6) ($n = 228$)	–0.3 (0.6) ($n = 219$)	< 0.001
LVID in systole (mm), mean change (SE)[b]	–4.0 (0.7) ($n = 228$)	–0.7 (0.7) ($n = 219$)	< 0.001
Peak VO_2 (ml/kg/minute), mean change (SE)[b]	0.8 (0.3) ($n = 216$)	0.0 (0.3) ($n = 201$)	0.030
6-minute walk distance (m), mean change (SE)[b]	35 (7) ($n = 224$)	15 (7) ($n = 220$)	0.043

LVID, left ventricular internal diameter.

a Two of these deaths are not accounted for in the division between deaths occurring during treatment and deaths occurring during long-term follow up.

b Data are assumed to be mean (SE) although this is not specifically stated anywhere in the paper.

c Not clear whether the p-value relates to the specific comparison for improved by one class or to the comparison for NYHA class changes overall.

Comments

- Results are also presented separately for patients in NYHA class III/IV at randomisation and patients in 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.
- The overall relative reduction in composite HF progression was 15% with CRT.
- Kaplan–Meier curves illustrating time to event for all-cause mortality, all-cause mortality plus HF hospitalisation, and 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 I of the study[128] have not been data extracted. It is not clear whether some or all these participants are included in the data from Higgins *et al.*[126] reported in this table.

Adverse effects of treatment

Adverse effect	CRT-D and ICD		
Operative mortality[126,129]	12/567 (2.1%) (95% CI 0.9% to 3.3%)		
Causes of death for operative mortality,[129] *n*	Implants (*n* = 501)	Attempts (*n* = 66)	Total (*n* = 567)
Total deaths	10	2	12
Cardiac: pump failure	5	1	6
Cardiac: arrhythmic	2	1	3
Non-cardiac[a]	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, *n*/*N*	53/448		
Procedure-related, *n*/*N*	27/517		
Severe device-related events, *n* 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%)		
VT 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 because of 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), *n* (%)			
Loss of left ventricular 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), *n* (%)			
Infections	7 (1.4)		

a In Higgins *et al.*[126] two of the 10 'implant' deaths were described as perioperative (one attributed to pulseless electrical activity resulting from defibrillation threshold testing and one attributed to incessant VT 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.*[126] state that none of these eight deaths were attributed to the implant procedure.

Comments

- Adverse events reported in the summary of safety and effectiveness[129] focus on adverse events related to the 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 who were 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 extracardiac stimulation (nine 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 (six patients, 1.2%) and transient renal failure (five 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 rate (2.1%) was reported to be significantly less than the hypothesized rate of 9% ($p < 0.01$).

Comments

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 3-month treatment phase and patients from phase II contributed data from a 6-month treatment phase for the analysis of the primary end point. The 3-month treatment phase correlates to the first study period (i.e. before any crossover). Cox proportional hazards models were fitted for the combination of events with the treatment effect adjusted for covariates chosen by the Heart Failure Events Committee before the 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 and took full advantage of the correlation structure, and all of 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 using the ITT principle. 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 using the ITT principle. No reasons are given for the missing data. The study authors do not comment on whether the alteration of the 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.*[126] 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/dropout*: initially 581 patients were enrolled (248 in phase I and 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 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 (222 in phase I and 279 in phase II) with the intervention system. Of these, 448/501 (89%) received a transvenous system and 53/501 (11%) received a transthoracic system (phase I: 51, phase II: 2). Of the 501 patients implanted, 11 did not enter the randomised part of the study 30 days after the implant procedure [10 patients died (see *Adverse effects*) and one withdrew in the 30-day post-implant recovery period before the randomised therapy was programmed]. As noted above, not all analyses used the ITT principle and, when data are missing, no reasons for this are provided.
- *Other*: (1) the study design was modified because of 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 (crossover to occur after the first 3 months of randomised therapy) to a parallel RCT design with 6 months of follow-up in phase II. (2) 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, focusing 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 may have 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 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[a]). Therefore, the effects of atrial pacing as well as adaptive-rate pacing delivered with the DDD(R) modes[b] are not known.
- *Outcome measures*: appear to be appropriate; however, the reason(s) why the study sponsor decided to change the primary end point from peak VO_2 to a composite HF outcome are not provided.
- *Intercentre variability*: the key paper for this study[126] and the summary of safety and effectiveness for the device used[129] state that the centres were based in the USA. However, an earlier paper reporting on phase I of the study[128] 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.*,[126] Saxon *et al.*[127] and Lozano *et al.*[128] As operative mortality was the only adverse event reported by the key trial paper,[126] the summary of safety and effectiveness[129] submitted by the manufacturer, Guidant Corporation, to the FDA as part of its approvals process was used as a source of adverse event data.

LVID, left ventricular internal diameter.

a The pacemaker senses atrial and ventricular activity, but paces only in the ventricle.

b Dual-chamber pacing and sensing, both triggered and inhibited mode, with rate modulation (increases the patient's heart rate in response to exercise).

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	Study described as randomised controlled study but no further details provided
Allocation concealment	Unclear	No details provided
Performance bias		
Blinding of participants and personnel	Low	Study described as double blind. 'Both the patient and the heart failure specialist treating the patient are blinded to the pacing mode'[127]
Detection bias		
Blinding of outcome assessment	Low	Study described as double blind. 'Both the patient and the heart failure specialist treating the patient are blinded to the pacing mode'[127] 'A Heart Failure Event Committee (HFEC) adjudicated all deaths and hospitalisations'.[126] It is not clear whether this committee was 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 HF (composite including mortality, HF hospitalisations and VT and VF events)	Low	From the data provided these analyses appear to account for all participants
Change in QoL, NYHA class, LVEF, LVID in diastole and systole, peak VO_2 and 6-minute walk distance	High	It is clear from the numbers provided that there are missing data. No reasons for missing data are given
Reporting bias		
Selective reporting	Low	A description of the study is available[127] 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	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 6 months. The potential for these issues to introduce a bias into the results is unknown

LVID, left ventricular internal diameter.
a 'Low risk', 'high risk' or 'unclear risk' of bias.

Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Moss *et al.* 2005[131] and 2009,[130] Solomon *et al.* 2010,[132] Goldenberg *et al.* 2011,[133,134] Arshad *et al.* 2011[135] *Study design*: RCT *Countries*: USA, Canada and Europe *No. of centres:* text states 110: 88 in the USA, 2 in Canada and 20 in Europe (the Czech Republic 1, Denmark 1, France 1, Germany 4, Hungary 1, Italy 3, Israel 3, Poland 1, Spain 2, Switzerland 1, the Netherlands 3, UK 1). Inconsistency between numbers reported in the text and appendix *Funding*: supported by a research grant from Boston Scientific to the University of Rochester with funds distributed to the co-ordination and data centre, enrolling centres, core laboratories, committees and boards under subcontracts from the University of Rochester, NY	*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[a] 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 used *Other interventions used*: OPT for HF[131]	*Indication for treatment*: mild cardiac symptoms, reduced ejection fraction and wide QRS complex. All met the guideline indication for ICD therapy *No. of participants:* 1820 (1271 in the USA, 22 in Canada, 527 in Europe); CRT-ICD: 1089, ICD only: 731 *Inclusion criteria*: NYHA class I or II, LVEF $\leq$ 30%, QRs interval $\geq$ 130 milliseconds, age $\geq$ 21 years with ischaemic cardiomyopathy (NYHA class I or II) or non-ischaemic cardiomyopathy (NYHA class II only), sinus rhythm, ejection fraction < 30% and prolonged intraventricular conduction with QRs duration of > 130 milliseconds; 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 CABG surgery, percutaneous coronary intervention or an enzyme-positive MI up to 3 months before enrolment; NYHA class I with non-ischaemic cardiomyopathy; those with angiographic evidence of coronary disease who are candidates for coronary revascularisation and who are likely to undergo a procedure in the foreseeable future; second- or third-degree heart block; irreversible brain damage from pre-existing cerebral disease; women who are pregnant or planning to become pregnant; reversible non-ischaemic cardiomyopathy; chronic atrial fibrillation up to 1 month before enrolment; presence of other life-limiting disease, e.g. cancer; participating in other trials; unwilling to co-operate; 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	*Primary outcomes*: death or non-fatal HF events (whichever came first) *Secondary outcomes*: none reported *Method of assessing outcomes*: baseline 12-lead ECG and echocardiogram; baseline physical examination and 6-minute walk test. Two-dimensional echocardiography assessed changes in left 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 reference provided). States that ejection fraction was calculated in the usual fashion (no further details or reference) Diagnosis of HF required signs and symptoms consistent with CHF 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 22 June 2009. Average follow-up was 2.4 years *Recruitment dates*: 22 December 2004–23 April 2008

bpm, beats per minute.
a Pacemaker has dual-chamber pacing and sensing, but inhibited mode only.

Participant characteristics

Characteristic	CRT-ICD (*n* = 1089)	ICD (*n* = 731)
Age (years), mean (SD)	65 (11)	64 (11)
Sex, male, *n* (%)	814 (74.7)	553 (75.6)
Ethnicity, *n*/*N* (%)		
White	979/1083 (90.4)	657/724 (90.7)
Black	87/1083 (8.0)	56/724 (7.7)
Other	17/1083 (1.6)	11/724 (1.5)
Cardiac history and NYHA class, *n* (%)		
Ischaemic heart disease, class I	152 (14.0)	113 (15.5)
Ischaemic heart disease, class II	446 (41.0)	288 (39.4)
Non-ischaemic heart disease, class II	491 (45.1)	330 (45.1)
NYHA class III or IV > 3 months before enrolment, *n* (%)	109 (10.0)	73 (10.0)
Cardiac findings at enrolment		
Blood pressure (mmHg), mean (SD)		
Systolic	124 (17)	121 (18)
Diastolic	72 (10)	71 (10)
Blood urea nitrogen ≥ 26 mg/dl (9.3 mmol/l), *n*/*N* (%)	260/1082 (24.0)	177/721 (24.5)
Creatinine (mg/dl), mean (SD)	1.2 (0.4)	1.2 (0.4)
LBBB, *n*/*N* (%)	761/1088 (69.9)	520/729 (71.3)
RBBB, *n*/*N* (%)	136/1088 (12.5)	92/729 (12.6)
QRS duration ≥ 150 milliseconds, *n* (%)	699 (64.2)	476 (65.1)
LVEF, mean (SD)	0.24 (0.05)	0.24 (0.05)
6-minute walk distance (m), mean (SD)	359 (107)	363 (108)
Heart rate	NR	NR
ECG or Doppler findings (ml), mean (SD)		
Left ventricular end-diastolic volume	245 (60)	251 (65)
Left ventricular end-systolic volume	175 (48)	179 (53)
Medication, *n* (%)		
Aldosterone antagonist	352 (32.3)	226 (30.9)
Amiodarone	78 (7.2)	51 (7.0)
ACE inhibitor	839 (77.0)	563 (77.0)
ARB	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)

Characteristic	CRT-ICD ($n = 1089$)	ICD ($n = 731$)
Previous treatment	NR	NR
Cardiac risk factors, *n*/*N* (%)		
Treatment for hypertension	691/1085 (63.7)	461/730 (63.2)
Atrial fibrillation > 1 month before enrolment	118/1063 (11.1)	90/717 (12.6)
Diabetes mellitus	329/1088 (30.2)	223/729 (30.6)
Cigarette smoking	122/1069 (11.4)	92/717 (12.8)
Body mass index $\geq 30\ kg/m^2$	385/1072 (35.9)	263/723 (36.4)
Coronary bypass surgery	317/1088 (29.1)	208/730 (28.5)

NR, not reported; RBBB, right bundle branch block.

Comments

- Evidence for some missing baseline data (in some cases total *N* differs from total randomised to group).
- Percentages may not sum to 100 because of rounding.
- Baseline characteristics for the subgroup who completed the ECG protocol are reported,[132] but not extracted.

Results

Outcome	CRT-ICD ($n = 1089$)	ICD only ($n = 731$)	HR (95% CI), p-value
Death from any cause or non-fatal HF event, *n/N* (%)	187/1089 (17.2)	185/731 (25.3)	0.66 (0.52 to 0.84), 0.001
Deaths	36/1089 (3.3)	18/731 (2.5)	NR
HF events only	151/1089 (13.9)	167/731 (22.8)	0.59 (0.47 to 0.74), < 0.001
HF events occurring in hospital, *n/N*	136/151	140/167	
HF 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
HRQoL	NR	NR	
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalisations	NR	NR	
Change in NYHA class	NR	NR	
Left ventricular remodelling			
Change in LVEF	0.11 ($n = 746$)	0.03 ($n = 620$)	< 0.001
Left ventricular end-diastolic volume average change[b] from baseline to 1 year (ml)	–52 ($n = 746$)	–15 ($n = 620$)	< 0.001
Left ventricular end-systolic volume average change[b] from baseline to 1 year (ml)	–57 ($n = 746$)	–18 ($n = 620$)	< 0.001
Exercise capacity outcomes	NR	NR	

NR, not reported.
a Total of 127 deaths including those that occurred after the first HF event; annual rate approximately 3% in each group.
b Average change is not defined further; 95% CIs are represented on a figure but have not been data extracted.

Comments

- Kaplan–Meier estimates of the probability of survival free of HF are presented but have not been data extracted.
- For the primary outcome of death or HF the HR of 0.66 indicates that there was a 34% reduction in the risk of death or non-fatal HF (whichever occurred first) among patients in the CRT-ICD group compared with patients in the ICD only group.
- HRs for HF alone and for death at any time for the total population and in the ischaemic and non-ischaemic subgroups (subgroup data below) indicate that the benefit from resynchronisation therapy was driven by a 41% reduction in the risk of HF.
- An analysis[145] based on ECG 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 HF events has been published[134] but has not been data extracted.

Adverse effects of treatment

Adverse effect	CRT-ICD ($n = 1089$)	ICD only ($n = 731$)
Death in hospital after device implantation, *n*	1 (pulmonary embolus)	–
Serious adverse events in the 30 days after device implantation (% of patients)		
Pneumothorax	1.7	0.8
Infection	1.1	0.7
Pocket haematoma requiring evacuation	3.3	2.5
Coronary venous dissection with pericardial effusion during CRT-D + ICD implantation, *n* (%)	5 (0.5)	–
Left ventricular coronary vein lead repositioned during first 30 days, *n* (%)	44 (4.0%)	–
Frequency of serious device-related adverse events during long-term follow-up after the first 30 days	4.5 per 100 device-months	5.2 per 100 device-months
Removal of device, *n* (%)	14 (1.3)	5 (0.7)

Subgroup data

Subgroup	CRT-ICD	ICD only	HR (95% CI), *p*-value
Patients with ischaemic cardiomyopathy (NYHA class I or II)	***(n = 598)***	***(n = 401)***	
Death from any cause or non-fatal HF event, *n/N* (%)	122/598 (20.4)	117/401 (29.2)	0.67 (0.52 to 0.88), 0.003
HF events only	96/598 (16.1)	105/401 (26.2)	0.58 (0.44 to 0.78), < 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 non-ischaemic cardiomyopathy (NYHA class I or II)	***(n = 491)***	***(n = 330)***	
Death from any cause or non-fatal HF event, *n* (%)	65 (13.2)	68 (20.6)	0.62 (0.44 to 0.89), 0.01
HF events only	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
	No. of events/no. of patients		**HR (95% CI), *p*-value**
Risk of death or HF according to selected clinical characteristics			
Age (years)			
< 65	142/852		0.80[a]
≥ 65	230/968		0.60[a]
Sex			
Male	294/1367		0.76 (0.59 to 0.97)
Female	78/453		0.37 (0.22 to 0.61), 0.01 for interaction

Subgroup	CRT-ICD	ICD only	HR (95% CI), *p*-value
NYHA class			
Ischaemic I	53/265		0.76[a]
Ischaemic II	186/734		0.62[a]
Non-ischaemic II	133/821		0.60[a]
QRS duration (ms)			
< 150	147/645		1.06 (0.74 to 1.52)
≥ 150	225/1175		0.48 (0.37 to 0.64), 0.001 for interaction
LVEF (%)			
≤ 25	101/646		0.70[a]
> 25	271/1174		0.60[a]
Left ventricular end-diastolic volume (ml)			
≤ 240	184/828		0.70[a]
> 240	184/969		0.62[a]
Left ventricular end-systolic volume (ml)			
≤ 170	190/835		0.66[a]
> 170	178/962		0.70[a]
All patients	372/1820		0.66

a HRs estimated from figure but 95% CIs have not been data extracted.

Comments

- Only data from prespecified 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 a greater benefit in patients with a QRS duration ≥ 150 milliseconds than in those with a QRS duration < 150 milliseconds. All other interaction *p*-values exceeded 0.10.
- No significant interaction effects were identified between the 37 centres with low enrolment (< 10 patients) and the remaining 73 centres with higher enrolment or between patients with an elevated blood urea nitrogen level [≥ 26 mg/dl (≥ 9.3 mmol/l)] and those without an elevated level. No data are presented.

Subgroup analysis by gender[135]

	Women ($n = 453$)		Men ($n = 1367$)		
Outcome	**CRT-D**	**ICD**	**CRT-D**	**ICD**	***p*-value**
HF or death (primary end point)	29/275 (11%)	51/178 (29%)	159/814 (20%)	137/553 (25%)	
	CRT-D vs. ICD HR 0.31 (95% CI 0.19 to 0.50), $p < 0.001$		CRT-D vs. ICD HR 0.72 (95% CI 0.57 to 0.92), $p < 0.01$		< 0.01 for interaction
HF only	$n = 73$ events		$n = 249$ events		< 0.01 for interaction
	CRT-D vs. ICD HR 0.30 (95% CI 0.18 to 0.50), $p < 0.001$		CRT-D vs. ICD HR 0.65 (95% CI 0.50 to 0.84), $p = 0.001$		
Death at any time	$n = 20$ events		$n = 107$ events		< 0.03 for interaction
	CRT-D vs. ICD HR 0.28 (95% CI 0.10 to 0.79), $p = 0.02$		CRT-D vs. ICD HR 1.05 (95% CI 0.70 to 1.57), $p = 0.83$		

Comments

- Patient characteristics are reported by gender, but have not been extracted.
- The primary end point included 54 deaths and 322 HF events.
- A Kaplan–Meier plot of the probability of the primary end point in women and men receiving CRT-D and ICD therapy 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 an average follow-up of 2.4 years.
- HRs are also provided separately for men and women by disease aetiology, QRS duration and conduction disturbance but these data have not been extracted.
- Results from the ECG study[132] have not been extracted.

Comments

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 was made by the co-ordinating 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.[131]
- *Blinding*: treating physicians were aware of study group assignments. Diagnosis of HF and decisions about therapy or hospital admission for patients with HF were made by physicians aware of study group assignments. Adjudication of end points was carried out by an independent mortality committee and a HF committee who was unaware of study group assignments, according to prespecified criteria.
- *Comparability of treatment groups*: baseline characteristics and use of cardiac medications at enrolment are described as similar in the two groups.
- *Method of data analysis*: ITT 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 HRs. 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 HF alone, 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 was evaluated with paired-sample *t*-tests in patients in each study group who had paired baseline and 12-month 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 HF events and a number of tertiary analyses was outlined. Of the tertiary analyses, only ECG changes at 1 year are reported. The authors state 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 chance of getting two or more false positives is small, and the analyses showed a relatively constant treatment effect over time.
- *Sample size/power calculation*: a Wang–Tsiatis ($\Delta = 0.1$ category) group sequential design (reference provided) was used with a power of 95% to detect a HR of 0.75 at a two-sided significance level of 0.05.
- *Attrition/dropout*: in the CRT-ICD arm 11/1089 patients (1.0%) did not receive a device; in the ICD only arm 19/731 patients (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 an ICD only, 91 (12.4%) received CRT-ICD (30 at discretion of the physician before reaching an end point and 61 after a HF event); in patients assigned to CRT-ICD, 82 (7.5%) received an ICD only 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 in the adverse effects section; reasons not provided). 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 compared with 55 patients (7.5%) in the ICD only group. In total, 201 patients in the CRT-ICD group underwent the 1-year ECG 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 combined CRT-ICD in mildly symptomatic or asymptomatic patients and thus the results are unlikely to be transferable to more severe HF patients.
- *Outcome measures*: the primary end point was a composite measure but the discussion section describes this as appropriate and widely used in HF trials. Other outcomes appear appropriate; however, not all were analysed according to the ITT principle.
- *Intercentre variability*: authors state that no significant interaction effects were identified between the 37 centres with low enrolment (< 10 patients) and the remaining 73 centres with higher enrolment.
- *Conflict of interests*: 11/14 authors named on the publication declared one or more potential conflicts of interest in the form of grant support, lecture fees, consulting fees or institutional fellowships from one or more company.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information provided
Allocation concealment	Low	'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'[131]
Performance bias		
Blinding of participants and personnel	High	'The treating physicians were aware of study group assignments'[130]
Detection bias		
Blinding of outcome assessment	High	'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'.[130] Authors acknowledged that 'it is possible that the investigators' knowledge of study-group assignment contributed in some way to the lower frequency of HF in the CRT-ICD group'[130]
Attrition bias		
Incomplete outcome data addressed		
Survival/HF outcomes	Low	'Data analysis was performed according to the intention-to-treat principle'[130] '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'[131]
Ventricular remodelling outcomes	High	201/1820 participants not included in the paired volume and ejection fraction studies
Reporting bias		
Selective reporting	Low	Paper available describing design and clinical protocol. Outcomes of interest reported as expected[131]
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD)

Reference and design	Intervention and comparator	Participants	Outcome measures
Young *et al.* 2003[136] *Study design*: RCT *Countries*: USA and Canada *No. of centres:* Not stated; reviewer counted 63 listed *Funding*: Medtronic Inc. (manufacturer of the device used in the trial)	*Intervention*: ICD-CRT + OPT Mode programmed that paced both ventricles simultaneously following atrial-sensed events at rate of ≤ 130/minute. ICD active. Atrial pacing occurred only for sinus rates < 35/minute *Comparator*: ICD + OPT Mode programmed that inhibited atrial or ventricular pacing unless intrinsic rate < 35/minute. ICD active. Participants implanted with Model 7272 InSync ICD (Medtronic Inc.), which can deliver atrial-synchronised biventricular pacing for cardiac resynchronisation, antitachycardia pacing through right ventricular or right ventricular and left ventricular leads, and cardioversion and defibrillation to treat ventricular tachyarrhythmias delivered through the right ventricular lead only *Other interventions used*: stable and appropriate drug regimen, which included an ACE inhibitor or ARB, if tolerated, for at least 1 month. A beta-blocker had to have been initiated at least 3 months before enrolment. Initiation of a beta-blocker was not permitted during the trial period	*Indication for treatment*: moderate to severe HF, wide QRS interval, LVSD and an established indication for an ICD *No. of participants:* 369; ICD-CRT + OPT 187, ICD + OPT 182 *Inclusion criteria*: indications for an ICD: cardiac arrest (loss of consciousness) due to VT or VF without a transient reversible cause, patients with recurrent, poorly tolerated and sustained VT (spontaneously or induced); NYHA class III or IV CHF; LVEF ≤ 35%, LVEDD ≥ 55 mm; QRS interval ≥ 130 milliseconds; age ≥ 18 years; stable drug regimen for ≥ 1 month *Exclusion criteria*: life expectancy < 6 months; baseline 6-minute walk test > 450 m; bradycardia requiring pacemaker; unstable angina, MI, CABG, PTCA, cerebral vascular accident or transient ischaemic attack within previous 3 months; more than two infusions of inotropic drug per week; systolic blood pressure > 170 or < 80 mmHg; resting heart rate > 140 bpm; serum creatinine > 3.0 mg/dl; hepatic enzymes more than three times the upper limit of normal; severe lung disease; chronic atrial arrhythmias or cardioversion or paroxysmal atrial fibrillation within previous 1 month; heart transplant recipient; severe valvular heart disease	*Primary outcomes:* NYHA class, QoL score, distance walked covered in 6 minutes *Secondary outcomes:* included peak VO_2, treadmill exercise duration, LVEF, left ventricular end-systolic and end-diastolic volumes, LVEDD, severity of mitral regurgitation, QRS duration, neurohormone concentrations and a clinical composite response (worsened, improved or unchanged). Worsened defined as death, hospitalised because of worsening HF, permanently discontinued double-blind treatment (because of worsening HF, withdrawal of consent or other administrative reason), worsening NYHA class at LOCF or moderate to marked worsening of patient global assessment score at LOCF; improved defined as not worsened and demonstrated improvement in NYHA class at LOCF or a moderate to marked improvement in patient global assessment score at LOCF; unchanged defined as neither improved nor worsened Complication definition: a sign, symptom, illness or other medical event that was resolved invasively (penetrated the skin, parenteral fluids or drugs) or resulted in death or serious injury to patient; termination of a significant device function *Method of assessing outcomes*: visits at 1, 3 and 6 months. At each visit: interrogation of implanted device, QoL assessment, 6-minute walk distance, estimation of NYHA class and monitoring of drug regimen. At 6 month visit: ECG, cardiopulmonary exercise test and measurement of plasma neurohormones *Length of follow-up:* 6 months Recruitment: October 1999–August 2001

bpm, beats per minute; LOCF, last observation carried forward; LVEDD, left ventricular end-diastolic diameter; PTCA, percutaneous transluminal coronary angiography.

