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[Intervention Review]

Implantable cardiac defibrillators for people with non-ischaemic cardiomyopathy

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ABSTRACT

Background

There is evidence that implantable cardioverter-defibrillator (ICD) for primary prevention in people with an ischaemic cardiomyopathy improves survival rate. The evidence supporting this intervention in people with non-ischaemic cardiomyopathy is not as definitive, with the recently published DANISH trial finding no improvement in survival rate. A systematic review of all eligible studies was needed to evaluate the benefits and harms of using ICDs for primary prevention in people with non-ischaemic cardiomyopathy.

Objectives

To evaluate the benefits and harms of using compared to not using ICD for primary prevention in people with non-ischaemic cardiomyopathy receiving optimal medical therapy.

Search methods

We searched CENTRAL, MEDLINE, Embase, and the Web of Science Core Collection on 10 October 2018. For ongoing or unpublished clinical trials, we searched the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the ISRCTN registry. To identify economic evaluation studies, we conducted a separate search to 31 March 2015 of the NHS Economic Evaluation Database, and from March 2015 to October 2018 on MEDLINE and Embase.

Selection criteria

We included randomised controlled trials involving adults with chronic non-ischaemic cardiomyopathy due to a left ventricular systolic dysfunction with an ejection fraction of 35% or less (New York Heart Association (NYHA) type I-IV). Participants in the intervention arm should have received ICD in addition to optimal medical therapy, while those in the control arm received optimal medical therapy alone. We included studies with cardiac resynchronisation therapy when it was appropriately balanced in the experimental and control groups.

Data collection and analysis

The primary outcomes were all-cause mortality, cardiovascular mortality, sudden cardiac death, and adverse events associated with the intervention. The secondary outcomes were non-cardiovascular death, health-related quality of life, hospitalisation for heart failure, first ICD-related hospitalisation, and cost. We abstracted the log (hazard ratio) and its variance from trial reports for time-to-event survival data.

We extracted the raw data necessary to calculate the risk ratio. We summarised data on quality of life and cost-effectiveness narratively. We assessed the certainty of evidence for all outcomes using GRADE.

Main results

We identified six eligible randomised trials with a total of 3128 participants. The use of ICD plus optimal medical therapy versus optimal medical therapy alone decreases the risk of all-cause mortality (hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.66 to 0.92; participants = 3128; studies = 6; high-certainty evidence). An average of 24 patients need to be treated with ICD to prevent one additional death from any cause (number needed to treat for an additional beneficial outcome (NNTB) = 24). Individuals younger than 65 derive more benefit than individuals older than 65 (HR 0.51, 95% CI 0.29 to 0.91; participants = 348; studies = 1) (NNTB = 10). When added to medical therapy, ICDs probably decrease cardiovascular mortality compared to not adding them (risk ratio (RR) 0.75, 95% CI 0.46 to 1.21; participants = 1781; studies = 4; moderate-certainty evidence) (possibility of both plausible benefit and no effect). Implantable cardioverter-defibrillator was also found to decrease sudden cardiac deaths (HR 0.45, 95% CI 0.29 to 0.70; participants = 1677; studies = 3; high-certainty evidence). An average of 25 patients need to be treated with an ICD to prevent one additional sudden cardiac death (NNTB = 25). We found that ICDs probably increase adverse events (possibility of both plausible harm and benefit), but likely have little or no effect on non-cardiovascular mortality (RR 1.17, 95% CI 0.81 to 1.68; participants = 1781; studies = 4; moderate-certainty evidence) (possibility of both plausible benefit and no effect). Finally, using ICD therapy probably has little or no effect on quality of life, however shocks from the device cause a deterioration in quality of life. No study reported the outcome of first ICD-related hospitalisations.

Authors' conclusions

The use of ICD in addition to medical therapy in people with non-ischaemic cardiomyopathy decreases all-cause mortality and sudden cardiac deaths and probably decreases mortality from cardiovascular causes compared to medical therapy alone. Their use probably increases the risk for adverse events. However, these devices come at a high cost, and shocks from ICDs cause a deterioration in quality of life.

PLAIN LANGUAGE SUMMARY

Preventive use of implantable heart defibrillators in people with poor heart function

What was the aim of this review?

The aim of this Cochrane Review was to compare the benefits and harms of using versus not using implantable devices that restore heart rhythm (implantable cardioverter-defibrillators (ICDs)) in addition to medications in people with non-ischaemic heart disease.

Key message

The use of ICD in addition to medications in people with non-ischaemic heart disease decreases the rate of death compared to not using the device.

What was studied in the review?