Participant characteristics

Characteristic	ICD-CRT + OPT ($n = 187$)	ICD + OPT ($n = 182$)	p-value
Age (years), mean (SD)	66.6 (11.3)	67.6 (9.2)	
Gender, male, *n* (%)	142 (75.9)	141 (77.5)	
Ethnicity	NR	NR	
Underlying heart disease, *n* (%)			0.02
Ischaemic	119 (64.0)	138 (75.8)	
Non-ischaemic	67 (36.0)	48 (26.4)	
Indication for ICD, *n* (%)			
Cardiac arrest	17 (9)	20 (11)	
Sustained VT	71 (38)	76 (42)	
Induced VF and sustained VT	99 (53)	85 (47)	
NYHA class, *n* (%)			
III	165 (88.2)	163 (89.6)	
IV	22 (11.8)	19 (10.4)	
LVEF (%), mean (SD)	24.2 (6.5)	23.9 (6.0)	
Resting heart rate/minute, mean (SD)	71.0 (12.4)	71.3 (12.9)	
Blood pressure (mmHg), mean (SD)			
Systolic	113 (18)	114 (17)	
Diastolic	66 (11)	67 (10)	
QRS duration (milliseconds), mean (SD)	165 (22)	162 (22)	
Isolated right bundle branch block, *n* (%)	25 (13)	24 (13)	
LVEDD (mm), mean (SD)	75.6 (9.6)	76.7 (10.4)	
LVESD (mm), mean (SD)	248 (93)	240 (87)	
LVEDV (ml), mean (SD)	322 (100)	311 (96)	
Mitral regurgitation, average jet area (cm^2), mean (SD)	7.5 (5.9)	7.3 (6.7)	
QoL life score, mean (SD)	56.8 (22.6)	55.2 (22.6)	
6-minute walk distance (m), mean (SD)	243 (129)	243 (117)	
Peak VO_2 (ml/kg/minute), mean (SD)	13.3 (3.6)	13.4 (3.8)	
Exercise duration (seconds), mean (SD)	468 (205)	506 (230)	
Baseline medications, *n* (%)			
ACE inhibitor or ACE inhibitor substitute	173 (92.5)	162 (89.0)	
Antiarrhythmic	79 (42.3)	60 (33.0)	
Beta-locker	116 (62.0)	106 (58.2)	
Diuretic	174 (93.1)	172 (94.5)	

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; NR, not reported.

Results

Outcomes	ICD-CRT + OPT ($n = 187$)	ICD + OPT ($n = 182$)	Control vs. CRT p-value
No. of deaths during 6 months	14	15	NR
Sudden deaths	3	3	
6-month cumulative survival, %	92.4 (95% CI 87.5 to 95.4)	92.2 (95% CI 87.2 to 95.3)	log-rank $p = 0.96$
Primary outcomes (including all patients with data), median change (95% CI), n			
Change in QoL score[a]	–17.5 (–21 to –14), 162	–11 (–16 to –7), 157	0.02
Change in NYHA functional class	–1 (–1 to –1), 165	0 (–1 to 0), 162	0.007
Change in 6-minute walk distance (m)	55 (44 to 79), 152	53 (43 to 75), 153	0.36
Primary LOCF analysis (excluding patients who died and those with either no baseline or no follow-up data at 1, 3 and 6 months), median change (95% CI), n			
Change in QoL score	–17 (–21 to –13), 170	–11 (–16 to –6), 163	0.01
Change in NYHA functional class	–1 (–1 to –1), 171	0 (–1 to 0), 166	0.006
Change in 6-minute walk distance (m)	54.5 (40 to 75), 166	52 (40 to 74), 163	0.32
Secondary outcomes, median change (95% CI), n			
Cardiopulmonary exercise			
Change in peak VO_2 (ml/kg/minute)	1.1 (0.7 to 1.6), 120	0.1 (–0.1 to 0.8), 121	0.04
Change in exercise duration (seconds)	55.5 (30 to 79), 120	–11 (–55 to 12), 123	< 0.001
Echocardiographic left ventricular size and function			
Change in end-diastolic volume (ml)	–19.9 (–39.7 to –6.3), 132	–5.7 (–16.2 to 1.8), 133	0.06
Change in end-systolic volume (ml)	–22.2 (–32.8 to –10.7), 132	–8.2 (–19.1 to 0.6), 133	0.06
Change in ejection fraction (absolute %)	2.1 (1.2 to 4.1), 132	1.7 (0.7 to 2.4), 133	0.12
Change in end-diastolic diameter (mm)	–0.1 (–0.3 to 0.1), 70	–0.2 (–0.3 to 0), 67	0.81
Change in end-systolic diameter (mm)	–0.1 (–0.4 to 0.1), 69	–0.3 (–0.5 to –0.1), 65	0.53
Change in mitral regurgitant jet area (mm)	–0.55 (–2.00 to 0), 130	–0.33 (–0.85 to 0), 126	0.58
Change in overall clinical status, n (%)			
Improved	98 (52.4)	78 (42.9)	0.07
Unchanged	28 (15.0)	43 (23.6)	
Worsened	61 (32.6)	61 (33.5)	
Change in QRS duration (milliseconds)	–20 (–21 to –14), 162	0, $n = 160$	< 0.001
Changes in plasma neurohormones (pg/ml)			
Brain natriuretic peptide	–50 (–163 to –6), 119	–68 (–133 to –6), 121	0.77
Dopamine	0, $n = 112$	0, $n = 117$	0.37
Norepinephrine (ng/dl)	4 (–12 to 68), 113	–17 (–54 to 49), 117	0.58
Epinephrine	0 (–4 to 0), 112	–3 (–8 to 0), 115	0.05
Big endothelin	–2.5 (–6.0 to 1.3), 110	–1.8 (–3.7 to 0.9), 119	0.98

Outcomes	ICD-CRT + OPT ($n = 187$)	ICD + OPT ($n = 182$)	Control vs. CRT p-value
Hospitalisations between randomisation and 6-month visit, *n*/*N* (%)	85/187 (45.5)	78/182 (42.9)	
Length of hospital stay (days), mean (SD)	4.8 (4.9)	5.4 (4.7)	0.06
Probability of hospitalisation for worsening HF or death from any cause, %	25.7 (95% CI 19.6 to 32.3)	25.9 (95% CI 19.8 to 32.5)	0.69
Risk of death or all cause hospitalisation, %	47.4 (95% CI 40.0 to 54.4)	48.3 (95% CI 40.6 to 55.6)	0.88
Experienced one or more spontaneous episode of VT or VF, *n*/*N* (%)	42/187 (22)	47/182 (26)	0.47
Episode not successfully terminated within interval determined by device criteria,[b] *n*/*N* (%)	1/678 (0.1)	4/233 (1.7)	
Appropriate ICD shocks	89 events, 24/187 patients (13%)	154 events, 26/182 patients (14%)	0.76
Inappropriate ICD shocks	18 events, 8/187 patients (4%)	59 events, 13/182 patients (7%)	0.27
Appropriate: only antitachycardia pacing used	608 events, 33/187 patients (18%)	229 events, 31/182 patients (17%)	0.89
Inappropriate: only antitachycardia pacing used	35 events, 13/187 patients (7%)	32 events, 8/182 patients (4%)	0.37
Therapy compliance	94% ventricular paced for ≥ 90% of the time	86% received no right ventricular pacing	

NR, not reported.

a For QoL score more negative change scores indicate greater improvement.

b For the spontaneous and treated VT/VF episodes for which outcomes of ICD therapy were recorded. All five episodes eventually terminated spontaneously.

Comments

- Median duration of successful implantation procedure 2.75 hours (IQR 2.2–3.6).
- In addition to the 6-month median changes in QoL and 6-minute walk distance, changes at 1 and 3 months' follow-up are shown in a figure but have not been data extracted.
- An analysis of appropriate and inappropriate ICD treatment by CRT treatment received (not randomised assignment) is also presented but has not been extracted. Results were broadly similar.

Adverse effects of treatment

Adverse effect	All patients undergoing implant attempt ($n = 429$)	
Experienced complication from implant to hospital discharge[a]	120/429 patients (28%), 159 complications	
Complications related to left ventricular lead	37/159 (23%) (including 15 coronary sinus dissections and 4 cardiac perforations)	
HF decompensation	6 patients (received intravenous medication)	
Heart block	3 patients (required bradycardia pacing support)	
Muscle stimulation	4 patients (required either lead repositioning or replacement)	
Pericardial effusion	2 patients (treated with a pericardiocentesis)	
Pericarditis	1 patient (received intravenous medication)	
Haemo/pneumothorax	3 patients (placement of chest tube)	
VT and VF	5 patients (3 received external defibrillation, 2 intravenous medications)	
Elevated pacing thresholds or loss of capture	7 patients (6 received lead repositioning, 1 set screw tightened in connector block)	
Died within 30 days of latest implant attempt[b]	5/429 (1.2%)	
	ICD-CRT + OPT ($n = 187$)	**ICD + OPT ($n = 182$)**
For patients successfully implanted and randomised: complications after hospital discharge to 6-month follow-up		
Left ventricular lead-related complication	21 complications in 20 patients (11%)	14 complications in 13 patients (7%)
ICD system related	9 complications in 9 patients (5%)	14 complications in 13 patients (8%)
Procedure related	10 complications in 10 patients (5%)	13 complications in 11 patients (6%)
HF decompensation	63 complications in 36 patients (19%)	71 complications in 40 patients (22%)
Other	81 complications in 45 patients (24%)	74 complications in 44 patients (22%)
Total	184 complications in 88 patients (47%)	186 complications in 80 patients (44%)
Crossed over to alternative treatment	10 (5%) to ICD only (2 ventricular lead dislodgement, 2 diaphragmatic stimulation, 6 programming errors)	14 (8%) to CRT (11 worsening HF, 2 bradycardia, 1 programming error)

a Not stated but not all complications are reported in detail.
b For those with at least one implant attempt.

Comments

- Adverse events after hospital discharge to 6-month follow-up also shown for 60 participants who had an implant attempted but who were not randomised (unsuccessful CRT but successful ICD only $n = 50$; CRT system implanted $n = 10$) but these have not been extracted.
- From hospital discharge to 6-month follow-up 175/379 patients (46%) with successful implants experienced 398 complications. States that the rate of device-related events was substantially lower than anticipated in the prespecified criteria of the original study protocol.
- States that the frequency of adverse events unrelated to the device or to HF did not differ significantly between the groups.

Comments

Methodological comments

- *Allocation to treatment groups*: randomisation occurred within 7 days of successful implantation but after a cardiopulmonary exercise test. Random assignment in blocked groups of four by centre (to balance CRT and control assignments at each centre). Random allocation sequence was generated by SAS software version 8.2 (SAS Institute Inc., Cary, NC, USA). Centres were unaware of randomisation method. Assignment provided to unblinded electrophysiology staff in consecutively numbered and opaque sealed envelopes opened at the time of randomisation.
- *Blinding*: states double blind. Patients and physicians from HF team (not involved in programming of the device) remained unaware of assignment until after the 6-month visit. Blinded phase of study complete at 6 months. Independent core laboratories, unaware of assignment, interpreted data. Adverse events classified by clinical events review committee without knowledge of random assignment.
- *Comparability of treatment groups*: states similar except that the control group had a higher percentage of participants with ischaemic heart disease.
- *Method of data analysis*: only participants with both baseline and follow-up data were included in efficacy analyses. All randomised patients who underwent an implant attempt were included in the adverse event analysis. For all other analyses all randomised patients were included. States that all end points were analysed by ITT principle but this appears to conflict with earlier statement that both baseline and follow-up data were required for participants to be included in efficacy analyses. Data presented as median changes between baseline and 6-month follow-up. CIs for medians computed using a distribution-free approach. Mean values presented with SDs. Continuous variable (including NYHA) changes from baseline in control vs. CRT group and demographic characteristics compared using the Wilcoxon rank-sum test. Differences in distribution of categorical end points between the two groups compared with Fisher's exact test. Survival curves constructed using the Kaplan–Meier method (time zero = date of implant) and differences between curves examined using the log-rank test statistic. CIs for survival computed on the log-log survival scale. Objectives considered reached for the three primary efficacy variables if differences between the groups for all three end points had $p \leq 0.05$ or if two had $p \leq 0.025$ or if one had $p \leq 0.017$, using the Hochberg criterion. For secondary end points $p < 0.05$ was considered significant. All p-values were calculated using two-sided tests. Details of analysis that was not prespecified were not data extracted.
- *Sample size/power calculation*: estimated based on the assumption that the study would have 80% power (two-sided $\alpha = 0.017$) to detect a difference in NYHA class of 0.75, in QoL of 13 points or in 6-minute walk distance of 50 m. There were 112 patients per treatment group. Study was not powered to detect a morbidity or mortality difference.
- *Attrition/dropout*: of 639 patients initially enrolled, 210 had mild HF symptoms and as per protocol were not included in this analysis; 60 NYHA class III or IV patients had an implant attempted but did not enter the randomised therapy phase. This left 369 patients included in the randomisation. In the CRT-D + OPT group 10 (5%) crossed over to ICD therapy only (these were included in the analysis), 14 died, six missed the 6-month follow-up and two received cardiac transplantation (these 22 not included in the analysis), leaving 165/187 included in the primary efficacy analysis. In the ICD + OPT group 14 (8%) crossed over to CRT (included in analysis), 15 died and five missed the 6-month follow-up (these 20 not included in the analysis), leaving 162/182 included in the primary efficacy analysis.

General comments

- *Generalisability*: only those with successful implantation were randomised. Generalisable to those with moderate to severe HF; however, relatively short length of follow-up (6 months) and so results may not be generalisable over long time periods.
- *Outcome measures*: appear appropriate but QoL tool not specified.
- *Intercentre variability*: not commented on.
- *Conflict of interests*: eight of the 11 listed authors made financial disclosures. The sponsor had responsibility for the initial study design, day-to-day study operations, data collection, data management and statistical analysis in conjunction with the co-principal investigators. The study sponsor also participated in preparation and review of the manuscript for accuracy. States that investigators performed analyses without restrictions or limitations from sponsors.
- *Other*: except for ICD indication, patient inclusion criteria and study design were identical to those of the MIRACLE trial.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Low	Sequence generated by computer software
Allocation concealment	Low	Consecutively numbered and opaque sealed envelopes
Performance bias		
Blinding of participants and personnel	Low	States double blind, participants and physicians blinded
Detection bias		
Blinding of outcome assessment	Low	States double blind, use of independent lab and blinded committee
Attrition bias		
Incomplete outcome data addressed		
Primary outcomes	Unclear	Numbers and reasons for missing data are given; appear balanced between groups for primary outcomes. Crossovers were included as assigned. However, denominator should be $n = 165$ for CRT and $n = 162$ for ICD but this is only the case for NYHA class and not for the other two primary outcomes QoL and 6-minute walk distance
Secondary outcomes	High	Amount of missing data varies between different secondary outcomes although appears to be a similar proportion in each group. Reasons not provided
Reporting bias		
Selective reporting	Low	Protocol not available but expected outcomes reported
Other bias		
Other sources of bias	Unclear	Study sponsor appears to have been involved in all aspects of the study

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Multicenter InSync ICD II Randomized Clinical Evaluation (MIRACLE ICD II)

Reference and design	Intervention and comparator	Participants	Outcome measures
Abraham *et al.* 2004[138] *Study design*: RCT *Countries*: USA and Canada *No. of centres:* 63[136] *Funding*: Medtronic, Inc., St Paul, MN	*Intervention*: CRT-D + OPT Combined cardiac resynchronisation/ICD device (model 7272 InSync ICD, Medtronic), with three pacing leads: standard right atrial pacing lead, standard right ventricular pacing/ defibrillation lead, and one of several left ventricular transvenous leads positioned in a distal cardiac vein via coronary sinus Device programmed to pace both ventricles after atrial sensed events at rates of ≤ 130 bpm. Atrial pacing occurred only for sinus rates of ≤ 35 bpm *Comparator*: ICD + OPT Active ICD therapy only. Device as above. Device programmed to inhibit atrial or ventricular pacing unless intrinsic rate was < 35 bpm *Other interventions used*: all appropriate treatments for HF, including diuretic, ACE inhibitor or ARB and usually digitalis and beta-blocker. Doses stable for ≥ 1 month except for beta-blocker, stable for 3 months	*Indication for treatment*: mild NYHA class II HF symptoms, a wide QRS complex and an established indication for an ICD *No. of participants:* enrolled 222, implant attempt 210, successful implant 191, randomised 186; CRT-D 85, ICD 101 Completed study: CRT-D 82, ICD 98 *Inclusion criteria*: NYHA class II chronic HF, LVEF ≤ 35%, LVEDD ≥ 55 mm, QRS interval ≥ 130 milliseconds, indication for ICD *Exclusion criteria*: variety of medical reasons including having an indication for or contraindication to cardiac pacing	*Primary outcome*: change in peak VO_2 *Secondary outcomes*: ventilatory response to exercise [minute ventilation/ minute carbon dioxide production (VE/VCO_2)], NYHA class, QoL, 6-minute hall walk test, left ventricular volume, LVEF, composite clinical response (worsened, improved or unchanged) *Method of assessing outcomes*: 7 days before implantation: NYHA class, 6-minute hall walk test, QoL assessed using MLWHFQ, 2-dimensional Doppler ECG, plasma neurohormone concentrations, QRS interval assessed using 12-lead ECG; before randomisation: exercise capacity measured using baseline treadmill cardiopulmonary exercise test using modified Naughton protocol; at 1, 3 and 6 months: interrogation of CRT-ICD, QoL, 6-minute hall walk distance, NYHA class, monitor drug regimen, ECG, metabolic exercise testing, plasma neurohormone measurements at 6-month visit Adverse events: complication defined as a sign, symptom, illness or other medical event that was resolved invasively or resulted in death or serious injury; termination of a significant device function *Length of follow-up*: blinded phase of study completed at 6-month follow-up. CRT activated in control group *Recruitment*: July 2002

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter.

Participant characteristics

Characteristic	CRT-ICD ($n = 85$)	ICD ($n = 101$)	p-value
Mean (SD) unless stated otherwise			
Age (years)	63.0 (12.8)	63.1 (12.1)	
Gender, men, *n* (%)	75 (88.2)	91 (90.1)	
Ethnicity	NR	NR	
NYHA functional class II, *n* (%)	85 (100)	101 (100)	
LVEF (%)	24.4 (6.6)	24.6 (6.7)	
LVEDD (cm)	7.6 (1.0)	7.5 (1.0)	
LVESD (cm)	6.5 (1.2)	6.5 (1.2)	
LVEDV (cm^3)	337 (147)	329 (108)	
LVESV (cm^3)	260 (134)	252 (98)	
QRS duration (ms)	166 (25)	165 (23)	
Mitral regurgitation, average jet area (cm^2)	5.9 (6.0)	6.1 (5.3)	
QoL score	41.8 (25.1)	39.8 (21.2)	
6-min walk test (m)	355 (125)	383 (108)	
Peak VO_2 (ml/kg/minute)	16.4 (4.4)	16.8 (5.0)	
VE/VCo_2 (ml/minute)	39.3 (9.7)	38.7 (9.4)	
Exercise duration (seconds)	647 (242)	664 (228)	
Resting heart rate (bpm)	69.7 (11.5)	68.6 (12.3)	
Blood pressure (mmHg)			
Systolic	116.2 (15.8)	116.8 (16.8)	
Diastolic	69.9 (10.4)	69.4 (10.2)	
Underlying heart disease, *n* (%)			
Ischaemic	47 (55.3)	59 (58.4)	
Right bundle branch block, *n* (%)	10 (11.8)	21 (20.8)	
Baseline neurohormones (pg/ml)			
Brain natriuretic peptide	631 (909)	538 (806)	
Norepinephrine	413 (379)	355 (249)	
Epinephrine	29 (28)	31 (28)	
Big endothelin	15 (12)	18 (15)	
Dopamine	23 (51)	12 (7)	
Baseline medications, *n* (%)			
ACE inhibitor	83 (97.6)	96 (95.0)	
Antiarrhythmic	30 (35.3)	33 (32.7)	
Beta-blocker	54 (63.5)	64 (63.4)	
Diuretic	74 (87.1)	81 (80.2)	

bpm, beats per minute; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NR, not reported.

Comment

- States that all differences between the control group and the CRT group are not statistically significant.

Results

Outcomes	CRT-ICD ($n = 85$)	ICD ($n = 101$)	p-value
Mortality during 6-month follow-up, *n*	2 (2 cardiac arrests)	2 (1 cardiac arrest, 1 MI with cardiogenic shock)	
Change from baseline to 6 months, mean (SD), *n*			
Change in QoL score	–13.3 (25.1), 81	–10.7 (21.7), 96	0.49
Symptoms and complications related to tachyarrhythmias and/or HF	NR	NR	
HF hospitalisations	NR	NR	
Change in NYHA class	–0.18 (0.61), 82	0.01 (0.63), 98	0.05
Change in peak VO_2 (ml/kg/minute)	0.5 (3.2), 66	0.2 (3.2), 79	0.87
Change in exercise duration (seconds)	42 (167), 66	37 (186), 79	0.56
Change in VE/VCO_2, (ml/minute)	–1.8 (6.2), 66	0.5 (5.2), 78	0.01
Change in 6-minute walk distance (m)	38 (109), 78	33 (98), 93	0.59
Echocardiographic left ventricular size and function			
Change in LV end-diastolic volume (ml)	–41 (76), 69	–16 (62), 85	0.04
Change in LV end-systolic volume (ml)	–42 (77), 68	–14 (57), 85	0.01
Change in LVEF (absolute %)	3.8 (8.0), 68	0.8 (6.2), 85	0.02
Change in mitral regurgitant jet area (mm)	–1.7 (4.7), 62	–1.0 (3.7), 84	0.25
Change in overall clinical status, *n* (%)			
Improved	49 (58)	36 (36)	0.01
Unchanged	19 (22)	34 (34)	(all)
Worsened	17 (20)	31 (31)	
Change in QRS duration	–9 (24), 78	–9 (22), 95	0.97
Changes in plasma neurohormones (pg/ml)			
Brain natriuretic peptide	–195.2 (831.6), 64	–96.3 (581.6), 71	0.81
Dopamine	–10.3 (59.7), 60	5.5 (18.2), 71	0.26
Norepinephrine	10.1 (396.0), 60	63.3 (248.3), 71	0.86
Epinephrine	–6.5 (34.2), 60	–4.7 (25.8), 71	0.67
Big endothelin	–2.3 (15.6), 61	–4.3 (15.6), 70	0.69
One or more appropriately detected, spontaneous episodes of VT or VF, *n/N* (%)	19/85 (22)	26/101 (26)	0.61
Percentage of inappropriately detected VT/VF			
Treated	NR	NR	0.21
Shocked	NR	NR	0.78

NR, not reported; VE/VCO_2, ventilatory response to exercise (minute ventilation/minute carbon dioxide production).

Comments

- Primary outcome of study was change in peak VO_2.

Adverse effects of treatment

Adverse effect	
From implant to hospital discharge	46/210 (22%) patients,[a] 56 complications
Complication related to placement of left ventricular lead	19/56 (34%) (including 3 coronary sinus dissections, 3 cardiac perforations, 5 lead dislodgements)
Failed initial implant attempt	23/210
From hospital discharge to 6-month follow-up	66/191 (35%) patients,[b] 109 complications
Complications related to left ventricular lead	19/109 (17%) (including 11 lead dislodgements, 1 cardiac perforation, 3 diaphragmatic muscle stimulation, 4 elevated pacing threshold)

a Note that this is all patients undergoing implantation, not the number randomised.
b Note that this is the number of patients undergoing successful implantation, not the number randomised.

Comments

Methodological comments

- *Allocation to treatment groups*: patients randomly assigned, in permuted groups for each centre. SAS software used to generate the random allocation sequence. Method of randomisation not disclosed to participating centres and was accomplished in blocked groups of four for each centre to ensure balance of CRT and control assignments at each participating institution. Randomisation occurred after a successful implant.
- *Blinding*: patients and physicians treating for HF and performing study evaluations unaware of treatment assignment. At each site an electrophysiologist unblinded to treatment programmed the device and performed all tests that could reveal the identity of assigned mode. The clinical events review committee reviewed and classified adverse events without knowledge of the randomised assignment.
- *Comparability of treatment groups*: states no statistically significant differences noted between the groups.
- *Method of data analysis*: states that all end points were analysed according to ITT principle; results were assessed on the basis of the original treatment assignment. Changes in continuous variables, including NYHA class, from baseline to 6 months in the control group were compared with changes in the CRT group using the Wilcoxon rank-sum test. For categorical end points, compared differences in distribution of responses to treatment at 6 months using Fisher's exact test, except for inappropriately detected VT/VF episodes, for which generalised estimating equation methods were used. $p < 0.05$ was considered statistically significant. All *p*-values were calculated using two-sided tests. States that in an analysis that was not prespecified, potential clinically relevant covariates were analysed by ANOVA with random assignment as independent variables; however data are not reported in the paper.
- *Sample size/power calculation*: not reported.
- *Attrition/dropout*: 222 participants were enrolled and implant was attempted in 210 (reasons for no implant not reported); 191 (91%) were successfully implanted (reasons for implant failure not reported): one patient died and four patients had left ventricular lead dislodgements that were not corrected. The remaining 186 patients were randomised. In each group two patients died and one missed the 6-month follow-up visit. Five ICD patients (5%) crossed over to CRT-D before 6 months (biventricular pacing was activated early because of bradycardia in three patients, there was a centre error in one patient and there was pacemaker dependency after atrioventricular node ablation for atrial flutter in one patient). Two CRT-D patients (2%) crossed over to no pacing (biventricular pacing was deactivated because of left ventricular lead dislodgement in one patient and there was diaphragmatic stimulation in biventricular and right ventricular pacing modes in one patient).

General comments

- *Generalisability*: participants had mildly symptomatic class II HF. Exercise capacity was not moderately or severely impaired at baseline. Randomisation occurred after a successful implant; therefore, patients not representative of all patients eligible for CRT.
- *Outcome measures*: appropriate but follow-up only 6 months. Composite outcome not defined in paper but reference provided. Adverse events not reported separately for treatment groups.
- *Intercentre variability*: not reported.
- *Conflict of interests*: study supported by Medtronic, Inc. Conflicts declared by authors, including receiving honoraria from and/or being a consultant and/or investigator for Medtronic, Guidant, St Jude Medical and/or GlaxoSmithKline and/or shareholder in Medtronic.

ANOVA, analysis of variance.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Low	'SAS software (SAS Institute) was used to generate the random allocation sequence'[137]
Allocation concealment	Low	'Method of randomisation was not disclosed to participating centres'[137] 'At each site, an electrophysiologist unblinded to treatment opened a sealed envelope at the time of randomisation, programmed the device, and performed all tests that could reveal the identity of the assigned mode'[137]
Performance bias		
Blinding of participants and personnel	Low	'Neither the patients nor the physicians treating them were aware of the treatment assignment. At each site, an electrophysiologist unblinded to treatment opened a sealed envelope at the time of randomisation, programmed the device, and performed all tests that could reveal the identity of the assigned mode'[137] 'Clinical events review committee reviewed and classified adverse events without knowledge of randomised assignment'[137]
Detection bias		
Blinding of outcome assessment	Low	'Cardiopulmonary gas exchange analysis was done at a core laboratory with personnel blinded to CRT activation status'[137] 'Standard protocols used to perform echocardiograms and collect plasma neurohormones, Independent core laboratories, blinded to patient study assignment, interpreted the data'[137] 'Clinical events review committee reviewed and classified adverse events without knowledge of randomised assignment'[137]

Domain	Judgement[a]	Support for judgement
Attrition bias		
Incomplete outcome data addressed	Unclear	States ITT but reports various patient numbers for each outcome. Not clear why these data are missing
Reporting bias		
Selective reporting	Low	Protocol not available but expected outcomes reported. Analysis described in methods section not reported in the results section, but not relevant to this review as not prespecified
Other bias		
Other sources of bias	Low	

a 'Low risk' or 'unclear risk' of bias.

Piccirillo and colleagues study

Reference and design	Intervention and comparator	Participants	Outcome measures
Piccirillo *et al.* 2006[138] *Study design*: RCT *Country*: Italy *No. of centres*: one *Funding*: not reported	*Intervention*: CRT-D *Comparator*: ICD Biventricular pacemaker (Guidant Corporation); the final pace setting was VDD with a lower rate well below the patient's lowest intrinsic heart rate to maintain natural atrial tracking at rest (setting essential to allow power spectral analysis of heart rate variability) Both groups were taking standard medications for HF, including ramipril (2.5–10 mg/day) or losartan (50 mg/day), furosemide (25–250 mg/day), spironolactone (25–50 mg/day), carvedilol (6.25–50 mg/day) or bisoprolol (2.5–5 mg/day), digoxin (0.125 mg/day or 0.250 mg/day) and acetylsalicylic acid (100 mg/day) *Other interventions used*: none reported	*Indication for treatment*: CHF (with low ejection fraction and prolonged QRS interval) secondary to ischaemic dilated cardiomyopathy *No. of randomised participants:* 31; CRT-D: 16, ICD: 15 Also reported data for healthy non-randomised control group ($n = 12$). Data not extracted *Inclusion criteria*: LVEF $\leq 35\%$, QRS interval > 120 milliseconds and sinus rhythm *Exclusion criteria*: malignancy, primary valve disease, frequent extrasystoles (more than one per minute), atrial fibrillation or other arrhythmias requiring a pacemaker (atrioventricular disturbances) or defibrillator for secondary prevention because of a history of malignant arrhythmias	*Primary/secondary outcome (not stated which)*: spectral indices based on power spectral analysis and changes in spectral indices (not data extracted). Also reported mortality and 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 three expert cardiologists to evaluate appropriateness *Length of follow-up*: 1 year *Recruitment*: not reported

Participant characteristics

Characteristic	CRT-D ($n = 16$)	ICD ($n = 15$)	p-value
Age (years), mean (SD)	65 (4)	65 (8)	
Sex, male/female, *n*	13/3	12/3	
Ethnicity	NR	NR	
NYHA class, *n*			
III	5	5	
IV	11	10	
LVEF (%), mean (SD)	23 (4)	22 (8)	
QRS length (milliseconds), mean (SD)	160 (4)	159 (8)	
Heart rate (bpm), mean (SD)	79 (4)	81 (8)	
Blood pressure (mmHg), mean (SD)			
Systolic	112 (12)	109 (19)	
Diastolic	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, *n*			
Digoxin	12	11	
Ramipril	16	15	
Furosemide	16	15	
Spironolactone	9	10	
Carvedilol	13	12	
Biskoprolol	2	1	
Acetylsalicylic acid	16	14	
Cardiac history, *n*			
Unstable symptoms of HF	0	0	
Hospitalisation	0	0	
Recent previous treatment, *n*			
Coronary angioplasty	0	0	
Revascularisation procedures	0	0	
Change of therapy during the past 3 months, *n*	0	0	
Comorbidities	NR	NR	
Body mass index (kg/m^2), mean (SD)	26 (4)	26 (4)	

bpm, beats per minute; NR, not reported.

Comments

- Data for the healthy control group not data extracted; *p*-values for comparison between CHF patients before treatment and control group not data extracted.
- None of the three CRT-D 'non-responders' received ICD shocks.

Results

Outcome	CRT-D ($n = 16$)	ICD ($n = 15$)	*p*-value
Deaths, *n*	0	0	
HRQoL	NR	NR	
Received appropriate shocks, *n*	2	4	
Sustained VT	1	3	
Sustained VF	1	1	
Hospitalisation because of worsening CHF, *n*	0	2	
NYHA class after 12 months,[a] *n*			
I	1	0	
II	3[a]	1	
III	6	1	
IV	6[a]	13	
LVEF (%),[b] mean	28	22	
Exercise capacity outcomes	NR	NR	
Heart rate (bpm), mean (SD)	75 (4)	76 (4)	
Blood pressure (mmHg), mean (SD)			
Systolic	115 (4)[c]	108 (11)	
Diastolic	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	

bpm, beats per minute; NR, not reported.

a Data for the CRT-D group differ between table 3 and the text (class II amounts to seven in the text and class IV amounts to two in the text, but three participants were considered as non-responders as their NYHA class did not change).

b SDs reported in text and table 3 differ (CRT-D group: SD 1 in text, SD 4 in table; ICD group: SD 1 in text, SD 8 in table) (*p*-value for within CRT-D group comparison from baseline to follow-up not extracted).

c *p*-values for within-group comparisons from baseline to follow-up not extracted.

Comments

- CRT-D: three patients were considered non-responders as their NYHA class did not change. Text states that, from baseline, four CRT-D patients improved from NYHA class IV to class II, five improved from NYHA class IV to class III, three improved from NYHA class III to class II and one improved from NYHA class III to class I; however, these changes do not correspond with the data presented in table 3.
- ICD: three patients worsened from NYHA class III to class IV and one patient improved from NYHA class III to class II.
- Results from the power spectral analysis for heart rate and blood pressure variability reported, but not extracted.

Adverse effects of treatment

Adverse effect	CRT-D ($n = 16$)	ICD ($n = 15$)	*p*-value
	NR	NR	

NR, reported.

Comment

- Authors state that there were no major complications following implantation.

Comments

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*: authors state that there were no significant differences in age, body mass index, sex distribution or blood pressure between the two CHF groups and the control group (no *p*-values reported; *p*-values were reported for the CHF groups vs. the control group but were not data extracted).
- *Method of data analysis*: linear data expressed as mean ± SD. Non-linear data expressed as median (IQR). ITT analysis not reported. Baseline ICD and CRT-D group data before implantation compared with control group data. The data for the ICD and CRT-D groups were then compared at baseline and at 1 year. One-way analysis of variance was used to compare the general characteristics and other linear data between the study groups. The Kruskal–Wallis test and Mann–Whitney *U* test were used for non-normally distributed data. The Wilcoxon test was used for variables with a non-linear distribution. Event-free survival functions were estimated using the Kaplan–Meier method and differences between the curves were tested for significance using the log-rank statistic; RRs were computed using a Cox proportional hazards regression model. As spectral analysis outcomes were not extracted (because not specified for review), the methods for the analysis of these outcomes were also not extracted.
- *Sample size/power calculation*: none reported.
- *Attrition/dropout*: 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.
- *Intercentre variability*: not applicable, one centre only.
- *Conflict of interests*: not reported.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	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	No blinding reported
Detection bias		
Blinding of outcome assessment	High	Assessment of spectral recordings blinded (outcomes not extracted), but no other blinding reported
Attrition bias		
Incomplete outcome data addressed	Low	No ITT analysis reported, but all data appear to have been reported and authors state that all patients completed the study

Domain	Judgement[a]	Support for judgement
Reporting bias		
Selective reporting	Low	No protocol available, but all stated outcomes were reported
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Pinter and colleagues study

Reference and design	Intervention and comparator	Participants	Outcome measures
Pinter *et al.* 2009[139] *Study design*: RCT *Country*: Canada *No. of centres:* 7 *Funding*: Guidant Inc., Minneapolis, MN	*All patients*: CONTAK CD CHF device, model 1823, or CONTAK RENEWAL heat failure device, model H135 (Guidant Corporation). Standard atrial pacing lead, ventricular defibrillator lead and Easytrak left ventricular pacing lead (Guidant Corporation) *Intervention*: CRT-D (CRT on). Pacing programmed to dual-chamber tracking pacing mode (DDD) with lower rate limit at 40 bpm and maximum tracking rate 20 bpm less than the tachycardia detect rate. Atrioventricular delay determined by a proprietary algorithm. Right ventricular and left ventricular pacing were simultaneous *Comparator*: ICD (CRT off). Dual-chamber non-tracking pacing mode (DDI) with 40 bpm back-up biventricular pacing *Other interventions used*: not reported but inclusion criteria state ≥ 2 weeks of treatment with maximal tolerated doses of ACE inhibitors or beta-blockers unless adverse effects or contraindicated	*Indication for treatment*: Mild to moderate HF at high risk of sudden death and eligible for an ICD but not a candidate for CRT based on guidelines at the time of the study *No. of randomised participants:* 72; CRT-D: 36, ICD: 36 *Inclusion criteria*: HF: unequivocal symptoms of dyspnoea or fatigue on climbing two or fewer flights of stairs or a 6-minute walk distance ≤ 450 m; LVEF ≤ 35% within 6 months of implant; QRS interval > 120 milliseconds; ≥ 2 weeks of treatment with maximal tolerated doses of ACE inhibitors or beta-blockers unless adverse effects or contraindicated; age 18–80 years *Exclusion criteria*: pacing for symptomatic bradycardia; not in sinus rhythm; MI or unstable angina within 6 weeks; CABG surgery within 4 weeks; Canadian Cardiovascular Society class 3 or worse angina; typical RBBB morphology in lead V1; pregnant	*Primary outcome*: LVESV change from baseline to 6 months *Secondary outcomes*: change in QoL, stroke volume, cardiac volume, mitral jet area, cardiac output, LVEF, serum B-type natriuretic peptide, average heart rate, SDANN. Also reports 6-minute walk distance, death and hospitalisations *Method of assessing outcomes*: at baseline and 6 months. LVESV measured by quantitative resting radionuclide angiogram (multigated acquisition scan), 6-minute walk test, 24-hour Holter monitoring for heart rate and SDANN. QoL measured with the MLWHFQ, SF-36, DASI and one-item Global Visual Analogue Scale *Length of follow-up*: 6 months *Recruitment*: not reported

bpm, beats per minute; LVESV, left ventricular end-systolic volume; RBBB, right bundle branch block; SDANN, standard deviation of adjacent sinus beat intervals.

Participant characteristics

Characteristic	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
Sex, % male	77.8	80.6	NS
Ethnicity	NR	NR	
NYHA classification	NR	NR	
Left ventricular measurements by multigated acquisition scan, mean (SD)			
LVESV (ml)	242 (96)	251 (147)	NS
LVEDV (ml)	314 (108)	335 (156)	NS
LVEF (%)	24.2 (7.5)	26.8 (8.4)	NS
Left ventricular measurements by ECG, mean (SD)			
LVESV (ml)	217 (72)	213 (101)	NS
LVEDV (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
Blood pressure (mmHg), mean (SD)			
Systolic	113 (19.6)	114.1 (20.8)	NS
Diastolic	65.7 (10.0)	65.2 (10.7)	NS
Current pharmacological therapy	NR	NR	
Cardiac history, %			
Coronary artery disease	77.8	80.6	NS
Previous MI	66.7	75.0	NS
CABG 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	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-minute walk distance (m), mean (SD)	314 (114)	338 (110)	NS
DASI, mean (SD)	11.3 (9.8)	12.4 (9.3)	NS
Global Visual Analogue Scale, mean (SD)	6.4 (2.0)	6.5 (1.9)	NS

Characteristic	CRT on (CRT-D) ($n = 36$)	CRT off (ICD) ($n = 36$)	p-value
MLWHFQ, mean (SD)			
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, mean (SD)			
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, mean (SD)			
PCS	39.5 (5.7)	39.1 (5.7)	NS
MCS	43.7 (11.6)	46.0 (13.7)	NS

bpm, beats per minute; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NR, not reported; NS, not significant.

Results

Outcome[a]	CRT on (CRT-D) ($n = 36$)	CRT off (ICD) ($n = 36$)	p-value
Deaths in 6 months' follow-up from cardiac causes, *n/N*	1/36	1/36	
Left ventricular measurements by multigated acquisition scan, change from baseline to 6 months[b]			
LVESV (ml) (primary outcome)	–7 (52)	–30 (47)	NS
LVEDV (ml)	–7 (61)	–34 (65)	NS
LVEF (%)	1.7 (5.4)	0.6 (6.8)	NS
Left ventricular measurements by ECG, change from baseline to 6 months[b]			
LVESV (ml)	–21 (45)	–5 (22)	NS
LVEDV (ml)	–16 (44)	–13 (47)	NS
LVEF (%)	3.9 (8.9)	1.9 (6.8)	NS
Cardiac output measured by multigated acquisition scan (l/minute)[b]			
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 (%)[c]	30.6	36.1	
Jugular venous pressure (cm) above the sternal angle[b]			
Baseline	2.1 (2.3)	2.1 (2.1)	NS
6 months	2.9 (2.27)	4.3 (2.5)	NR
B-type natriuretic peptide level (ng/l)[b]			
Baseline	198.7 (167.2)	200.9 (208.7)	
6 months	119.4 (131.7)	107.6 (99.4)	NS
SDANN (milliseconds)			
Baseline	83.2 (31.1)	93.7 (29.4)	NS
6 months	83.0 (30.6)	109.8 (41.5)	NR
Interventricular dyssynchrony (milliseconds)			
Baseline	40 (48)	47 (36)	
6 months	13 (40)	48 (34)	
Horizontal extent of the mitral regurgitation jet area (cm^2)[b]			
Baseline	4.79 (3.06)	3.58 (3.66)	
6 months	3.90 (3.65)	3.00 (2.74)	
QRS duration (milliseconds)[b]			
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* (%)	7 (19.4)	6 (16.7)	NS
No. of treated VT episodes per patient	5.9 (6.1)	3.4 (2.7)	NS

Outcome[a]	CRT on (CRT-D) ($n = 36$)	CRT off (ICD) ($n = 36$)	p-value
Assessment of functional status, change from baseline to 6 months[b]			
6-minute walk distance (m)	53.3 (113.3)	27.3 (71.1)	NS
DASI	4.63 (9.20)	1.08 (7.02)	NS
Global Visual Analogue Scale	–0.07 (2.22)	–0.17 (1.64)	NS
MLWHFQ			
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[b]			
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
PCS	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
MCS	5.1 (10.1)	0.5 (12.4)	NS

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NR, not reported; NS, not significant; SDANN, standard deviation of adjacent sinus beat intervals.

a It is assumed that values are mean (SD) as this is not specified in paper.

b Within-group p-values are reported but not data extracted.

c Authors state that 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 last two outcomes not reported).

Comments

- Authors state that systolic and diastolic blood pressure and heart rate were similar at baseline in the two groups and did not change significantly in either group at 6 months (data not presented).
- Authors state that there was no difference in the number of patients receiving a shock from the device or in the number of shocks per patient (data not presented).