Poor cardiac function decreases the capacity of the heart to pump enough blood to the various organ systems in the human body. This can occur due to poor blood supply to the heart muscles (ischaemic) or other causes (non-ischaemic). Either way, patients are at an increased risk of sudden death. The goal of treatment is to decrease this risk either through medications or through implantation of an ICD.

The available research shows that preventive use of ICD in the first category of patients (ischaemic) decreases the rate of death. In contrast, recent publication of a large trial showed no overall benefit in the second category of patients (non-ischaemic).

What are the main results of this review?

In this review, we synthesised the results of six major clinical trials that were identified through an extensive search to better understand the efficacy of ICDs in patients with non-ischaemic heart disease. Our analysis involved 3128 participants.

We found high-certainty evidence suggesting that the use of these devices (compared to no such use) in people with non-ischaemic heart disease decreases the risk of dying from any cause and of dying suddenly. There is moderate-certainty evidence suggesting that people on such devices probably have more complications than those not on these devices. The current evidence suggests that adding ICD therapy probably has little or no effect on quality of life when compared to not adding it, but electric shocks from ICDs worsen quality of life.

How up to date is this review?

We searched for studies that were available up to 10 October 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. ICD plus optimal medical therapy compared to optimal medical therapy alone for people with non-ischaemic cardiomyopathy

ICD plus optimal medical therapy compared to optimal medical therapy alone for people with non-ischaemic cardiomyopathy

Population: people with non-ischaemic cardiomyopathy

Setting: USA, Israel, New Zealand, Canada, Germany, and Denmark

Intervention: implantable cardioverter-defibrillator in addition to optimal medical therapy

Comparator: optimal medical therapy alone

Outcomes length of follow-up (range)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with optimal medical therapy alone	Risk difference with ICD plus optimal medical therapy
All-cause mortality (HR) - main analysis ^a 16.5 to 67.6 months	3128 (6 RCTs)	⊕⊕⊕⊕ HIGH ¹	HR 0.78 (0.66 to 0.92)	Study population 216 per 1000	 43 fewer per 1000 (68 fewer to 15 fewer)
Cardiovascular mortality (RR) ^b 22.8 to 67.6 months	1781 (4 RCTs)	⊕⊕⊕⊖ MODERATE ²	RR 0.75 (0.46 to 1.21)	Study population 142 per 1000	 35 fewer per 1000 (77 fewer to 30 more)
Sudden cardiac death (HR) ^a 24 to 67.6 months	1677 (3 RCTs)	⊕⊕⊕⊕ HIGH	HR 0.45 (0.29 to 0.70)	Study population 74 per 1000	 40 fewer per 1000 (52 fewer to 22 fewer)
Adverse events 67.7 months	1116 (1 RCT)	⊕⊕⊕⊖ MODERATE ³	-	The adverse events reported were: device infection, serious device infection, bleeding requiring intervention, and pneumothorax. An analysis of 1116 participants showed that ICD when added to optimal medical therapy probably increases the risk of device infection and pneumothorax (RR 1.36, 95% CI 0.77 to 2.40 and RR 1.85, 95% CI 0.69 to 4.96, respectively). Implantable cardioverter-defibrillator probably slightly increases the risk for serious device infection (RR 1.16, 95% CI 0.56 to 2.42) and may increase the risk for bleeding requiring intervention (RR 3.02, 95% CI 0.12 to 74.01).	

Noncardiovascular mortality (RR) ^b	1781 (4 RCTs)	⊕⊕⊕⊖ MODERATE ²	RR 1.17 (0.81 to 1.68)	Study population	
22.8 to 67.6 months				57 per 1000	10 more per 1000 (11 fewer to 39 more)
Health-related quality of life	561 (2 RCTs)	⊕⊕⊕⊖ MODERATE ^{4, 5}	-	The health-related quality of life of 561 participants extracted from 2 studies was evaluated using 4 different scales. None of the studies showed a statistically significant difference in score between the ICD and the control group.	
24 to 29 months					
First ICD-related hospitalisation - not reported	-	-	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **ICD:** implantable cardioverter-defibrillator; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aBoth HR and RR were calculated. However, we reported HR since it is more informative for this outcome, pooling more participants than RR.

^bBoth HR and RR were calculated. However, we reported RR since it is more informative for this outcome, pooling more participants than HR.

¹One of six studies appears to be at high risk of bias ([COMPANION](#)). However, the weight of this study in the meta-analysis was only 5.3%. We conducted a sensitivity analysis excluding this study, and the results did not change significantly.

²We downgraded the certainty of evidence by one level to moderate due to imprecision. The confidence interval of the absolute effect includes values suggesting clinically significant benefit and values suggesting no effect.