Adverse effects of treatment

Adverse effect	CRT on (CRT-D) ($n = 36$)	CRT off (ICD) ($n = 36$)	p-value
Not reported			

Comments

Methodological comments

- *Allocation to treatment groups*: all patients received a device. Left ventricular pacing was turned off in the immediate postoperative period. Patients were randomly assigned following completion of baseline procedures 14–28 days post implant.
- *Blinding*: patients were 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 end point analysed according to ITT principle. Data were analysed using the 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 was analysed using the 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 rate, it was estimated that 70 patients had to be included to show a clinically meaningful 12% decrease in end-systolic volume with 80% power and a two-tailed alpha of 0.05.
- *Attrition/dropout*: in total, 75/90 (83.3%) attempted implants were successful. Of these, two were not randomised because of device-related technical difficulties (double sensing) and one was not randomised because of worsening HF. Of the 72 randomised, five missed the 6-month visit (one from each group died from cardiac causes; two crossed over, one from the CRT off group to the CRT on group because of worsening CHF and one from the CRT on group to the CRT off group because of late left ventricular capture failure; and one in the CRT on group was too ill). Therefore, 67/72 (93%) completed the study (CRT on: 33; CRT-off: 34).

General comments

- *Generalisability*: only those with successful implantation were randomised. This is a study of prophylactic CRT for patients with mild to moderate HF; patients did not meet guidelines for CRT at the time of the study but may meet indications for CRT by current standards.
- *Outcome measures*: radionuclide angiography was selected for the measurement of the primary end point because of the assumption that it is more accurate than ECG in measuring left ventricular outcomes. NYHA class and adverse events were not reported.
- *Intercentre variability*: not reported.
- *Conflict of interests*: two authors have received honoraria and research funding from Guidant Corporation. The study was supported by an unrestricted educational grant from Guidant Corporation.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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	Low	States that patients were blinded, although not clear how this was maintained
Detection bias		
Blinding of outcome assessment	Low	States that all post-implant study evaluations were performed by personnel blinded to treatment allocation
Attrition bias		
Incomplete outcome data addressed	Low	Attrition and crossovers reported. ITT analysis performed
Reporting bias		
Selective reporting	Low	No protocol available but outcomes listed in the methods were reported on
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT)

Reference and design	Intervention and comparator	Participants	Outcome measures
Tang *et al.* 2009[141] and 2010[140] *Study design*: RCT *Countries*: Canada, Europe, Turkey and Australia *No. of centres:* 34 (Canada 24, Europe and Turkey 8, Australia 2) *Funding*: Canadian Institutes of Health Research. Medtronic of Canada (industry partner) provided funding and CRT components	*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: a beta-blocker, an ACE inhibitor or ARB, spironolactone, aspirin and statins when appropriate; uniform arrhythmia detection and therapy	*Indication for treatment*: initially mild to moderate (NYHA class II or III) HF despite OPT, later restricted to NYHA class II HF with LVSD and a wide QRS complex *No. of randomised participants:* 1798; ICD-CRT: 894, ICD: 904 *Inclusion criteria*: NYHA class II or III (revised in February 2006 to class II only) symptoms despite receiving OPT, LVEF $\leq$ 30% from ischaemic or non-ischaemic causes, QRS interval $\geq$ 120 milliseconds or a paced QRS duration of $\geq$ 200 milliseconds, sinus rhythm or permanent atrial fibrillation or flutter with a controlled ventricular rate ($\leq$ 60 bpm at rest and $\geq$ 90 bpm during a 6-minute walk test) or planned atrioventricular junction ablation after device implantation and planned ICD implantation for indicated primary or secondary prevention of SCD. Optimal HF pharmacological therapy[141] *Exclusion criteria*: major coexisting illness; recent cardiovascular event protocol;[141] life expectancy of < 1 year from non-cardiac cause; expected cardiac transplantation within 1 year (status 1); received intravenous inotropic agent in the last 4 days; acute coronary syndrome including MI can be included if the patient has had a previous MI with left ventricular dysfunction (LVEF $\leq$ 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	*Primary outcome*: composite outcome of death from any cause or HF leading to hospitalisation *Secondary outcomes*: death from any cause at any time during the study, death from any cardiovascular cause, and hospitalisation for HF among all patients (those with NYHA class II and class III HF at baseline) *Method of assessing outcomes*: hospitalisation for HF was defined as admission to a health-care facility lasting > 24 hours with symptoms of CHF and subsequent treatment for HF (admissions for other medical problems that then developed into HF in the hospital were not classified as hospitalisation for HF). An adjudication committee reviewed available documents and determined the cause of death and whether or not hospitalisations that lasted > 24 hours were due to the exacerbation of HF. All adverse events occurring within 30 days after ICD implantation were adjudicated as related to or unrelated to the ICD Follow-up visits 1 month after device implantation and then 6-monthly until $\geq$ 18 months until the end of the trial, with clinical assessment and device interrogation at each visit *Length of follow-up*: minimum of 18 months. Mean 40 (SD 20) months; mean follow-up for surviving patients 44 (SD 18) months *Recruitment*: January 2003–February 2009

Reference and design	Intervention and comparator	Participants	Outcome measures
		reversible form of cardiomyopathy; severe primary pulmonary disease such as cor pulmonale; tricuspid prosthetic valve; patients with an existing ICD (patients with an existing pacemaker can be included if they satisfy all other inclusion/exclusion criteria); coronary revascularisation (CABG or percutaneous coronary intervention) < 1 month if previous LVEF $> 30\%$ (more recent revascularisations can be included if previous LVEF $\leq 30\%$); included in other clinical trial that will affect the objectives of this study; history of non-compliance with medical therapy; unable or unwilling to provide informed consent	

Participant characteristics

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
Sex, male, *n* (%)	758 (84.8)	732 (81.0)	NR
Ethnicity	NR	NR	
NYHA class, *n* (%)			
II	708 (79.2)	730 (80.8)	NR
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 (ms)			
Intrinsic			
No. of patients	826	837	
Mean (SD)	157 (23.6)	158.3 (24.0)	NR
Paced			
No. of patients	68	67	
Mean (SD)	206.5 (24.0)	210.3 (18.3)	NR
QRS morphological type, *n* (%)			
RBBB	68 (7.6)	93 (10.3)	NR
LBBB	652 (72.9)	643 (71.1)	NR
Non-specific 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* (%)			
Ischaemic	614 (68.7)	587 (64.9)	NR
Non-ischaemic	280 (31.3)	317 (35.1)	NR
Hospitalisation for HF in last 6 months, *n* (%)	238 (26.6)	223 (24.7)	NR
Previous treatment, *n* (%)			
Percutaneous coronary intervention	220 (24.6)	208 (23.0)	NR
CABG surgery	293 (32.8)	313 (34.6)	NR
Comorbidities, *n* (%)			
Diabetes mellitus	293 (32.8)	313 (34.6)	NR
Hypertension	402 (45.0)	397 (43.9)	NR
Current cigarette smoking, *n* (%)	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

Characteristics	ICD–CRT ($n = 894$)	ICD ($n = 904$)	p-value
Spironolactone	372 (41.6)	378 (41.8)	NR
Digoxin	301 (33.7)	319 (35.3)	NR
Acetylsalicylic acid (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 AAD	12 (1.3)	8 (0.9)	NR
6-minute walk test			
No. of patients	789	765	
Distance (m), mean (SD)	351.3 (106.7)	354.9 (110.1)	NR
Estimated glomerular filtration rate			
No. of patients	885	897	
%, mean (SD)	59.5 (19.8)	60.8 (21.9)	NR
Rate (ml/minute/1.73 m^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

NR, not reported; RBBB, right bundle branch block.

Comment

- Enrolment breakdown: Canada $n = 1617$, Europe and Turkey $n = 137$, Australia $n = 44$.

Results

Outcome	ICD-CRT ($n = 894$)	ICD ($n = 904$)	HR (95% CI), p-value
All patients			
Primary outcome: death or hospitalisation for HF, *n/N* (%)	297/894 (33.2)	364/904 (40.3)	0.75 (0.64 to 0.87), < 0.001
Secondary outcomes			
Death from any cause, *n/N* (%)	186/894 (20.8)	236/904 (26.1)	0.75 (0.62 to 0.91), 0.003
Death from cardiovascular cause, *n/N* (%)	130/894 (14.5)	162/904 (17.9)	0.76 (0.60 to 0.96), 0.02
Hospitalisation for HF, *n/N* (%)	174/894 (19.5)	236/904 (26.1)	0.68 (0.56 to 0.83), < 0.001
Hospitalisation more than once during follow-up (mostly cardiovascular), *n*	509	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
	ICD-CRT ($n = 708$)	**ICD ($n = 730$)**	
Patients in NYHA class II			
Primary outcome: death or hospitalisation for HF, *n/N* (%)	193/708 (27.3)	253/730 (21.1)	0.73 (0.61 to 0.88), 0.001
Secondary outcomes, *n/N* (%)			
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 HF	115/708 (16.2)	159/730 (21.8)	0.70 (0.55 to 0.89), 0.003
	ICD-CRT ($n = 186$)	**ICD ($n = 174$)**	
Patients in NYHA class III			
Primary outcome: death or hospitalisation for HF, *n/N* (%)	104/186 (55.9)	111/174 (63.8)	0.76 (0.58 to 0.99), 0.04
Secondary outcomes, *n/N* (%)			
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 HF	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 to prevent one death.
- Kaplan–Meier curves were reported for the composite primary outcome and death from any cause for all patients and for NYHA class II and class III subgroups (not data extracted).
- For NYHA classes II and III, the two interventions were associated with a similar reduction in the composite primary outcome ($p = 0.91$ for interaction), death from any cause and hospitalisation for HF.
- Subgroup analysis on 11 prespecified subgroups showed a significant interaction between treatment and QRS duration ($p = 0.003$). ICD-CRT was more effective in those with an intrinsic QRS duration of ≥ 150 milliseconds (HR 0.59, 95% CI 0.48 to 0.73) than in those with an intrinsic QRS duration of < 150 milliseconds (HR 0.99, 95% CI 0.77 to 1.27, $p = 0.002$ for interaction) or those with a paced QRS duration of ≥ 200 milliseconds (HR 1.07, 95% CI 0.63 to 1.84, $p = 0.03$ for interaction).
- There was a weak interaction between treatment and QRS morphological type ($p = 0.046$) such that those with LBBB appeared to have a greater benefit than those with non-specific intraventricular conduction delay ($p = 0.04$ for interaction).
- HRs for prespecified subgroups were displayed in a figure only and were not data extracted (age: < 65 vs. ≥ 65 years, $p = 0.75$; sex: male vs. female, $p = 0.09$; NYHA class: II vs. III, $p = 0.91$; underlying heart disease: ischaemic vs. non-ischaemic, $p = 0.90$; QRS duration: intrinsic QRS < 150 milliseconds vs. intrinsic QRS ≥ 150 milliseconds vs. paced QRS ≥ 200 milliseconds, $p = 0.003$; LVEF: < 20% vs. ≥ 20%, $p = 0.05$; QRS morphological features: RBBB vs. LBBB vs. non-specific intraventricular conduction delay 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 glomerular filtration rate (ml/minute/1.73 m^2): < 60 vs. ≥ 60, $p = 0.70$).
- Authors state that patients with ischaemic or non-ischaemic causes of HF had a similar benefit from ICD-CRT.

Adverse effects of treatment

Adverse effect	ICD-CRT ($n = 888$)	ICD ($n = 899$)	HR (95% CI), p-value
Death from worsening HF within 24 hours of device implantation, *n*		1	
Device-related hospitalisation, *n* (%)	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, *n*/*N*[a]	118/888	61/899	– (–), < 0.001
Adverse effects at 30 days after device implantation, *n*/*N*[a]	124/888	58/899	– (–), < 0.001
Haemothorax or pneumothorax, *n* (%)	11 (1.2)	8 (0.9)	0.47 (–), –
Device pocket haematoma requiring intervention, *n* (%)	14 (1.6)	11 (1.2)	0.53 (–), –
Device pocket infection requiring intervention, *n* (%)	21 (2.4)	16 (1.8)	0.39 (–), –
Lead dislodgement requiring intervention, *n* (%)	61 (6.9)	20 (2.2)	– (–), < 0.0001
Device pocket problems requiring revision, *n* (%)	4 (0.5)	1 (0.1)	0.22 (–), –
Coronary sinus dissection, *n* (%)	11 (1.2)	0	0.0004 (–), –
Tamponade, *n* (%)	2 (0.23)	2 (0.22)	1 (–), –

a It is unclear why the numbers of patients in these categories differ for both groups.

Comment

- A left ventricular lead was successfully implanted in 841/888 patients (94.7%) in the CRT-ICD group (during an initial attempt $n = 802$; in a subsequent attempt $n = 39$). Of these, 53 patients (6.0%) did not receive CRT (left ventricular lead failure $n = 47$; lead malfunction $n = 6$).
- A total of 12 patients underwent cardiac transplantation: ICD-CRT group $n = 7$, ICD group $n = 5$.

Comments

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 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 HF 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*: authors state that baseline clinical characteristic are similar between the two groups.
- *Method of data analysis*: all analyses were conducted according to the ITT principle. Survival analysis techniques were used to compare the two groups with respect to the primary outcome and principal secondary outcomes. Survival in each of the two groups was summarised with the use of Kaplan–Meier product limit estimates. Survival curves were compared using non-parametric log-rank tests. HRs and associated 95% CIs were calculated with the use of the Cox proportional hazards model. Primary and secondary outcomes for patients with NYHA class II or III HF were analysed separately as NYHA class III patients were enrolled only during the first part of the study, before the protocol was revised 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 compared with no AF and NYHA class II compared with class III (p. 16).[141] Chi-squared tests were used to compare the Kaplan–Meier (actuarial) rate of event-free survival at 5 years. The HR was used to calculate the number needed to treat to prevent one death or hospitalisation for HF 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 Inc., Cary, NC, USA).
- *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.[140] To detect a 20% RRR in the primary end point for CRT-ICD, given an alpha value of 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 end point or termination of the study, and allows for a 5% inability to implant the left ventricular lead (based on the most recent data indicating a 96% implant success rate in a worldwide registry) and a 3% crossover rate from the control group (ICD) to the experimental group (CRT-ICD).[141] This sample size will also be able to detect a 25% RRR in total mortality with the assumption of 11% annual mortality in the control group, given an alpha value of 0.05 (two-sided) and 80% power.[141]
- *Attrition/dropout*: ICD-CRT group: 888/894 (99.3%) received ICD-CRT; leads were successfully implanted in 841/888 (94.7%); 53/888 (60%) did not receive CRT (47 leads failed, six lead malfunctions); of those who did not undergo implantation, four died and two declined to participate (the patient or physician). ICD group: 899/904 (99.4%) received ICD; of those who did not undergo implantation, four declined to participate (patient or physician) and in one there was a lack of venous access. Crossover: ICD to ICD-CRT: 36 (4%) before the occurrence of a primary outcome and 60 (6.6%) after hospitalisation for HF. ICD-CRT group: eight withdrew, two were lost to follow-up; ICD group: four withdrew, one was lost to follow-up.
- *Other*: (1) 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 two, Australia two, New Zealand one; see protocol, p. 16).[141] However, no enrolment for the centre in New Zealand is reported. (2) Two planned interim analyses were conducted for the data and safety monitoring board (first planned with 33% enrolled and followed for 2 years; second planned with 66% enrolled and followed for 2 years[141]) and an O'Brien–Fleming alpha spending function was used to adjust the sample size for these interim analyses.

General comments

- *Generalisability*: mild to moderate HF patients with LVSD and a wide QRS complex.
- *Outcome measures*: appear appropriate.
- *Intercentre 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 randomised controlled trials[65]

Domain	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	Double blind. Patients and general health-care providers were blinded, but not device caregivers
Detection bias		
Blinding of outcome assessment	Low	Members of the adjudication committee responsible for reviewing available documents and determining cause of death were blinded
Attrition bias		
Incomplete outcome data addressed	Low	ITT analysis; CONSORT (Consolidated Standards of Reporting Trials) flow chart (including numbers analysed) provided in an appendix
Reporting bias		
Selective reporting	High	The protocol[141] described 'other outcomes' (e.g. QoL), but no data for these were reported. However, this is a recent study and it is possible that further data will be published in the future
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
Beshai *et al.* 2007,[142] Beshai and Grimm 2007[143] *Study design*: RCT *Country*: USA *No. of centres:* 34 *Funding*: St Jude 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 treatment of tachyarrhythmias turned on[143] *Comparator*: ICD + OPT (device as above). Detection and treatment of tachyarrhythmias turned on[143] *Other interventions used*: OPT for both groups defined as a beta-blocker for a minimum of 90 days and an ACE inhibitor or ARB for a minimum of 30 days, unless contraindicated or not tolerated (for stable medical regimen no more than a 100% increase or a 50% decrease in dose). 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[143]	*Indication for treatment*: standard indication for an ICD (ischaemic or non-ischaemic cardiomyopathy and LVEF $\leq$ 35%), a narrow QRS interval and intraventricular mechanical dyssynchrony *No. of randomised participants:* 172; CRT-D on: 87, CRT-D off: 85 *Inclusion criteria*: NYHA class III caused by either ischaemic or non-ischaemic cardiomyopathy, LVEF $\leq$ 35%, QRS interval < 130 milliseconds, approved indication for an ICD, stable conventional medical regimen, evidence of mechanical dyssynchrony on ECG, able to complete exercise stress testing and a 6-minute walk test (limited only by cardiac fitness)[143] *Exclusion criteria*: standard indication for cardiac pacing or previous treatment with CRT, standard bradycardic indication for pacing, continuous atrial fibrillation (lasting > 1 month) < 1 year before enrolment, cardioversion for atrial fibrillation in the past month, ability to walk > 450 m during the 6-minute walk test, NYHA class I, II or IV, symptomatic COPD, classification of status 1 for cardiac transplantation or consideration for transplantation in the next 6 months, recent MI, unstable angina, cardiac revascularisation (PTCA or CABG) within 40 days of enrolment, recent stroke or transient ischaemic attack within 3 months of enrolment, severe musculoskeletal disorder/s, pregnant or a planned pregnancy in the next 6 months, life expectancy of $\leq$ 6 months, age < 18 years[143]	*Primary outcomes*: proportion of patients with an increase of $\geq$ 1.0 ml/kg body weight/minute in peak oxygen consumption during cardiopulmonary exercise testing[142] and survival from CRT-D system-related complications[143] *Secondary outcomes*: QoL and NYHA class *Method of assessing outcomes*: baseline evaluation 14 days after successful implantation, including cardiopulmonary exercise testing (maximum exercise tolerance on treadmill/bicycle ergonometry measuring heart rate, minute ventilation, oxygen uptake and carbon dioxide output), NYHA class assessment, 6-minute walk distance, QoL evaluation (MLWHFQ, score from 0 to 105, higher score indicates poorer QoL), assessment of medication stability, ECG for optimisation of atrioventricular and interventricular delay and 12-lead ECG. Evaluation repeated at 6 months Mechanical dyssynchrony definition: an opposing wall delay of $\geq$ 65 milliseconds on tissue Doppler imaging or a mechanical dyssynchrony in the septal to posterior wall of $\geq$ 130 milliseconds on M-mode ECG *Length of follow-up*: 6 months *Recruitment*: August 2005–January 2007

PTCA, percutaneous transluminal coronary angiography

Participant characteristics

Characteristic	CRT-D on + OPT ($n = 87$)	ICD + OPT ($n = 85$)	p-value
Age (years), mean (SD)	60 (12)	58 (14)	
Sex, male, *n* (%)	62 (71)	49 (58)	
Ethnicity	NR	NR	
NYHA class III, *n* (%)	87 (100)	84 (99)	
LVEF (%), mean (SD)	25 (5)	26 (6)	
End-diastolic diameter (mm), mean (SD)	66 (9) ($n = 85$)	65 (9) ($n = 84$)	
End-systolic diameter (mm), mean (SD)	56 (9) ($n = 85$)	53 (9) ($n = 84$)	
End-diastolic volume (ml), mean (SD)	216 (78)	210 (75)	
End-systolic volume (ml), mean (SD)	163 (65)	156 (64)	
QRS interval (milliseconds), mean (SD)	107 (12)	106 (13)	
< 120 ms, *n* (%)	66 (76)	60 (71)	
≥ 120 ms, *n* (%)	21 (24)	25 (29)	
Underlying heart disease, *n* (%)			
Ischaemic	47 (54)	43 (51)	
Non-ischaemic	40 (46)	42 (49)	
Indication for ICD, *n* (%)			
Primary prevention	74 (85)	73 (86)	
Secondary prevention	13 (15)	12 (14)	
Pre-ejection period (milliseconds), mean (SD)	112 (21) ($n = 86$)	112 (22) ($n = 86$)	
Interventricular mechanical delay (milliseconds), mean (SD)	9 (28) ($n = 85$)	8 (31) ($n = 82$)	
Intraventricular mechanical dyssynchrony (milliseconds), mean (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 inhibitor or substitute[b]	77 (89)	77 (91)	
Beta-blocker	84 (97)	79 (93)	
Diuretic	73 (84)	74 (87)	
AAD	7 (8)	10 (12)	

Characteristic	CRT-D on + OPT ($n = 87$)	ICD + OPT ($n = 85$)	p-value
Peak oxygen consumption (ml/kg/minute), mean (SD)	12.1 (3.3)	12.4 (4.5)	
Exercise duration (minute), mean (SD)	8.9 (3.0)	9.0 (3.8)	
QoL (MLWHFQ) score, mean (SD)	54 (24)	57 (26)	
6-minute walk distance (m), mean (SD)	301 (94)	297 (100)	

NR, not reported.

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 ECG.

b Includes ARBs and hydralazine.

Comments

- Authors state that none of the differences between the groups was significant, but no *p*-values are reported.
- In total, 97% of the left ventricular leads were implanted in a lateral position.