³We downgraded the certainty of evidence by one level to moderate due to imprecision. The confidence interval of effect estimate has a very wide range and includes values suggesting clinically significant benefit and values suggesting no effect.

⁴Clinical (population, intervention and control) and methodological (study design and quality) heterogeneity across the two studies was low.

⁵We downgraded the certainty of evidence by one level to moderate due to serious risk of bias. Lack of blinding could affect a subjective outcome.

BACKGROUND

Description of the condition

Heart failure is a clinical syndrome characterised by an impaired systemic delivery of blood, whereby the heart fails to pump enough blood to meet the body's metabolic demand (McMurray 2012). Ischaemic heart failure is caused by myocardial ischaemia due to an underlying coronary artery disease (Ho 1993). Various potential causes leading to non-ischaemic cardiomyopathy are described in the literature, which are classified into four main categories: dilated cardiomyopathy (idiopathic, viral illness, alcoholism, etc.), hypertrophic cardiomyopathy (genetic factors and hypertension), restrictive cardiomyopathy (amyloidosis, sarcoidosis, haemochromatosis, etc.), and arrhythmogenic right ventricular dysplasia (Wu 2007). Dilated cardiomyopathy is characterised by systolic dysfunction leading to a reduced left ventricular ejection fraction (LVEF) (Daughenbaugh 2007). While not all people with dilated cardiomyopathy display signs of heart failure, it is believed that longstanding dilated cardiomyopathy eventually leads to heart failure (McNally 2013; Dass 2015). In fact, people with dilated cardiomyopathy can be either asymptomatic (New York Heart Association (NYHA) class I), or can display signs and symptoms of heart failure (e.g. dyspnoea, fatigue, fluid retention) (NYHA class II-IV depending on severity), in which case they are considered to have non-ischaemic systolic heart failure (Yancy 2013; Ponikowski 2016).

People with cardiomyopathy, whether ischaemic or non-ischaemic, are at increased risk of developing ventricular arrhythmias due to underlying structural and mechanical factors (e.g. increased inward sodium and calcium currents due to myocardial stretch) (Wu 2007). These can range from non-sustained ones, such as premature ventricular beats, to life-threatening ones, such as ventricular fibrillation (VF) that leads to sudden cardiac death (SCD). Sudden cardiac death is defined as a rapid and fatal cardiovascular decompensation in a previously haemodynamically stable patient that happens within one hour, and its risk increases as the LVEF falls below 40% (Mosterd 2001; Yap 2005; Shiga 2009). Sudden cardiac death has long been considered the leading cause of death in people with heart failure (Bardy 2005; Packer 2009). However, a recent study (CERTITUDE) found that progressive heart failure is now the leading cause of death in people on cardiac resynchronisation therapy (CRT) (Marijon 2015). Other studies have also found that mortality due to progressive heart failure and to non-cardiovascular causes were more common than SCD in people with heart failure (Henkel 2008; Pons 2010). Nevertheless, current medical and device therapies are directed towards preventing and terminating arrhythmic events before their progression to fatal VF and SCD (Derfler 2004).

People with heart failure can also present with sudden severe symptoms (acute decompensated heart failure) or with an insidious onset (chronic heart failure). The two conditions are managed differently: acute heart failure therapy is mainly managed pharmacologically (diuretics, vasodilators, etc.), while chronic heart failure is managed through both device and medical therapy (Ponikowski 2016). Since our analysis focuses on device therapy, our target population are people with chronic heart failure.

The burden of heart failure has increased over the past decades. It is estimated that more than 37.7 million people were affected by this disease globally as of 2016 (Ziaeian 2016). The annual

global economic burden of the disease was estimated at USD 108,000 million per annum in 2012: USD 65,000 million in direct costs to healthcare systems and USD 43,000 million in indirect costs (through lost productivity, morbidity, premature mortality, etc.) (Ambrosy 2014). While the discovery of several evidence-based drug and device therapies has improved the outcomes for ambulatory patients with heart failure, postdischarge mortality and readmission rates of hospitalised patients with heart failure have not changed in the past two decades (Ambrosy 2014).