Results

Outcome	CRT-D on + OPT (*n* = 87)	ICD + OPT (*n* = 85)	*p*-value
Mortality before 6 months, *n*/*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*/*N* (%)		1/85 (1.2)[a]	
Cumulative overall survival at 6 months, % (95% CI)	94.2 (86.7 to 97.6)	98.8 (91.9 to 99.8)	0.11
Cumulative freedom from death caused by worsening HF, % (95% CI)	97.7 (91.1 to 99.4)	98.9 (91.9 to 99.8)	0.58
Change in peak VO_2	(*n* = 76)	(*n* = 80)	0.63
Median change (ml/kg/minute) (95% CI)	0.4 (–0.6 to 1.2)	0.5 (–0.3 to 1.1)	
Primary outcome: increase of ≥ 1.0 ml/kg/minute, *n*/*N* (%)	35/76 (46)	33/80 (41)	
Change in QoL (MLWHFQ) score	(*n* = 76)	(*n* = 80)	
Median change (95% CI)	–8 (–10 to –1)	–7 (–11 to 3)	0.91
Change in NYHA class, *n*/*N* (%)	(*n* = 76)	(*n* = 80)	0.006
Improved by one or more class	41/76 (54)	23/80 (29)	
No change	31/76 (41)	51/80 (64)	
Worsened	4/76 (5)	6/80 (8)	
Change in 6-minute walk distance (m)	(*n* = 75)	(*n* = 79)	
Median change (95% CI)	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 (ml)	(*n* = 68)	(*n* = 74)	
Median change (95% CI)	–16 (–29 to –8)	–11 (–30 to –2)	0.71
Change in end-systolic volume (ml)	(*n* = 68)	(*n* = 74)	
Median change (95% CI)	–19 (–34 to –12)	–18 (–28 to –8)	0.81
Change in end-diastolic diameter (mm)	(*n* = 72)	(*n* = 77)	
Median change (95% CI)	0 (–2 to 0)	–1 (–2 to 1)	0.49
Change in end-systolic diameter (mm)	(*n* = 72)	(*n* = 77)	
Median change (95% CI)	–1 (–3 to 0)	0 (–2 to 2)	0.34
Change in degree of mitral regurgitation, *n*/*N* (%)	(*n* = 76)	(*n* = 80)	> 0.99
Improved by one or more grade	8/76 (11)	9/80 (12)	
No change	60/76 (81)	61/80 (80)	
Worsened by one or more grade	6/76 (8)	6/80 (8)	

a Not included in survival analysis (included in efficacy analysis).

Adverse effects of treatment

Adverse effect	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, *n/N* (%)	13/172 (7.6)		
Left ventricular lead, *n/N* (%)	5/172 (2.9)		
Infection, *n/N* (%)	6/172 (3.5)		
Bleeding or haematoma, *n/N* (%)	2/172 (1.2)		
Loss of pacemaker lead capture, *n/N* (%)	2/172 (1.2)		
Phrenic nerve stimulation, *n/N* (%)	3/172 (1.7)		
Deep venous thrombosis, *n/N* (%)	3/172 (1.7)		
Pneumothorax, *n/N* (%)	2/172 (1.2)		
Pericarditis, *n/N* (%)	2/172 (1.2)		
Coronary sinus perforation, *n/N* (%)	1/172 (0.6)		

Comment
The authors state that the numbers of adverse events did not differ significantly between the two study groups but no *p*-values are reported.

Subgroup analysis

Subgroup analysis according to QRS interval at 6 months[a]

Subgroup	CRT-D on + OPT (QRS ≥ 120 milliseconds, $n = 17$; QRS < 120 milliseconds, $n = 59$)	ICD + OPT (QRS ≥ 120 milliseconds, $n = 25$; QRS < 120 milliseconds, $n = 55$)	p-value
Peak VO_2, proportion of patients with an increase of at least 1 ml/kg body weight/minute from baseline			
QRS ≥ 120 milliseconds	58.9	19.7	0.02
QRS < 120 milliseconds	42.2	51.2	0.45
NYHA class, proportion of patients whose condition improved by at least one class from baseline			
QRS ≥ 120 milliseconds	70.7	28.0	0.01
QRS < 120 milliseconds	49.4	29.3	0.04
QoL, median change from baseline (%)			
QRS ≥ 120 milliseconds	0	–3.7	0.24
QRS < 120 milliseconds	–8.9	–7.0	0.63
6-minute walk distance, median change from baseline (m)			
QRS ≥ 120 milliseconds	0.0	–19.1	0.76
QRS < 120 milliseconds	33.7	10.3	0.31

a All values were estimated by the reviewer using Engauge software. The *p*-values were extracted from the paper.

Subgroup analysis according to cardiomyopathy classification at 6 months[a]

Subgroup	CRT-D on + OPT (ischaemic, $n = 40$; non-ischaemic, $n = 36$)	ICD + OPT (ischaemic, $n = 41$; non-ischaemic, $n = 39$)	p-value
Peak VO_2, proportion of patients with an increase of at least 1 ml/kg body weight/minute from baseline			
Ischaemic	40.0	44.2	0.82
Non-ischaemic	52.6	38.4	0.25
NYHA class, proportion of patients whose condition improved by at least one class from baseline			
Ischaemic	55.3	29.5	0.02
Non-ischaemic	53.2	28.4	0.04
QoL, median change from baseline (%)			
Ischaemic	–5.9	–3.6	0.68
Non-ischaemic	–10.6	–6.5	0.60
6-minute walk distance, median change from baseline (m)			
Ischaemic	4.2	5.8	0.57
Non-ischaemic	55.0	2.5	0.01

a All values were estimated by the reviewer using Engauge software. The p-values were extracted from the paper.

Comments

Methodological comments

- *Allocation to treatment groups*: random assignment in a 1 : 1 ratio according to centre and stratified according to cardiomyopathy classification and QRS interval (< 120 milliseconds and ≥ 120 milliseconds) within each centre. Randomisation assignments were 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*: study paper reports that trial was 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*: authors state that none of the differences between the groups was significant but no *p*-values were reported.
- *Method of data analysis*: all end points were analysed according to the ITT principle. 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) group and the CRT-D on group 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 two 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 because of worsening HF. The last group of patients were included in the analysis with their worst values imputed as follows: 0 ml/kg/minute for peak VO_2, a score of 105 on the QoL scale, NYHA class IV and 0 m for the 6-minute walk distance.
- *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 compared with the CRT-D off group (control). The proportion who 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 of 250 participants.
- *Attrition/dropout*: total recruitment: 250, total randomised: 172 (four unsuccessful implantation, two deaths, three withdrawals, 69 did not meet inclusion criteria). CRT-D on: three died from other causes than HF, three withdrew for reasons other than worsening HF, three had < 6 months' follow-up and two had no exercise test at follow-up; 76 participants were included in efficacy analyses, two died from HF. CRT-D off: four had < 6 months' follow-up, one had no exercise test at 6 months; 80 participants were included in efficacy analyses, two died from HF and two did not have an exercise test because of worsening HF. Crossovers: three participants crossed from CRT-D off to CRT-D on because of worsening HF (included in the control group analysis); there were no crossovers from CRT-D on to CRT-D off.

General comments

- *Generalisability*: limited to participants with successful implantation, a QRS interval < 130 milliseconds, NYHA class III symptoms and evidence of mechanical dyssynchrony [authors state that only 4% of patients were eligible to participate in the study solely on the basis of mechanical dyssynchrony in the septal to posterior wall of ≥ 130 milliseconds on M-mode ECG; 96% qualified on the basis of the tissue Doppler imaging criterion (i.e. an opposing wall delay of ≥ 65 milliseconds)].
- *Outcome measures*: appear to be appropriate. The primary outcome measure was the proportion of patients with an increase of 1.0 ml/kg body weight/minute in peak oxygen consumption during cardiopulmonary exercise testing. The study was not powered for mortality.
- *Intercentre variability*: not reported.
- *Conflict of interests*: Drs Beshai, Grimm, Nagueh, Greenberg and Pires received lecture/consulting fees, support and/or grants from St Jude Medical, Medtronic, GE and/or Boston Scientific. The authors state that there was no other potential conflict of interest relevant to the publication and that investigators had full access to all data and performed analyses without restrictions or limitations from the sponsor.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	Judgement[a]	Support for judgement
Selection bias		
Random sequence generation	Low	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	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	Paper states that study was double blind but unclear who was blinded. Randomisation assignments were provided to site personnel, unclear if these personnel continued to be involved in the care of participants
Detection bias		
Blinding of outcome assessment	Low	Site personnel conducting evaluations at 6 months were unaware of treatment assignments, 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-minute walk distance, mortality before 6 months	Low	Paper states that all end points were analysed according to the 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 because of worsening HF. However, analysis was performed with 66 CRT-D on + OPT group participants and 80 ICD + OPT group participants, because of some participants not having completed a cardiopulmonary exercise test for reasons other than worsening HF. Numbers and reasons given
Other end points	High	Missing data; reasons not given
Reporting bias		
Selective reporting	Low	All protocol outcomes reported
Other bias		
Other sources of bias	Low	

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Resynchronization for the HemodYnamic Treatment for Heart failure Management Implantable Cardioverter Defibrillator (RHYTHM ICD) trial

Reference and design	Intervention and comparator	Participants	Outcome measures
US Food and Drug Administration 2004[144] and 2005[145] *Study design*: RCT *Country*: not stated *No. of centres:* 50 *Funding*: not stated but presumed to be the device manufacturer, St Jude Medical	*Intervention*: CRT-D (device: St Jude Medical Epic HF model V-338, maximum output 30 J, with Aescula left ventricular leads) *Comparator*: ICD *Other interventions used*: not stated	*Indication for treatment*: patients indicated for ICD therapy with NYHA class III/IV HF and a prolonged QRS duration *No. of randomised participants:* 205 enrolled, 182 successful implants, 179 baseline visit; CRT-D: 119, ICD: 60 *Inclusion criteria*: LVEF ≤ 35%, QRS interval ≥ 150 ms, ICD indication for treatment of life-threatening VT, symptomatic HF for ≥ 6 months, NYHA class III or IV despite ≥ 90 days of appropriate pharmacological therapy, receiving OPT for CHF (including ACE inhibitor and beta-blocker as tolerated), stable for 30 days before enrolment, ability to complete a cardiopulmonary exercise stress test and 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 atrial fibrillation lasting > I month) within 1 year or cardioversion for atrial fibrillation in the past month, able to walk > 450 m in the 6-minute walk test, NYHA class I or II, contraindication for an emergency thoracotomy, candidate for cardiac transplantation in the next 6 months, recent (within 1 month) MI, unstable angina or cardiac revascularisation, stroke or transient ischaemic attack in the last 3 months, severe musculoskeletal disorder(s), pregnancy, participation in other clinical investigations, life expectancy < 6 months	*Primary outcomes*: left ventricular lead-related complications at 6 months, Epic HF system-related complications at 6 months, defibrillation system effectiveness: VF detection/redetection times, CRT efficacy (peak VO_2) *Secondary outcomes*: improvement at 6 months in NYHA class, QoL (MLWHFQ) score and 6-minute walk test; Aescula left ventricular lead performance and lead pacing capture threshold *Method of assessing outcomes*: baseline visit approximately 2 weeks after implant. Follow-up at 1, 3 and 6 months. After 6 months crossover to CRT-D permitted and 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 pulse generator) *Length of follow-up*: average 12.1 months (SD 3.4 months), range 0.3–20.3 patient-months. Outcomes reported at 6 months *Recruitment*: July 2002–October 2003

Participant characteristics

Participant characteristics	CRT-D ($n = 119$)	ICD ($n = 59$)	p-value
Age (years), mean (SD)	NR	NR	
Sex	NR	NR	
Ethnicity	NR	NR	
NYHA class, *n* (%)			0.61
I	1 (0.8)	2 (3.4)	
II	6 (5.0)	4 (6.8)	
III	104 (87.4)	50 (84.7)	
IV	8 (6.7)	3 (5.1)	
LVEF (%), mean (SD), range	25.6 (8.3), 9–48	23.3 (6.4), 11–43	0.07
Heart rate	NR	NR	
QRS duration (milliseconds), mean (SD), range	169 (16), 120–210	167 (15), 130–200	0.40
Left ventricular end-diastolic dimension (mm), mean (SD), range	66.2 (8.5), 44.7–85.9	66.0 (9.4), 50.1–84.2	0.88
Left ventricular end-systolic dimension (mm), mean (SD), range	57.1 (9.4), 37.1–76.2	56.9 (10.5), 37.9–78.2	0.93
QoL score, mean (SD), range	48 (24), 0–103	46 (24), 4–100	0.53
6-minute walk distance (m), mean (SD), range	275 (103), 37–561	291 (89), 31–480	0.30
Cardiopulmonary exercise test			
Peak VO_2 (ml/kg/minute), mean (SD), range	10.8 (3.0), 4.3–26.9	12.3 (3.5), 6.0–23.1	0.006
Exercise time (minutes), mean (SD), range	8.0 (3.2), 0.7–16.5	8.9 (3.6), 2.3–19.8	0.08
Baseline medication, *n* (%)			
ACE inhibitors/substitutes	85 (71.4)	44 (74.6)	0.79
Beta-blockers	95 (79.8)	52 (88.1)	0.24
ARBs	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
Anticoagulants and antiplatelets	102 (85.7)	48 (81.4)	0.59
Calcium channel blockers	11 (9.2)	9 (15.3)	0.35
AADs	29 (24.4)	13 (22.0)	0.87

NR, not reported.

Results

Outcome	CRT-D ($n = 83$)	ICD ($n = 43$)	p-value
Total deaths[a] at 6-month visit, average 12.1 (SD 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,[144] average 15.1 (SD 4.1) patient-months of follow-up	4	1	
Cardiac arrhythmic	0	0	
Cardiac non-arrhythmic	1	0	
Cardiac unknown	1	0	
Non-cardiac	1	1	
Unknown	1	0	
QoL 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/minute), 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/minute), mean (SD) at 6 months	($n = 85$) 0.52 (2.5)	($n = 41$) –1.47 (4.7)	0.001
6-minute walk distance (m), 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)	($n = 82$)	($n = 40$)	
LVEDD (mm)	–4.3 (5.4)	–2.4 (6.5)	
LVESD (mm)	–4.6 (7.0)	–3.0 (6.4)	
LVEDV (ml)	–43 (69)	–37 (53)	
LVESV (ml)	–43 (58)	–36 (47)	
LVEF (%)	4.3 (9.9)	2.9 (6.2)	

Outcome	CRT-D ($n = 83$)	ICD ($n = 43$)	p-value
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 (milliseconds)	–1.5 (52)	7.3 (33)	
Intraventricular mechanical delay (milliseconds)	–14.5 (52)	–6.4 (48)	
Tei Index	–0.4 (0.8)	–0.05 (0.5)	
Contraction interval (milliseconds)	–94 (124)	–55 (103)	
Discontinuations and withdrawals (excluding withdrawals because of deaths and after unsuccessful implant), average of 15.1 (SD 4.1) patient-months of follow-up[144]			
System explant	$n = 1$,[d] day 1 after implant		
Heart transplant	$n = 1$, 75 days after implant		
At request of patient	$n = 1$, 28 days after implant; $n = 1$, 397 days after implant		
At request of patient's family	$n = 1$, 293 days after implant		

LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume.

a An additional five deaths (four cardiac non-arrhythmic and one non-cardiac) occurred in patients who did not have a successful implant or occurred before the baseline visit and randomisation. Total number of deaths is therefore 17, as detailed in *Methodological comments*, *Attrition/dropout*.

b Patients who crossed over from the ICD group to the CRT-D group were analysed according to their original treatment group.

c MR not defined; presumed to be mitral regurgitation.

d One patient was withdrawn before the baseline visit and randomisation and therefore was not assigned to either group.

Comments

- Mean detection and redetection times for induced VF episodes, Aescula left ventricular lead performance and Aescula left ventricular lead pacing capture threshold at 6 months have not been extracted because they were not analysed by treatment group.
- Authors state that the average percentage of biventricular pacing at 6 months in the CRT-D cohort ($n = 83$) was 95% (SD 6%), range 70–100%.

Adverse effects of treatment

Adverse effect	Reported for the whole study group before randomisation ($n = 205$)[a]
Total complications, *n* patients (%), *n* events; average 12.1 (SD 3.4) patient-months of follow-up[145]	21 (10.2), 29
Coronary sinus perforation/dissection	2 (1.0), 2
Diaphragmatic/phrenic nerve stimulation	3 (1.5), 3
Lead dislodgement or migration	8 (3.9), 9
Bleeding/haematoma[b]	6 (2.9), 6
Blood clot/thrombosis	1 (0.5), 1
High defibrillation/cardioversion requirements	2 (1.0), 2
Infection	1 (0.5), 1
Noise on EGM post shock (non-SJM right ventricular lead)[c]	1 (0.5), 1
Pneumothorax	2 (1.0), 2
Retained foreign body (surgical sponge)	1 (0.5), 1
Elevated pacing threshold – left ventricular lead	1 (0.5), 1

Adverse effect	Reported for the whole study group before randomisation ($n = 205$)[a]
Total observations, *n* patients (%), *n* events; average 12.1 (SD 3.4) patient-months of follow-up[145]	57 (27.8), 68
Asystolic episode during left ventricular lead placement	1 (0.5), 1
Bleeding/haematoma[b]	10 (4.9), 10
Blood clot/thrombosis	2 (1.0), 2
Coronary sinus perforation/dissection	6 (2.9), 6
Diaphragmatic/phrenic nerve stimulation – left ventricular lead	10 (4.9), 10
Diaphragmatic/phrenic nerve stimulation – right ventricular lead	2 (1.0), 2
Elevated pacing thresholds – left ventricular lead	10 (4.9), 10
Elevated pacing thresholds – right ventricular lead	2 (1.0), 2
Heart block at implant	2 (1.0), 2
High defibrillation/cardioversion requirements	1 (0.5), 1
Hypotension requiring ventilator support	1 (0.5), 1
Inappropriate therapy for SVT	10 (4.9), 13
Infection	3 (1.5), 3
pulmonary embolism	1 (0.5), 1
T-wave sensing	2 (1.0), 3
Pocket inflammation/seroma	1 (0.5), 1
Left ventricular 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 (%), *n* events; average 15.1 (SD 4.1) patient-months of follow-up (only those complications with added data detailed below)[144]	22 (10.7), 31
Lead dislodgement or migration	9 (4.4), 10
Infection	2 (1.0), 2
Total observations, *n* patients (%), *n* events; average 15.1 (SD 4.1) patient-months of follow-up (only those observations with added data detailed below)[144]	59 (28.8), 76
Diaphragmatic/phrenic nerve stimulation – left ventricular lead	14 (6.8), 14
Elevated pacing thresholds – left ventricular lead	12 (5.9), 12
Inappropriate therapy for SVT	11 (5.4), 14
Infection	4 (2.0), 4

SJM, St Jude Medical; SVT, supraventricular tachycardia.
a Some patients experienced more than one event; therefore, the number of patients is less than the number of events.
b In total, 15/16 patients with bleeding/haematoma-related events were on active anticoagulation therapy.
c Abbreviations not defined in the publication.

Comment

- A total of 97 adverse events (29 complications and 68 observations) were reported in 70 patients.

Comments

Methodological comments

- *Allocation to treatment groups*: states randomised in a ratio of 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 for peak VO_2 for the exercise test for which 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 data set because of attrition (see below).
- *Sample size/power calculation*: not reported.
- *Attrition/dropout*: in total, 17 (increasing to 22 with additional follow-up[144]) patients were withdrawn because of death (patients with unsuccessful implant, $n = 3$ deaths; death between implant and baseline visit, $n = 2$; death between baseline and 6-month visit, $n = 8$; death after 6-month visit, $n = 4$); 5/17 deaths were 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 the baseline visit and randomisation. Out of 205 enrolled patients, 23 implants were unsuccessful [unable to cannulate 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 were successfully implanted; of these, one patient withdrew before baseline, and two (as noted above) died before the baseline visit, leaving 179 patients. One further patient attended the baseline visit but refused randomisation and baseline evaluations except for device interrogation and electrical measurements. Thus, baseline evaluations for 178 patients are presented. Of the 179 patients who attended for the baseline visit a flow chart shows that 119 were assigned to CRT-D and 60 were assigned to ICD. A further 36 in the CRT-D group were not included in the analysable patient group for the effectiveness analysis (one refused the baseline CPET, two were withdrawn, two could not complete the baseline/6-month CPET for non-cardiac reasons, six died, four had an invalid baseline/6-month CPET and 21 had < 6 months' follow up) and 17 were not analysable in the ICD group (one refused the baseline CPET, two died, four had an invalid baseline/6-month CPET and 10 had < 6 months' follow-up). Consequently, the analysed data set included 83 CRT-D participants and 43 ICD participants.

General comments

- *Generalisability*: uncertain – no indication of age, sex or ethnicity of the participants. Country in which the trial took place also not reported. Patients had an indication for ICD therapy plus NYHA class III/IV HF 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 were randomised.
- *Outcome measures*: primarily this was a study of safety; effectiveness outcomes were on the whole secondary measures. Outcomes seem appropriate.
- *Intercentre 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.

CPET, cardiopulmonary exercise test; CS, coronary sinus.

Criteria for assessment of risk of bias in randomised controlled trials[65]

Domain	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	Unclear	States double blind but no detail about how this was achieved
Detection bias		
Blinding of outcome assessment	Unclear	States double blind but no detail about how this was achieved
Attrition bias		
Incomplete outcome data addressed	Low	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 or not only selected outcomes have been presented to meet the needs of the FDA approvals process
Other bias		
Other sources of bias	Unclear	Because of a lack of details, e.g. methodological and details on patient characteristics, the risks of other sources of bias are unclear

a 'Low risk', 'high risk' or 'unclear risk' of bias.

Appendix 10 Southampton Health Technology Assessments Centre's peer review of the manufacturers' submission

Comprehensiveness of ascertainment of published studies

Clinical effectiveness

The MS[151] contains a systematic review of clinical effectiveness. In addition, a NMA of IPD is presented (see table in *Southampton Health Technology Assessments Centre's critical appraisal of the individual patient data network meta-analysis*). The details and results of the studies included in the systematic review were tabulated. The risk of bias was also assessed and tabulated in appendix 3 of the MS 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,[61] and the inclusion criteria for the systematic review and NMA differ from those of the NICE scope. The statement of the decision problem defines the population of interest as 'adults with heart failure (NYHA I to IV) and LVEF $\leq$ 35%, and/or at risk of sudden cardiac death' (p. 44).[151] The population inclusion criteria for the systematic review are defined as 'adults with LVEF $\leq$ 40% or those who may not have (LVEF) $\leq$ 40% but are considered to be secondary prevention patients according to TA 95 criteria' or 'adults who have experienced prior myocardial infarction or coronary revascularisation; this must have occurred more than 45 days prior to enrolment' (p. 51).[151] 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 of the patient subgroups (for rationale see table 6, p. 45).[151] The MS states that this was either based on contraindication (e.g. CRT not being recommended for patients with a QRS duration of < 120 milliseconds) 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 27 and 28 June 2011; no update searches were reported. The MS states that timelines initially provided by NICE to all technology sponsors were followed. MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. The MS states that searches were restricted to the English language and a 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 of the MS.[151]
- *Was enough detail provided for it to be reproducible*? Yes.
- *Did the manufacturers search for/report on ongoing studies?* No.
- *Did the manufacturers 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 commercial-in-confidence/academic-in-confidence?* There are no commercial-in-confidence/academic-in-confidence data in the systematic review but the vast majority of the IPD are marked commercial-in-confidence (no academic-in-confidence data).

Cost-effectiveness

The MS did not report any additional searches for cost-effectiveness studies.

Studies identified

- *Clinical trials (details):* 22 RCTs reported in 46 publications (total records identified in the MS: 4749; total records identified by SHTAC: 4169), plus five trials (reported in 11 publications) of secondary prevention that were not data extracted.
- *Did any meet our inclusion criteria that we have not already included?* No additional trials were identified in the MS. However, there are differences in the included/excluded trials:
  - *People at risk of SCD* – the MS did not describe or report data for secondary prevention studies (listed in appendix 4 of the MS[151]) and provided justification for this (reduction in implant costs, absence of new studies since TA95;[42] in the MS it is stated that this patient group is believed to lie outside the scope of the current appraisal). SHTAC included four secondary prevention studies: AVID,[71] CASH,[81] CIDS[84] and DEBUT.[89] Of the primary prevention trials, SHTAC included three trials that were not included in the MS: DINAMIT,[95] IRIS[97] and CABG Patch.[75] The MS excluded DINAMIT and IRIS for the 'inappropriate population' and one paper linked to the CABG Patch trial was excluded for its 'end point' although other papers from this trial were not mentioned.
  - *People with HF* – SHTAC excluded three of the trials included in the MS: (1) RESPOND (Resynchronization in Patients with Heart Failure and a Normal QRS Duration;[241] participants did not have cardiac dyssynchrony), (2) REVERSE[208,242,243] (mixed population receiving the interventions CRT-P or CRT-D with the comparators OPT or ICD and results not presented separately) and (3) VECTOR (Ventricular Resynchronization Therapy Randomized Trial;[244] FDA report with insufficient information to allow the assessment of methods and results; no baseline characteristics reported).
  - The 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' (p. 54).[151] SHTAC did not exclude these patients and therefore included the DEBUT study.[89]
  - 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 the REVERSE trial including a mixed population, intervention (CRT-P or CRT-D) and comparators (OPT or ICD), the MS presents only patients randomised to CRT-D compared with ICD in tables for simplicity, and notes this on p. 55 of the MS.[151] 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, for example those with cardiomyopathy or MI. 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[64] and others.
- *Are the MS conclusions similar to those of the SHTAC review?* The MS does not explicitly report the conclusions from the systematic review in the main body of the submission. The executive summary states that 'there is a large body of RCT evidence confirming the efficacy and safety of ICD, CRT-P and CRT-D in patients with HF' (p. 4).[151] 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 the included studies were undertaken in 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 information?* A narrative overview of adverse events in the included studies and information from previous meta-analyses is presented.

Interpretation

- *Does the interpretation of the clinical data match the analyses?* The MS does not explicitly provide an interpretation of the systematic review. The interpretation of the IPD NMA is assessed below.

Questions

- *Any areas of uncertainty/discrepancy compared with the SHTAC review?*
  - Inclusion of the REVERSE trial.[208]
  - Population not defined according to the NICE scope.[1]

Southampton Health Technology Assessments Centre's critical appraisal of the individual patient data network meta-analysis

Appraisal criteria	Criteria met?
A. Conceptual basis	
1. Is a justification given for conducting a mixed treatment comparison?	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 HF. It is particularly important given the limited direct evidence for some comparisons. Also, it is helpful in identifying subgroups 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 subgroups is not addressed by most trials and is inconsistently reported in others. Provision of confidential IPD by the manufacturers 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 (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 systematic review (reported by the MS as 13 as two trials were combined). IPD were supplied by the manufacturers
3. Are inclusion/exclusion criteria adequately reported?	Yes. RCTs for which IPD could be obtained were from the systematic review. The criteria do not strictly accord with the decision problem specified in the NICE scope for the appraisal (see *Appendix 9 Comprehensiveness of ascertainment of published studies*)
4. Are the numbers of included/excluded studies from the mixed treatment comparison reported, with reasons for exclusions?	Yes. The number of trials excluded (13/22 RCTs, dated 1996–2010) and reasons for exclusion from the evidence network are reported. Justifications for exclusion include manufacturers' IPD data not available (two studies); available data sets could not be reconciled with the published data (two studies); two manufacturer-sponsored studies that the systematic review searches failed to identify until after the database for the NMA had been assembled (VECTOR: started in 2000 and details published in a 2005 US FDA report;[244] RESPOND: journal article published February 2011[241]); and two trials were not sponsored by the manufacturers contributing to the submission. In addition to these trials, SHTAC also included seven trials (DINAMIT,[95] IRIS[97] and CABG Patch[75] and four secondary prevention

Appraisal criteria	Criteria met?
	RCTs[71,81,84,89]) that were not included in the MS. Although the excluded studies account for only 5.3% of the data ($n = 712/13,350$), it is unclear what impact their exclusion has on the results. A flow chart is presented for the systematic review 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 systematic review (section 4, p. 103, of the MS[151]). An explanation is provided for the way that the different trials were handled within the network. The REVERSE trial[208] was treated as two trials [CRT-P and CRT-D, as well as split into EU and US populations because of the different protocol-specific duration of follow-up (24 months and 12 months respectively)]. The CONTAK-CD trial[126] was also treated as two trials as the crossover design was changed to a 6-month parallel-group trial halfway through (phase 2). The MIRACLE ICD trial[136] was combined with the MIRCALE ICD II trial[137] as the MS states that these were effectively a single trial. In addition, the MS pooled the data from the amiodarone and placebo arms in the SCD HeFT trial[105]
6. Are the data from included studies extracted and tabulated?	Yes. Baseline information was presented in the systematic review for the individual trials (see tables 7–11, pp. 57–72[151]). A summary table for the IPD trials with combined participant baseline characteristics per device (table 35, p. 110[151]) is presented for comparison with UK summary data (table 36, p. 111[151]). The MS suggests that differences in NYHA class between the two tables are distorted because of previous NICE decisions about the devices, differences in the format that other data are presented in and high levels of missing data in the UK National Audit. The MS suggests that, despite this, the IPD is broadly reflective of the UK population. Comparison is further complicated by QRS data being presented as means (milliseconds) in the MS table but as percentages (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 of the NMA trials were critically appraised in the systematic review. Risk of bias for all 22 studies is presented in Appendix 3 of the MS,[151] 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 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 three outcomes follows a similar two-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 subgroups of patients to be identified for whom the devices may have a differential effect

Appraisal criteria	Criteria met?
	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, when necessary, transformation undertaken (e.g. age as a time-dependent covariable). 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, 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 formed the basis for the final baseline model IPD NMA using meta-regression was undertaken with and without covariables to estimate relative treatment effects (i.e. HRs), 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[151]). The MS reports that caterpillar plots, Brooks–Gelman–Rubin statistics, autocorrelation and DIC 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[151]) 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' (excluding events within 60 days post randomisation as these were included in the economic model). Negative binomial regression was used to estimate baseline rates for OPT patients and the effects of treatment for all devices. The approach was decided through measures of goodness of fit (i.e. BIC, AIC and two times log-likelihood score) and the covariates were incorporated into the analyses through a stepwise process (included at a significance level of $p = 0.05$), although details are not reported. Limited data resulted in pooling of some categorical variables (e.g. NYHA groups). Justifications were provided for decisions and comparisons are made with previous evaluations *HRQoL* HRQoL was assessed using the 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 was estimated using a similar process to that for all-cause hospitalisation. Before analysis, raw data were transformed as they were skewed. Derived values were checked against population norms and trial values. Treatment impact was estimated through MDs from baseline to first follow-up (180 days). Limited and skewed data resulted in counterintuitive results so MLWHFQ 6-month IPD data and

Appraisal criteria	Criteria met?
	evidence from the systematic were used to adjust final values (justifications provided). Duration of effect was estimated when mean device vs. 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 account for the variation, the process for including covariables and the presentation and the discussion of the results for different subgroups. There is some limited discussion of measures 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 NMA results from IPD trials and all trials using both fixed- and random-effects models are reported and said to be broadly similar (p. 123[151]), although random-effects CIs are wider. The MS states for all-cause mortality that the DIC assessment of model fit supported the use of the fixed-effect model: all trials: fixed-effects DIC = 59.0 vs. random-effects DIC = 60.8; IPD trials: fixed-effects DIC = 1.4 vs. random-effects 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 covariables included in the baseline and treatment effect models through univariate and multivariate stepwise analyses (see appendix 9[151]). No sensitivity analyses were undertaken on the trials included or the quality of the 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 the 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 effect of disease severity on HRQoL at baseline, treatment effect on HRQoL, explorative analysis of change in MLWHFQ score at 6 months, HRQoL treatment benefit duration and addition IPD analyses (long-term MLWHFQ data from all studies and devices) – results were presented in tables, histograms and line graphs

Appraisal criteria	Criteria met?
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 limitations [i.e. dichotomisation may miss some of the heterogeneity in response to therapy in the 120–150 milliseconds QRS category (p. 128[151]); lack of power in the analysis to detect modest effect modifiers (p. 137[151])] or uncertainties [i.e. treatment effect beyond the included number of years (p. 137[151])]. The MS provides a cautionary note regarding not overinterpreting individual subgroups as anomalies may arise as a result of participant-level characteristics not accounted for (p. 130[151])
15. Does the discussion of the results reflect the data presented?	The discussion of the results for the three outcomes does reflect the results presented and a warning is provided about the limitations of the IPD available and the analyses undertaken. The discussion also places the results in the context of other evidence
16. Have the authors commented on how their results compare with other published studies (e.g. MTCs) and do they offer any explanation for discrepancies?	Partly. The MS comments on how some of the results compare with those of other reviews, meta-analyses and studies or with routinely collected data. It also undertakes additional analyses to check outcomes. In some instances the MS provides alternative values because of uncertainties in the results, providing justifications. Importantly, the MS recognises 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 evidence and the indirect evidence?	The MS reports that good concordance between pairwise meta-analysis and NMA suggests reasonable concordance between the indirect data and the direct data (p. 124[151]). Unable to establish if there were any discrepancies in the IPD data

Southampton Health Technology Assessments Centre's peer review of the economic evaluation within the manufacturers' submission

Study characteristics

Reference

Association of British Healthcare Industries. *Implantable Cardioverter Defibrillators for the Treatment of Arrhythmias and Cardiac Resynchronisation Therapy for the Treatment of Heart Failure (Review of TA95 and TA120).* ABHI; 2012.

Health technology

ICD and CRT.

Interventions and comparators

Implantable cardioverter defibrillators and CRT for the treatment of cardiac arrhythmias and HF.

Was a no treatment/supportive care strategy included?

Optimal pharmacological therapy.

Describe interventions/strategies

As above.

Research question
For adults with HF and a LVEF ≤ 35%, and/or at risk of SCD, which patients should receive an ICD, a CRT-P or a CRT-D device, based on their clinical parameters.

Study type
Cost–utility analysis.

Study population
Adults with HF (NYHA classes I–IV) and a LVEF ≤ 35%, and/or at risk of SCD.

Institutional setting
Secondary care.

Country/currency
UK pounds.

Funding source
Biotronik, Boston Scientific, Medtronic, Sorin and St Jude Medical.

Analytical perspective
National Health Service and PSS.

Effectiveness
The clinical effectiveness estimates were based on a NMA of IPD from 13 clinical trials (12,638 patients, followed up for up to 7.5 years). The clinical trials were CARE-HF,[109] COMPANION,[116] CONTAK-CD,[126] DEFINITE,[90] MADIT I,[99] MADIT II,[101] MADIT-CRT,[130] MIRACLE,[121] MIRACLE ICD,[136] RAFT,[140] RethinQ,[142] REVERSE[208] and SCD-HeFT.[105] These trials were identified through a systematic review of clinical effectiveness for all of the interventions. A further nine trials were also identified in the review but IPD were not available for these trials.

The NMA enabled trials that compared different sets of treatments to be combined within a single analysis and direct and indirect evidence to be used to inform a comparison between possible treatments.

All-cause mortality
The NMA found CRT-D to have the strongest effect on all-cause mortality with a HR of (commercial-in-confidence information has been removed). Treatment effects for the individual devices were (commercial-in-confidence information has been removed).

The parameters used in the cost-effectiveness model are shown in *Table 155*. This table shows the predicted treatment effect for each subgroup.

All-cause hospitalisation
Across all NYHA classes, device therapy was associated with a reduction in admission rates. In NYHA classes I–III, ICDs were associated with a (commercial-in-confidence information has been removed) reduction in monthly admission rates and CRT with a (commercial-in-confidence information has been removed) reduction. The effect in NYHA class IV was even more pronounced, with CRT offering a (commercial-in-confidence information has been removed) reduction in monthly admission rates.

Intervention costs
Individual patient data from the trials were used to estimate the mean number of all-cause hospitalisation events per month and the mean number of days hospitalised per month. The hospital costs were derived from the NHS Reference Costs[218] and combined with the average mean length of stay. The HF hospitalisation event cost was £2295 and the non-HF hospitalisation event cost was £2448.

TABLE 155 Preferred model for the IPD NMA

Variable[a]	HR	*p*-value
ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
LBBB	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Age ≥ 60 years	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Gender = male	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICD*QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICD*QRS ≥ 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICD*LBBB	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICD*Gender = male	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICD*Age ≥ 60 years	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTP*QRS ≥ 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTP*LBBB	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTP*Gender = male	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTP*Age ≥ 60 years	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTD*QRS ≥ 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTD*LBBB	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTD*Gender = male	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRTD*Age ≥ 60 years	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

a Reference category is a patient with the following characteristics: receiving OPT, < 60 years of age, female, QRS duration ≥ 150 milliseconds and with a non-LBBB conduction abnormality.
Note: Main effects for covariables greyed out as not included in cost-effectiveness model.

Device costs were sourced from the average selling prices from the manufacturers via 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.[218] The device-related infection cost was derived by inflating the value in Fox and colleagues[64] to £3139. Device costs, with implantation costs, are shown in *Table 156*.

Medication costs

The cost of HF medication cost included for the patients in the model. The proportion of patients using a range of HF medications, 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 purchase costs of the medications were taken from the BNF.[219] The total cost of treatment per 1-month model cycle was £14.28 for NYHA class I and between £22.13 and £22.30 for NYHA classes II–IV.

Indirect costs

Not applicable.

Health state valuations/utilities (if study uses quality-of-life adjustments to outcomes)

The approach taken for HRQoL was (1) to estimate UK-specific age- and gender-specific population utilities, (2) derive disease-specific decrements using IPD EQ-5D data and (3) derive treatment-specific increments associated with each device at first follow-up visit by NYHA class.

UK-specific age- and gender-specific population utilities were taken from a study of 3395 individuals resident in the UK.[152] Disease-specific decrements were taken from the CARE-HF,[109] MADIT-CRT[130] and RAFT[140] trials. For the impact of treatment, the utility increment was calculated as the difference between baseline and the first follow-up period.

The HRQoL benefit observed at 6 months is maintained up to 5 years and thereafter begins to recede in a linear manner over the time period 5–10 years. After 10 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.

TABLE 156 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)	8281	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)	8281	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 in the MS[151]
Device-related infection (CRT-P)	12,541	See section 5.5.3.3 in the MS[151]
Device-related infection (CRT-D)	21,568	See section 5.5.3.3 in the MS[151]
Battery replacement (ICD)	12,004	ABHI generator costs (excl. leads) and UK tariff EA39Z
Battery replacement (CRT-P)	8381	UK tariff
Battery replacement (CRT-D)	14,672	ABHI generator costs (excl. leads) and UK tariff EA39Z

List the utility values used in the evaluation

Individuals in NYHA class I/II have the same HRQoL as an age-equivalent member of the general public (*Table 157*). Patients in NYHA classes III and IV have extra decrements by sex and ischaemic aetiology (*Table 158*).

TABLE 157 Age- and gender-specific UK EQ-5D population norms [mean (SD)]

Age band (years)	Male	Female
< 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)

Reproduced from Kind *et al.*[152]

TABLE 158 Negative binomial regression model coefficients used to predict baseline utility decrements

Covariable	Beta coefficient	SE	Z-score	e^β
NYHA = III	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
NYHA = IV	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Age	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Ischaemic aetiology	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Gender = male	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Constant	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

a Variable included despite not being significant on the basis of the underlying disease. Lack of significance likely to have arisen because of small patient counts.

TABLE 159 Treatment-specific utility increments used in the economic model

Treatment	NYHA I/II	NYHA III	NYHA IV
OPT	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRT-P	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
CRT-D	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

Modelling

The model is a survival model with two states for alive and dead. Death is modelled through a series of covariate-based regression equations for baseline risk and treatment effect using long-term IPD. There is also a state for all-cause hospitalisation that is aligned to mortality.

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 NMA. 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 for all 4992 patient profiles [four NYHA classes × two aetiology status (ischaemic/non-ischaemic) × three QRS categories × four LVEF categories × LBBB status (yes/no) × two 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:

$$h(t) = \exp\left(-(\log(scale) - \beta \times X) \times shape\right) \times shape \times t^{shape} \quad (1)$$

$$S(t) = \exp\left(-\int_0^t h(t)dt\right) \quad (2)$$

where $h(t)$ is the instantaneous hazard, $S(t)$ is the survival curve, β are the coefficients on the covariables and X is the set of covariables (which can be time dependent).

All-cause hospitalisation The derived monthly probabilities are shown in *Table 161*, using a starting age of 66 years.

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

TABLE 160 Preferred baseline risk model

Variable	Coefficient	HR for prognostic variable[a]	*p*-value
Age (per year)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Male gender	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
NYHA class III	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
NYHA class IV	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Ischaemic aetiology	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS duration < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
LVEF > 20% and ≤ 25%	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
LVEF > 25% and ≤ 30%	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
LVEF > 30%	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
log(scale)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
log(shape)	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

a $HR = \exp(\beta/shape)$.

TABLE 161 Monthly probability of hospitalisation by covariate pattern (OPT)

	NYHA class I/II	NYHA class III	NYHA class IV
Non-ischaemic aetiology			
QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Ischaemic aetiology			
QRS < 120 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS 120–149 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
QRS ≥ 150 milliseconds	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed

inform transition probabilities of device failure in the model. Median time to device failure in the model was 7.1 years for an ICD device, 10.4 years for a CRT-P device and 5.8 years for a CRT-D device.

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
The 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) (*Tables 162* and *163*). All individuals are assumed to have a LVEF ≤ 35%. The authors stated that ischaemia did not substantively impact on cost-effectiveness and so the results presented are therefore applicable to both ischaemic and non-ischaemic patients

TABLE 162 Deterministic base-case results (patients without LBBB)

NYHA class	Aetiology	QRS duration (milliseconds)	*n*	Cost-effectiveness sequence				ICER (£)			
				First	Second	Third	Fourth	First	Second	Third	Fourth
I	Non-ischaemic	< 120	66	OPT	ICD	NA	NA	Referent	24,304	NA	NA
I	Non-ischaemic	≥ 120, < 150	11	OPT	CRT-D	ICD	NA	Referent	Dominated	16,619	NA
I	Non-ischaemic	≥ 150	8	OPT	ICD	CRT-D	NA	Referent	18,074	1,080,057	NA
I	Ischaemic	< 120	272	OPT	ICD	NA	NA	Referent	24,016	NA	NA
I	Ischaemic	≥ 120, < 150	216	OPT	CRT-D	ICD	NA	Referent	Dominated	16,234	NA
I	Ischaemic	≥ 150	106	OPT	ICD	CRT-D	NA	Referent	Extendedly dominated	21,086	NA
II	Non-ischaemic	< 120	710	OPT	ICD	N/A	NA	Referent	£25,110	NA	NA
II	Non-ischaemic	≥ 120, < 150	232	OPT	CRT-D	ICD	NA	Referent	Dominated	17,016	NA
II	Non-ischaemic	≥ 150	141	OPT	ICD	CRT-D	NA	Referent	20,312	27,175	NA
II	Ischaemic	< 120	788	OPT	ICD	NA	NA	Referent	23,884	NA	NA
II	Ischaemic	≥ 120, < 150	756	OPT	CRT-D	ICD	NA	Referent	Dominated	16,749	NA
II	Ischaemic	≥ 150	470	OPT	ICD	CRT-D	NA	Referent	20,697	22,777	NA
III	Non-ischaemic	< 120	255	OPT	ICD	NA	NA	Referent	29,402	NA	NA
III	Non-ischaemic	≥ 120, < 150	150	OPT	CRT-P	ICD	CRT-D	Referent	Extendedly dominated	19,760	27,336
III	Non-ischaemic	≥ 150	109	OPT	ICD	CRT-P	CRT-D	Referent	Dominated	13,227	24,350

continued

TABLE 162 Deterministic base-case results (patients without LBBB) (*continued*)

NYHA class	Aetiology	QRS duration (milliseconds)	*n*	Cost-effectiveness sequence				ICER (£)			
				First	Second	Third	Fourth	First	Second	Third	Fourth
III	Ischaemic	< 120	438	OPT	ICD	NA	NA	Referent	26,923	NA	NA
III	Ischaemic	≥ 120, < 150	426	OPT	CRT-P	ICD	CRT-D	Referent	19,670	Extendedly dominated	27,796
III	Ischaemic	≥ 150	192	OPT	ICD	CRT-P	CRT-D	Referent	Dominated	14,392	25,734
IV	Non-ischaemic	< 120	5	OPT	NA	NA	NA	Referent	NA	NA	NA
IV	Non-ischaemic	≥ 120, < 150	12	OPT	CRT-P	CRT-D	NA	Referent	17,324	30,624	NA
IV	Non-ischaemic	≥ 150	9	OPT	CRT-P	CRT-D	NA	Referent	16,304	33,901	NA
IV	Ischaemic	< 120	42	OPT	NA	NA	NA	Referent	NA	NA	NA
IV	Ischaemic	≥ 120, < 150	52	OPT	CRT-P	CRT-D	NA	Referent	24,366	43,500	NA
IV	Ischaemic	≥ 150	10	OPT	CRT-P	CRT-D	NA	Referent	18,065	37,802	NA

NA, not applicable.

TABLE 163 Deterministic base-case results (patients with LBBB)

NYHA class	Aetiology	QRS duration (milliseconds)	*n*	Cost-effectiveness sequence				ICER (£)			
				First	Second	Third	Fourth	First	Second	Third	Fourth
I	Non-ischaemic	< 120	0	OPT	NA	NA	NA	Referent	N/A	NA	NA
I	Non-ischaemic	≥ 120, < 150	21	OPT	ICD	CRT-D	NA	Referent	Extendedly dominated	21,021	NA
I	Non-ischaemic	≥ 150	33	OPT	ICD	CRT-D	NA	Referent	Extendedly dominated	18,118	NA
I	Ischaemic	< 120	0	OPT	NA	NA	NA	Referent	N/A	NA	NA
I	Ischaemic	≥ 120, < 150	76	OPT	ICD	CRT-D	NA	Referent	19,989	24,343	NA
I	Ischaemic	≥ 150	165	OPT	ICD	CRT-D	NA	Referent	Extendedly dominated	17,335	NA
II	Non-ischaemic	< 120	0	OPT	NA	NA	NA	Referent	N/A	NA	NA
II	Non-ischaemic	≥ 120, < 150	385	OPT	ICD	CRT-D	NA	Referent	Extendedly dominated	26,608	NA
II	Non-ischaemic	≥ 150	1308	OPT	ICD	CRT-D	NA	Referent	Extendedly dominated	17,794	NA
II	Ischaemic	< 120	0	OPT	NA	NA	NA	Referent	N/A	NA	NA
II	Ischaemic	≥ 120, < 150	477	OPT	ICD	CRT-D	NA	Referent	20,640	21,277	NA
II	Ischaemic	≥ 150	982	OPT	ICD	CRT-D	NA	Referent	Extendedly dominated	17,479	NA
III	Non-ischaemic	< 120	0	OPT	NA	NA	NA	Referent	NA	NA	NA
III	Non-ischaemic	≥ 120, < 150	189	OPT	ICD	CRT-P	CRT-D	Referent	Dominated	12,550	23,831
III	Non-ischaemic	≥ 150	775	OPT	ICD	CRT-P	CRT-D	Referent	Dominated	9798	27,592

continued

TABLE 163 Deterministic base-case results (patients with LBBB) (*continued*)

NYHA class	Aetiology	QRS duration (milliseconds)	*n*	Cost-effectiveness sequence				ICER (£)			
				First	Second	Third	Fourth	First	Second	Third	Fourth
III	Ischaemic	< 120	0	OPT	NA	NA	NA	Referent	NA	NA	NA
III	Ischaemic	≥ 120, < 150	355	OPT	ICD	CRT-P	CRT-D	Referent	Dominated	15,449	25,540
III	Ischaemic	≥ 150	773	OPT	ICD	CRT-P	CRT-D	Referent	Dominated	11,408	29,912
IV	Non-ischaemic	< 120	0	OPT	NA	NA	NA	Referent	NA	NA	NA
IV	Non-ischaemic	≥ 120, < 150 seconds	22	OPT	CRT-P	CRT-D	NA	Referent	14,715	31,920	NA
IV	Non-ischaemic	≥ 150	81	OPT	CRT-P	CRT-D	NA	Referent	12,076	35,660	NA
IV	Ischaemic	< 120 seconds	0	OPT	NA	NA	NA	Referent	NA	NA	NA
IV	Ischaemic	≥ 120, < 150	38	OPT	CRT-P	CRT-D	NA	Referent	23,340	41,695	NA
IV	Ischaemic	≥ 150	97	OPT	CRT-P	CRT-D	NA	Referent	17,722	46,445	NA

NA, not applicable.

Summary of results

NYHA class I/II

- QRS duration < 120 milliseconds: the ICERs for ICD compared with OPT are < £25,200 per QALY gained.
- QRS duration 120–149 milliseconds: ICD is a cost-effective treatment option (ICER < £17,000 per QALY) for patients with no LBBB. For CRT-D, all ICERs are < £25,000 per QALY gained in LBBB patients (£20,608–24,343).
- QRS duration ≥ 150 milliseconds: CRT-D is a cost-effective treatment with an ICER of < £28,000 per QALY for all options.

NYHA class III

- QRS duration < 120 milliseconds: ICD compared with OPT generates ICERs of < £30,000 per QALY.
- QRS duration 120–149 milliseconds: CRT-P is cost-effective. CRT-D generates ICERs of between £23,900 and £27,400 per QALY gained relative to CRT-P.
- QRS duration > 150 milliseconds: CRT-P is cost-effective compared with OPT (ICER < £20,000 per QALY). Compared with CRT-P, CRT-D generates ICERs of < £30,000 per QALY gained. ICD is either dominated or extendedly dominated.

NYHA class IV

- QRS duration < 120 milliseconds: no comparative analysis was possible in this patient group.
- QRS duration ≥ 120 milliseconds: For CRT-P compared with OPT, all ICERs are close to or < £20,000 per QALY gained. For the comparison of CRT-D with CRT-P, all ICERs are > £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 ICERs), and there may be other issues that clinicians wish to take into account; they conclude that there seems to be a reasonable case for building clinical flexibility into the recommendations in those cases in which the ICER differences between technologies are small and the uncertainty over which is the preferred device is high.

Give results of any statistical analysis of the results of the evaluation

Not applicable.

Was any sensitivity analysis performed?

Yes, deterministic sensitivity analysis.

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 and 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 and 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 HRQoL were explored, the ICERs in all patient groups were lower than in the base case.

According to the MS, there may be a lower mortality treatment effect of CRT-D in patients in NYHA class IV than in patients in NYHA classes I–III. The economic model was run using the estimated all-cause mortality treatment effects based on the grouping of NYHA class IV patients compared with

NYHA class I–III patients. This analysis results in CRT-D becoming dominated in all NYHA class IV groups. The ICERs for all other groups are lower than in the base case.

Device longevity was investigated by increasing the time to device failure by 10%. This resulted in only minimal changes to the ICERs.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis

This analysis reconfirms the clinical and economic value of ICD, CRT-P and CRT-D in NYHA class I–IV HF patients.

What are the implications of the evaluation for practice?

The recommendations from this analysis would lead to a widening of the eligibility criteria for an ICD or a CRT device and consequently an increase in implant rates. The analysis estimates that the additional annual expenditure incurred by the NHS would range from £41.6M to £230.2M, depending on the choice of scenario and year of interest.

Southampton Health Technology Assessments Centre commentary

Selection of comparators

The interventions compared in the MS consist of those included in NICE's scope.[1] However, not all of them were included as comparators for all patient subgroups:

- ICD was excluded for NYHA class IV
- CRT-P was excluded for NYHA class I/II and QRS duration < 120 milliseconds
- CRT-D was excluded for QRS duration < 120 milliseconds.

These exclusions seem to conflict with NICE's scope, for example some patients in the scoped population with HF and ventricular arrhythmia considered eligible for an ICD are likely to be in 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 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 11 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 Health* 2011;**14**(Suppl. 1):S33–8. [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. *Br Heart J* 1993;**69**: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. *Int J Technol Assess Health Care* 2007;**23**: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. *J Card Fail* 2010;**16**:734–41. [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. *Eur Heart J* 2010;**31**(Suppl. 1):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**:646–53. [Reason for exclusion: no economic evaluation.]

Hauer RN, Derksen R, Wever EF. Can implantable cardioverter-defibrillator therapy reduce healthcare costs? *Am J Cardiol* 1996;**78**:134–9. [Reason for exclusion: comparator.]

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. *Eur Heart Jl* 2012;**33**:896. [Reason for exclusion: abstract.]

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. [Reason for exclusion: no economic evaluation.]

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). *Eur Heart J* 2011;**32**:1631–9. [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**:1597–603. [Reason for exclusion: excluded in error.]

Medical Advisory Service. Internet-based device-assisted remote monitoring of cardiovascular implantable electronic devices. *Ont Health Technol Assess Ser* 2012;**12**(1). [Reason for exclusion: intervention.]

Mushlin AI, Zwanziger J, Gajary E, Andrews M, Marron R. Approach to cost-effectiveness assessment in the MADIT trial. *Am J Cardiol* 1997;**80**:F33–41. [Reason for exclusion: no economic evaluation.]

Neyt M, Stroobandt S, Obyn C, Camberlin C, Devriese S, De Laet C, *et al.* Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure. *Value Health* 2011;**14**:A253. [Reason for exclusion: abstract.]

Health Improvement Scotland. *The Use of Cardiac Resynchronization Therapy (CRT) for Heart Failure.* Evidence Note 10. URL: www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/earlier_evidence_notes/evidence_note_10.aspx (accessed April 2014). [Reason for exclusion: no economic evaluation.]

Pons JM, Granados A. *Implantable Cardioverter Defibrillator: Experience in Catalonia (1989–1995) and Elements of its Evaluation*. Catalonia, Spain: Department of Health; 1997. [Reason for exclusion: unobtainable.]

Poggio R, Augustovsky F, Caporale J, Irazola V, Miriuka S. Cost-effectiveness of cardiac resynchronization therapy: perspective from Argentina. *Int J Technol Assess Health Care* 2012;**28**:429–35. [Reason for exclusion: population.]

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? *J Heart Lung Transplant* 2012;**31**:S50–1. [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*. Report no. 55. Birmingham: Department of Public Health and Epidemiology, University of Birmingham; 2005. [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. *Can J Cardiol* 2012;**28**(Suppl.):S419. [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**:489–96. [Reason for exclusion: comparator.]

Appendix 12 Data extraction: cost-effectiveness

Buxton and colleagues 2006[153]

Country	UK
Analysis type	Cost–utility analysis/cost-effectiveness analysis
Study type	Markov model
Perspective	UK NHS
Time horizon	20 years
Discounting (rate)	Base-case discount rates were 6% for costs and 1.5% for benefits
Costing year, currency	2001/2 prices, UK pounds
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[84] (for OPT patients) and UK sampled observational data (for ICD patients)
Health outcomes	A cross-sectional survey collected HRQoL data (using the NHP, SF-36, Hospital Anxiety and Depression questionnaire and EQ-5D) on a sample of 229 patients
Device cost	Cost of ICD (with leads) £16,402
Results	Over a 20-year time horizon, the mean discounted incremental cost was £70,900. The mean discounted incremental gain was 1.24 years or 0.93 QALYs for ICD compared with 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
Authors' 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

?, unclear; N, no; Y, yes.

Bond and colleagues 2009,[203] derived from Fox and colleagues 2007[64]

Country	UK
Analysis type	Cost–utility analysis
Study type	Markov model
Perspective	UK NHS
Time horizon	Lifetime
Discounting (rate)	Costs and QALYs 3.5%
Costing year, currency	2005 UK pounds for all costs except drug costs (2006 UK pounds)
Population	A mixed-age cohort of patients with NYHA class III and IV HF, evidence of LVSD (LVEF ≤ 35%) and evidence of electrical dyssynchrony (QRS duration > 120 milliseconds)
Intervention(s), comparator(s)	CRT vs. OPT;[a] CRT-D[b] vs. CRT; OPT vs. CRT vs. CRT–D
Intervention effect[c]	RR of death from 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) RR 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 years, 5.8 years and 6.2 years for OPT, CRT and CRT-D respectively. NYHA class-specific estimates of QoL were used to derive time-dependent utility estimates (derived from the CARE-HF trial[109] and the study by Kirsch and McGuire,[210] which used EQ-5D and UK population values) and utility of hospitalisation because of HF (from McAlister *et al.*[194])
Device cost	Surgery to implant new system (includes cost of the device): CRT £5074; CRT-D £17,266; ICD £11,596

Results

Discounted	Mean cost (£)	Mean QALYs	Incremental cost (£)	Incremental QALYs	ICER (£) (95% CI)	*p*(CE) (%)
OPT	9367	3.10	–	–	–	–
CRT	20,997	3.80	–	–	–	–
CRT-D	32,687	4.09	–	–	–	–
CRT vs. OPT	–	–	11,630	0.70	16,738 (14,630 to 20,333)	91.3
CRT-D vs. CRT	–	–	11,689	0.29	40,160 (26,645 to 59,391)	26.3

p(CE), probability of being cost-effective at a WTP threshold of £30,000 per QALY.

Sensitivity analysis	Deterministic univariate and probabilistic sensitivity analyses were conducted. One-way sensitivity analyses show the sensitivity of the results to structural parameters, event probabilities and RRs. 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 SCD. A cost-effectiveness probability frontier shows that CRT is most likely to be 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 the highest expected net benefit (approximately 50% probability of being cost-effective)
Authors' conclusions	CRT-D is not cost-effective for LVSD. 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 a high risk of SCD who would qualify for CRT
Reviewer's comments	PenTAG's cost–utility analysis in the UK setting using clinical effectiveness data from accompanying systematic review and meta-analysis of RCTs

PenTAG, Peninsula Technology Assessment Group.
a Referred to as medical therapy.
b Referred to as CRT-ICD.
c Source: Fox *et al.*[64]

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

?, unclear; N, no; Y, yes.

Appendix 13 List of excluded quality-of-life 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. *Transplant Proc* 2006;**38**:2524–6. [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. *Eur J Heart Fail* 2005;**7**:411–17. [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. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:162–7. [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. *Eur J Cardiovasc Nurs* 2009;**8**:34–9. [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. *Eur J Heart Fail* 2011;**10**(Suppl. 1):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. *Qual Life Res* 2008;**17**:1229–38. [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. *Am Heart J* 2009;**158**:S64–71. [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. *Eur J Heart Fail* 2010;**12**:1002–8. [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. *J Clin Epidemiol* 2011;**64**: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 Econ* 2000;**9**:149–58. [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. *Eur J Health Econ* 2011;**12**:383–91. [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). *Eur Heart J* 2011;**32**:1631–9. [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 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. *Am Heart J* 2005;**150**:707–15. [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. *Hellenic J Cardiol* 2008;**49**:241–7. [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. *Am J Geriatr Cardiol* 2004;**13**:252–60. [Reason for exclusion: uses EQ-5D VAS.]

Appendix 14 Development of Southampton Health Technology Assessments Centre model

From the review of published economic evaluations, the study by Fox and colleagues[64] was found to be the most adequate for the derivation of a model that would allow the questions of the current assessment to be addressed, with the necessary adaptations to reflect current clinical practice.

The structure of Fox and colleagues' model for the OPT arm was considered appropriate for the SHTAC population 1 model. The Fox and colleagues model structure for the OPT arm allowed patients initially managed with OPT alone to be upgraded to ICD + OPT in case of hospitalisation for arrhythmia (assumed direct referral to ICD implantation) or following hospitalisation for HF [given that in the CARE-HF trial[109] a proportion of those in the OPT alone arm who were hospitalised for HF were then referred to a device with a defibrillation function (CRT-D), Fox and colleagues assumed the same probability for referral to an ICD]. Clinical advice to SHTAC indicated that referral from OPT alone to ICD implantation would occur in clinical practice only for population 1 patients. Fox and colleagues' model structure, including health states modelled and transitions allowed, was therefore replicated for population 1.

According to clinical advice, population 2 patients would be referred to CRT-P implantation (given their HF severity) and, in case of also being at high risk of severe arrhythmia, could be referred to CRT-D implantation. Clinical opinion confirmed that Fox and colleagues' model structure for the population 2 CRT-P arm was appropriate for the SHTAC population 2 model and that it could form the basis for modelling population 3.

Adaptations common to all models

Fox and colleagues[64] used a specific set of transitions between health states for each of the treatment arms, that is, patients in each arm were eligible only for some of the available treatments (e.g. HF patients initially managed with OPT could upgrade only to ICD + OPT whereas those in the CRT-P arm could upgrade to CRT-D or ICD or explant and be managed with OPT alone). Following feedback from clinical experts, we decided that all treatment arms in each model should use the same transition matrix, allowing the modelled cohort of patients to start with the respective treatment and be referred for upgrades according to probability estimates derived from clinical trials included in SHTAC's clinical effectiveness review (see *Chapter 4*).

For consistency with other surgical procedures and devices modelled and following clinical advice, the risk of death as a result of transplantation, the risk of hospitalisation for arrhythmia with ICD and CRT-D therapy, and the risk of lead displacement for ICD therapy were incorporated in the models for all populations.

The model developed by Fox and colleagues[64] assumed that all patients being managed with a device would be subject to routine device replacement, including patients who were stable with the device, those having a device-related complication (perioperative, lead displacement or lead infection), those hospitalised because of HF with a device or those referred for an upgrade following hospitalisation because of HF. For modelling simplicity and acknowledging the risk of underestimation, in SHTAC's model only patients who are stable with the device were subject to routine device replacement, assuming that this allows for a reasonable estimation of the number of replacements in the patient cohorts over a lifetime.

Model-specific adaptations

Surgical failure was incorporated in the model for population 1 for consistency with the models for populations 2 and 3. As clinical advice suggested that returning to management with OPT alone after unsuccessful ICD implantation would be very unlikely, the population 1 model assumes that patients who survive unsuccessful ICD implantation reattempt it the following cycle.

In accordance with the model developed by Fox and colleagues,[64] in the models for populations 2 and 3, patients receiving CRT-P who experience lead infection or displacement were assumed to return to being managed with OPT alone if experiencing surgical failure. For consistency among health states, the risk of surgical failure was explicitly accounted for in all health states involving surgery (including first device implantation and routine device replacements). For model simplicity and consistency, patients who survive unsuccessful ICD implantation were also assumed to return to management with OPT alone. Those with unsuccessful CRT-D implantation were assumed to undergo ICD implantation.

The model structure for population 2 differs slightly from that in the study by Fox and colleagues.[64] The main variations relate to the transitions allowed for patients managed with OPT alone. In SHTAC's model, patients with OPT alone who are hospitalised because of HF or severe arrhythmia can be referred to CRT-P or CRT-D implantation in the following cycle, according to the probabilities reported in the relevant trials. Patients can receive an ICD only following unsuccessful CRT-D implantation, as patients who survive unsuccessful CRT-D implantation are assumed to undergo ICD implantation.

The main adaptation introduced to Fox and colleagues' model structure for population 3 relates to the referral of patients to CRT-D implantation. Patients being managed with OPT alone or CRT-P + OPT who are hospitalised because of a serious arrhythmic event are assumed to undergo CRT-D implantation in the same cycle. Those being managed with OPT alone because of unsuccessful CRT-P implantation can be referred to ICD implantation if they experience a life-threatening arrhythmia.

Appendix 15 Parameters included in the probabilistic sensitivity analyses

Parameter inputs for the population 1 model

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	Log-normal
All causes multiplier	HR 18–59	0.62	0.0459	0.54	0.72	Log-normal
	HR 75+	1.41	0.0051	1.40	1.42	
Because of 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 for HF	OPT	0.0082	0.0061	–0.0036	0.0201	Beta
	RR ICD	1	0.1	0.804	1.196	
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	
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	
Upgrade after HF hospitalisation	OPT to ICD	0.0018	0.002	–0.0023	0.0059	Beta

LL, lower limit; UL, upper limit.

Parameter inputs for the population 2 model

Parameter type	Parameter	Source estimate				Distribution
		Mean	SE	LL	UL	
Death from HF, age 65–74 years, OPT	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	Log-normal
	HR CRT-D	0.73	0.163	0.47	1.11	Log-normal
	HR ICD	1.14	0.153	0.88	1.48	Log-normal
Post-transplant mortality	RR Transplant	0.35	0.035	0.281	0.419	Log-normal
Death from 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	Log-normal

Parameter type	Parameter	Source estimate				Distribution
		Mean	SE	LL	UL	
	HR CRT-D	0.44	0.1607	0.23	0.86	Log-normal
	HR ICD	0.44	0.0765	0.31	0.61	Log-normal
All-cause mortality RR by age (years)	18–64	0.62	0.05	0.54	0.72	Log-normal
	75+	1.41	0.01	1.4	1.42	
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 for 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	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	

LL, lower limit; UL, upper limit.

Parameter inputs for the population 3 model

Parameter type	Parameter	Source estimate				Distribution
		Mean	SE	LL	UL	
All-cause mortality, baseline – CRT-D	ln(λ)	–6.334	0.068	–6.467	–6.202	Normal
	γ	1.234	0.018	1.199	1.270	Normal
	HR CRT-P	1	0.100	0.804	1.196	Log-normal
	HR ICD	1.190	0.084	1.042	1.370	Log-normal
	HR OPT	1.563	0.235	1.163	2.083	Log-normal
All-cause mortality RR by age (years)	18–64	0.621	0.046	0.54	0.72	Log-normal
	75+	1.410	0.005	1.4	1.42	

		Source estimate				
Parameter type	Parameter	Mean	SE	LL	UL	Distribution
Event probabilities (per cycle)	CRT-D	0.008	0.003	0.003	0.013	Beta
Hospitalisation for 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 ln(λ)	–15.784	0.203	–16.182	–15.385	Normal
	CD γ	1.943	0.027	1.889	1.996	
	CRT-P ln(λ)	–14.222	0.242	–14.697	–13.747	
	CRT-P γ	1.677	0.032	1.613	1.740	
	CRT-D ln(λ)	–15.465	0.273	–16	–14.931	
	CRT-D γ	1.935	0.036	1.863	2.006	

LL, lower limit; UL, upper limit.

For all populations: utilities

Parameter type	Parameter	Mean	SE	UL	LL	Distribution
	No HF	0.855	0.0048	0.845	0.864	Beta
Per NYHA class	NYHA I	0.855	0.0048	0.845	0.864	Beta
	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	Beta

Parameter type	Parameter	Mean	SE	UL	LL	Distribution
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

Parameter type	Parameter	Mean (£)	SE (£)	UL (£)	LL (£)	Distribution
Implantation	CRT-P	8281	1479	6098	11,895	Gamma
	CRT-D	17,849	4521	15,246	32,969	
	ICD	15,248	4261	13,155	29,858	
Lead displacement/implantation failure	CRT-P	5681	1219	4008	8786	Gamma
	CRT-D	6097	3346	5798	18,914	
	ICD	6099	3346	5799	18,916	
Battery failure/device malfunction	CRT-P	5348	788	3884	6974	Gamma
	CRT-D	17,308	1704	14,811	32,322	
	ICD	14,705	4207	12,718	29,209	
Infection	CRT-P	12,553	2036	7285	15,265	Gamma
	CRT-D	21,580	5552	17,202	38,966	
	ICD	18,977	5292	15,109	35,853	
Operative complications	CRT-P	4884	1869	2442	9768	Gamma
	CRT-D	6634	2539	3317	13,268	
	ICD	3432	1313	1716	6864	
Non-elective hospitalisation	HF hospitalisation	2308	232	1669	2578	Gamma
	Arrhythmia hospitalisation	1372	173	922	1601	
Transplant	Heart transplant	35,606	5578	21,449	43,315	Gamma
Outpatient appointments, 6-monthly	Outpatient cardiology specialist follow-up	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.[220] 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 and the extracted data points were then exported to Microsoft Excel for further analysis.

For a Weibull distribution the survival function is given by:

$$S(t) = \exp(-\lambda t^{\gamma}) \quad (3)$$

with scale parameter λ and shape γ.

Taking the log of both sides gives:

$$\log(S(t)) = -\lambda t^{\gamma} \quad (4)$$

Taking the log of both sides again gives:

$$\log(-\log(S(t))) = \log(\lambda) + \gamma \log(t) \quad (5)$$

which is a linear function and can be fit using least-squares methods to provide estimates of λ and γ.

Population 1

Table 164 shows the parameters derived for estimation of all-cause mortality for the OPT arm in the model for population 1.

Secondary prevention

Figure 43 shows the Weibull approximation fitted to the Kaplan–Meier curve for overall survival of patients in the AVID trial,[71] who survived VF or sustained VT that had caused haemodynamic compromise. Goodness of fit can be inspected visually as well as being 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 < 1, indicating that the hazard rate decreases with time.

Primary prevention: remote myocardial infarction

Figure 44 illustrates the curve-fitting process for patients with remote MI and reduced LVEF using data extracted from the MADIT II trial,[101] 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 indicates that the distribution could potentially be reduced to the exponential form.

Primary prevention: mild to moderate heart failure

The Kaplan–Meier curve for overall survival of patients in the control group with mild to moderate HF at increased risk of SCD using data extracted from the SCD-HeFT trial[105] is shown in *Figure 45*, 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. The shape parameter ($\gamma = 1.08$) is slightly above 1, indicating that the hazard rate slightly increases with time.

TABLE 164 Weibull model parameters for all-cause mortality

Parameter	Mean (SE)			
	AVID[71] ($R^2 = 0.994$)	MADIT II[101] ($R^2 = 0.9903$)	SCD-HeFT[105] ($R^2 = 0.993$)	SCD-HeFT,[105] 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: $\ln(-\ln(S)) = \ln(\lambda) + \gamma\ln(t)$; $S(t) = \exp(-\lambda.t^{\wedge}\gamma)$.

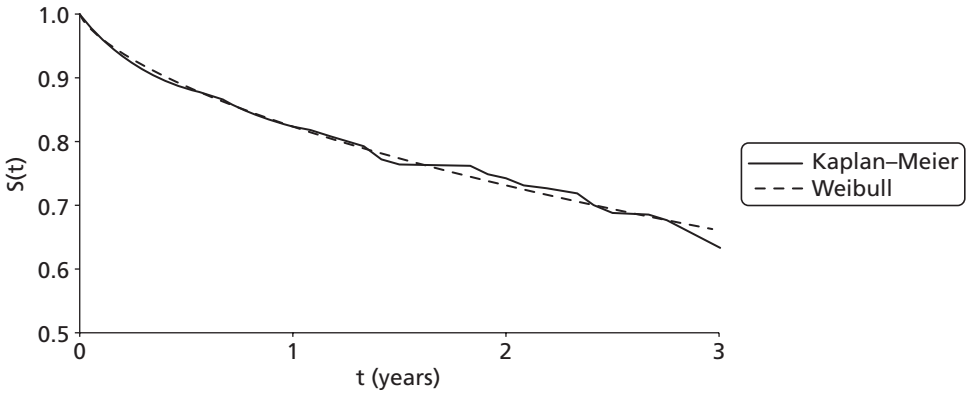

FIGURE 43 Kaplan–Meier survival estimates and Weibull approximation for all-cause mortality: AVID trial population.[71]

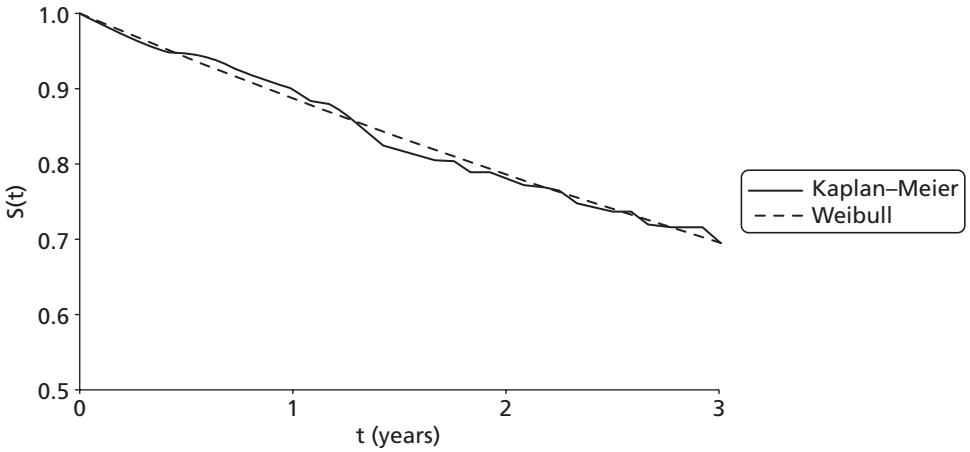

FIGURE 44 Kaplan–Meier survival estimates and Weibull approximation for all-cause mortality in patients with remote MI and reduced LVEF: MADIT II trial population.[52]

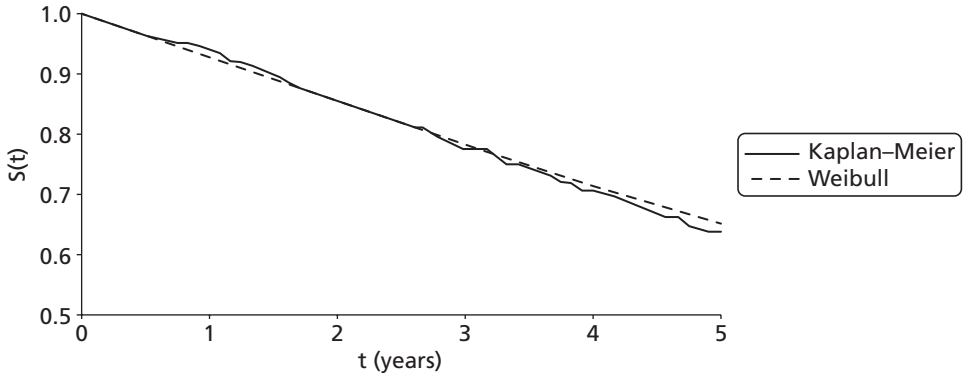

FIGURE 45 Kaplan–Meier survival estimates and Weibull approximation for overall survival in patients with mild to moderate HF: SCD-HeFT trial population.[105]

Primary prevention: cardiomyopathy

The SCD-HeFT trial[105] reported all-cause mortality for the subgroup of patients with non-ischaemic CHF. The Kaplan–Meier curve for the placebo arm was used to derive the baseline mortality for the subgroup analysis of patients with cardiomyopathy (*Figure 46*). The R^2 from the regression (0.99) and visual inspection of the Weibull approximation suggest that the model fits the Kaplan–Meier estimates well.

Table 165 provides a comparison between the observed survival reported at given years for each trial and the model predictions.

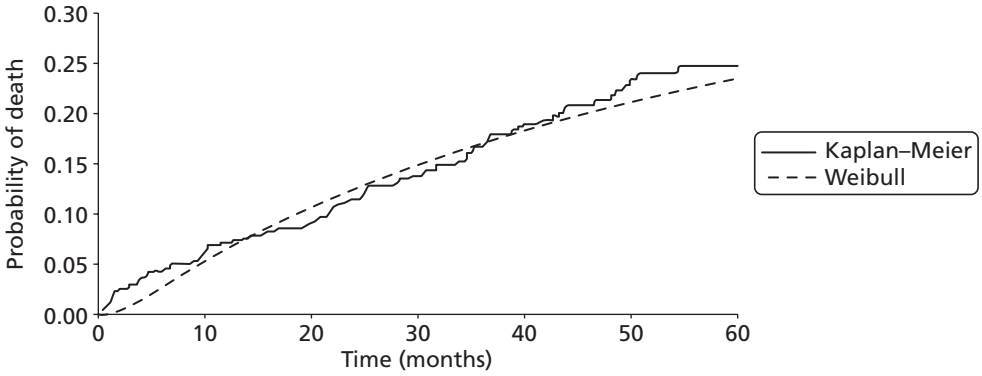

FIGURE 46 Kaplan–Meier survival estimates and Weibull approximation for all-cause mortality in patients with non-ischaemic CHF: SCD-HeFT trial population.[105]

TABLE 165 Regression results and comparison of observed survival against Weibull model predictions: all-cause mortality in the AVID,[71] MADIT-II[101] and SCD-HeFT[105] trials

	Study report		Weibull approximation	
Year	AAD	ICD	AAD	ICD[a]
***AVID*[71] ($R^2 = 0.994$), $\lambda = 0.0340$, $\gamma = 0.6962$**				
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
	Conventional medical therapy	ICD	Conventional medical therapy	ICD[b]
***MADIT II*[101] ($R^2 = 0.9903$), $\lambda = 0.0098$, $\gamma = 1.0068$**				
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
	Placebo[c]	ICD[c]	Placebo	ICD[d]
***SCD-HeFT*[105] ($R^2 = 0.993$), $\lambda = 0.0051$, $\gamma = 1.0831$**				
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 HR (defibrillator vs. AAD) for total mortality is not reported in the AVID trial publication.[71] Survival probabilities with a defibrillator were calculated by applying the RR (0.66) calculated in the systematic review.
b Survival probabilities with a defibrillator were calculated by applying the HR of 0.69 from the trial report[101] to the Weibull approximation.
c Survival probabilities for each year are not reported in the SCD-HeFT trial publication.[105] These values were estimated from the scanned Kaplan–Meier curves.
d Survival probabilities with a defibrillator were calculated by applying the HR of 0.77 from the trial publication[105] to the Weibull approximation.

Population 2

Cardiac mortality

The CARE-HF trial[111] is the trial with the longest follow-up period of those included in SHTAC's clinical effectiveness review for people with HF as a result of LVSD and cardiac dyssynchrony despite receiving OPT. Hence, baseline time-dependent probabilities of SCD and death from worsening HF were derived from CARE-HF survival curves.[111] *Table 166* shows the parameters derived for the estimation of SCD and HF deaths for the OPT arm.

TABLE 166 Weibull model parameters for SCD and HF mortality

Parameter	Mean	95% CI
SCD		
ln(λ)	–6.069	–6.173 to –5.964
γ	1.140	1.107 to 1.173
HF		
ln(λ)	–6.115	–6.256 to –5.974
γ	1.223	1.179 to 1.266

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

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[135] and RAFT[140]) 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 167* presents the regression results using data extracted from both trials.[135,140]

The R^2 statistics reported for the regressions in *Table 167* confirm that the Weibull models fit the data well. *Figure 47* shows the Weibull approximation to the Kaplan–Meier estimates obtained from the curve published for the ICD-CRT arm of the RAFT trial.[140] The γ value (1.24, 95% CI 1.20 to 1.27) is > 1, indicating that the probability of death increases over time.

Table 168 provides a comparison between observed survival at times reported for the trials and model predictions.

TABLE 167 Regression results: parameters used to fit the Weibull models

Parameter	Mean	95% CI
RAFT[140]		
ICD-CRT arm ($R^2 = 0.9894$)		
ln(λ)	–6.334	–6.202 to –6.467
γ	1.243	1.20 to 1.27
MADIT-CRT[135]		
Men, CRT-D arm ($R^2 = 0.989$)		
ln(λ)	–6.935	–7.005 to –6.865
γ	1.287	1.266 to 1.308

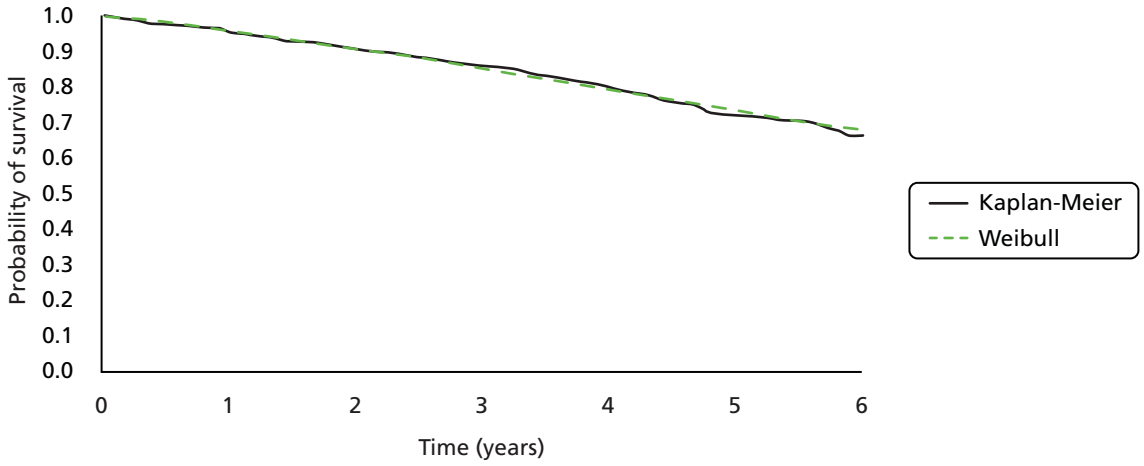

FIGURE 47 Weibull approximation to Kaplan–Meier survival for all-cause mortality of patients receiving CRT-D in the RAFT trial.[140]

TABLE 168 Comparison between observed survival and Weibull model predictions: all-cause mortality in the RAFT[140] and MADIT-CRT[135] trials

	Study report		Weibull approximation	
Year	ICD-CRT[a]	ICD[a]	ICD-CRT	ICD[b]
***RAFT*[140]**				
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[c]	0.654[c]	0.736	0.664
6	0.663	0.553	0.681	0.599
	CRT-D[a]	ICD[a]	CRT-D	ICD[d]
***MADIT-CRT men*[135]**				
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 each year are not reported in the trial publication. These values were estimated from the scanned Kaplan–Meier curves.
b Survival probabilities with a defibrillator were calculated by applying the reverse HR of 0.75 for ICD-CRT from the trial report[140] to the Weibull approximation.
c Survival probabilities reported in the RAFT trial publication.[140]
d Survival probabilities with a defibrillator were calculated by applying the reverse HR of 1.05 for men in the ICD-CRT arm from the trial report[135] to the Weibull approximation.

Appendix 17 Validation of the independent economic model

Validation against the model developed by Fox and colleagues[64]

At an early stage of model development, the OPT arm of the model developed by Fox and colleagues[64] for TA120[43] was replicated. The OPT arm consisted of a cohort of patients with HF initially managed with OPT alone who are eligible for ICD implantation. *Table 169* summarises the outputs 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.

Having reproduced this model arm, the model was adapted according to clinical advice to reflect disease progression for the populations defined in the scope developed by NICE[61] for this assessment.

Validation against trial data

Population 1

The model was validated against trial data for all-cause mortality from the AVID,[71] MADIT II[101] and SCD-Heft[105] trials. The model used the all-cause mortality regression parameters calculated for these trials and the trial RR for ICDs, that is, 0.66 for AVID, 0.71 for MADIT II and 0.77 for SCD-HEFT. *Figures 48–50* show the results from these analyses. The model-generated results show a good fit against the AVID trial[71] data. The model results show a reasonable fit against the MADIT II and SCD-HeFT trial data, although the model appears to slightly underestimate the benefit of ICD compared with OPT and therefore may be a conservative fit.

Population 2

The model was validated against the trial data for all-cause mortality from the CARE-HF trial.[111] The model used the SCD and HF mortality regression parameters calculated for this trial and the trial RR for ICD, that is 0.55 for HF and 0.54 for SCD. *Figure 51* shows the results from this analysis. The model-generated results show a reasonable fit against the CARE-HF trial[111] data, 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 the CARE-HF trial, although the model appears to underestimate the benefit of CRT compared with OPT and therefore may be a conservative fit.

Population 3

The model was validated against the trial data for all-cause mortality from the RAFT trial.[140] The model used the all-cause mortality regression parameters calculated for this trial and the trial RR of 0.75 for CRT-D compared with ICD. *Figure 52* shows the results from this analysis. The model-generated results show a good fit against the RAFT trial data.

TABLE 169 Model outputs for an average 70-year-old patient with HF initially managed with OPT

	Life-years		Discounted QALYs	
Health state	Fox and colleagues[64]	Replica	Fox and colleagues[64]	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
Perioperative 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

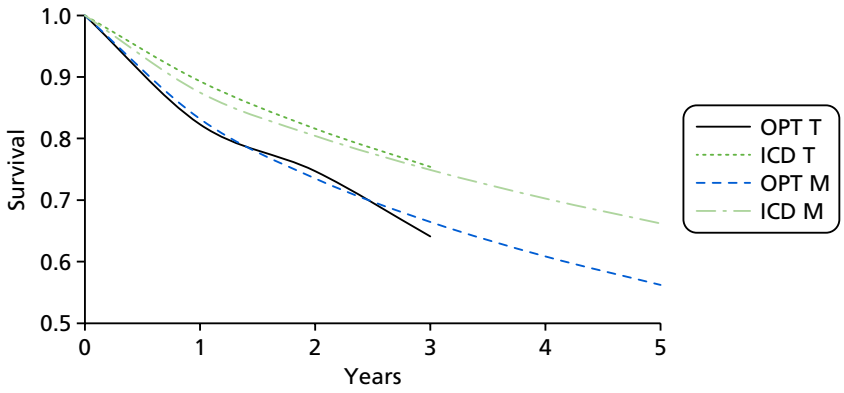

FIGURE 48 Overall survival curves for OPT and ICD compared with AVID trial data.[71] M, model; T, trial.

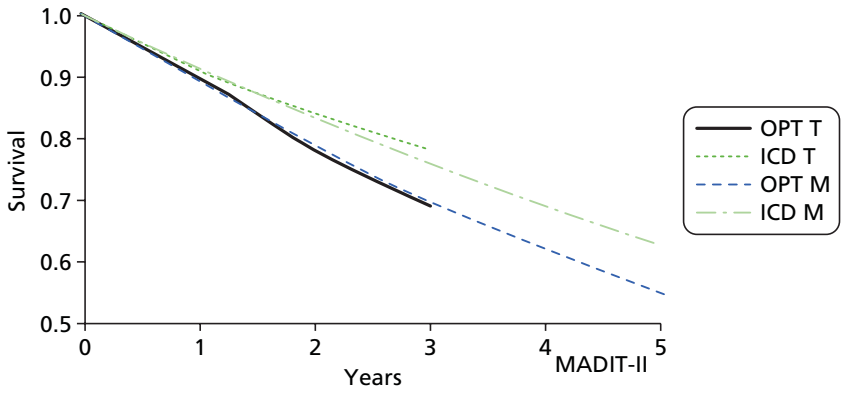

FIGURE 49 Overall survival curves for OPT and ICD compared with MADIT II trial data.[101]

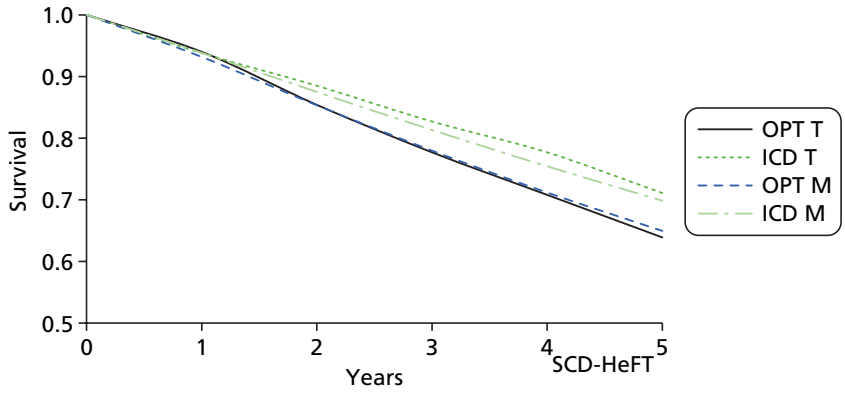

FIGURE 50 Overall survival curves for OPT and ICD compared with SCD-HeFT trial data.[105]

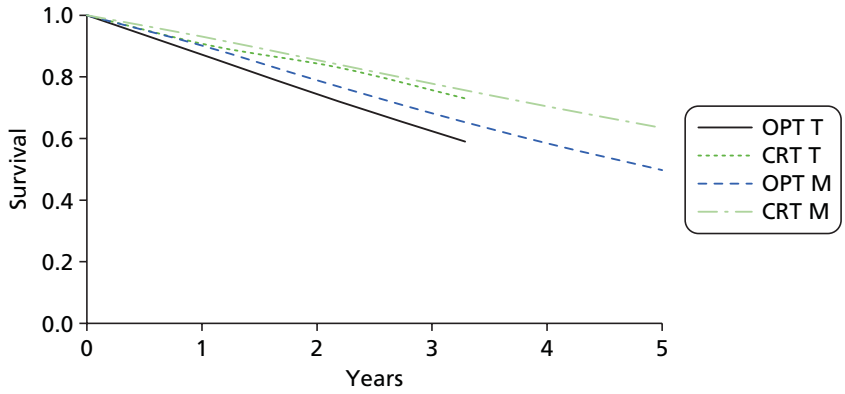

FIGURE 51 Overall survival curves for CRT and OPT compared with CARE-HF trial data.[111]

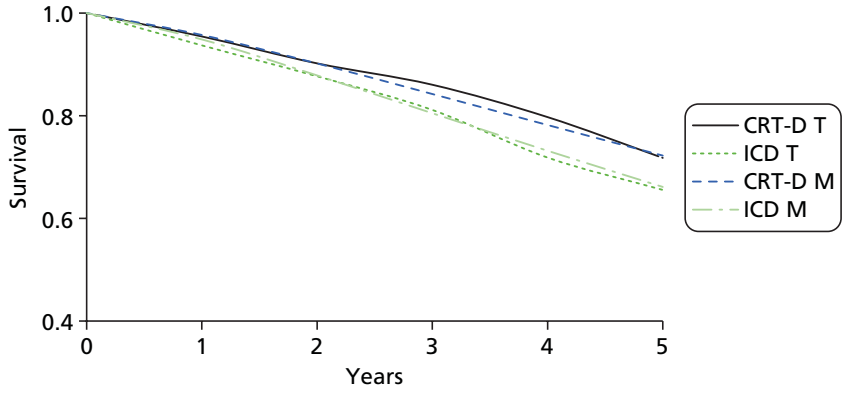

FIGURE 52 Overall survival curves for CRT-D and ICD compared with RAFT trial data.[140]

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