Description of the intervention

Guidelines recommend (primarily Class I recommendations) optimal medical therapy as a first-line treatment for people with heart failure, either with or without device therapy (Ponikowski 2016; Al-Khatib 2017b). Treatment with angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) in addition to a beta-blocker (Class I Level A) is the mainstay for the pharmacological treatment of heart failure with reduced ejection fraction (i.e. LVEF $\leq$ 40%) (Ponikowski 2016; Al-Khatib 2017b). Studies have linked the use of these drugs with decreased morbidity and mortality in people with heart failure (Heran 2012; Chatterjee 2013). If symptoms persist despite treatment with ACE-I and a beta-blocker, a mineralocorticoid receptor antagonist (MRA) is recommended (Class I Level A) to reduce the risk of heart failure hospitalisation and death (Ponikowski 2016; Al-Khatib 2017b). Long-term control of weight, blood pressure, glucose, and lipid levels, and reduction in smoking and alcohol consumption also improves survival and reduces the risk of heart failure in at-risk patients (McMurray 2012).

Implantable cardioverter-defibrillators (ICDs) are devices that deliver electrical energy to the heart during episodes of ventricular arrhythmias, thus ending the life-threatening event and resetting the sinus rhythm. They have been efficacious in reducing mortality in people with tachycardia, fibrillation, and other arrhythmic anomalies (Kuck 2000; Young 2003; Josephson 2004). The very first guidelines that discussed the use of ICD in clinical practice were based on the Antiarrhythmics Versus Implantable Defibrillators (AVID) study, a large, multicentre trial that showed a reduction in all-cause mortality in cardiac arrest survivors (AVID Investigators 1997). Hence, a Class I recommendation was established by the American College of Cardiology (ACC)/American Heart Association (AHA) for the use of ICD in secondary prevention in people meeting enrolment criteria for AVID (Poole 2014). The Canadian Implantable Defibrillator Study (CIDS) and the Cardiac Arrest Study Hamburg (CASH) trials supported the results of this trial. A meta-analysis of secondary prevention trials showed that the use of ICD extended the survival of people with previous ventricular fibrillation or sustained ventricular tachycardia by a mean of 4.4 months over a six-year follow-up period (Connolly 2000). While these studies lacked statistical significance, a pattern of mortality reduction in ICD-treated patients started to emerge (Connolly 2000; Kuck 2000).

It was not until after the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) that guidelines upgraded ICD from a secondary to a primary and secondary prevention therapy (Moss 2002). Furthermore, guidelines were once again updated in 2006 based on the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), assigning Class I recommendation for ICD implantation in people with non-ischaemic heart failure as well. As a matter of fact, the recommendations have not changed since: ICD implantation is a Class I recommendation for

the primary and secondary prevention of SCD due to ventricular tachycardia/ventricular fibrillation (VT/VF) in more severe cases of non-ischaemic heart failure (LVEF $\leq$ 35% despite $\geq$ three months of optimal medical therapy) as an adjunct to medical therapy (Ponikowski 2016; Al-Khatib 2017b).

Patients who meet the criteria for ICD implantation may present with a pre-existing device therapy: a cardiac resynchronisation therapy device (CRT). Cardiac resynchronisation therapy is recommended for symptomatic patients with heart failure in sinus rhythm with a QRS interval duration $\geq$ 150 msec (normal 80 to 100 msec) and left bundle branch block (LBBB) QRS morphology and with LVEF $\leq$ 35% despite optimal medical therapy in order to improve symptoms and reduce morbidity and mortality (Ponikowski 2016; Al-Khatib 2017b). There are other indications for CRT implantation, the strength of which depends on the QRS duration and presence or absence of LBBB. In fact, ICDs can be implanted alone, or in conjunction with a CRT device, in which case the device is upgraded to a CRT defibrillator (CRT-D), maintaining its initial function as a pacemaker, and also taking on a new function, which is that of the defibrillator. In other words, if these patients to whom a pacemaker (CRT-P) was already implanted meet the criteria for ICD implantation, their device is upgraded to a CRT-D.

Implantable cardioverter-defibrillator implantation is associated with a number of adverse events that are both physical (e.g. haemothorax, pneumothorax) and psychological (Rosenqvist 1998). The AVID trial found that participants randomised to the ICD arm of the study had a significant decline in quality of life manifested by a decrease in physical functioning and mental well-being and increased anxiety (Schron 2002). Implantable cardioverter-defibrillators deliver unexpected shocks to patients without warning, which creates distress to them and their family members (Dunbar 1993; Dougherty 1995). Patients live in a state of anxiety, constantly anticipating an electric shock, which results in an elevated incidence of anxiety disorders and panic attacks (Sears 2002). Finally, post-traumatic stress disorder has also been reported to be elevated in people with ICD, who re-experience the events of shock and manifest emotions associated with them (Hamner 1999; Ladwig 2008).

How the intervention might work

Beta-blockers suppress the firing of these action potentials by blocking the sodium and calcium channels. However, ICDs work through a different mechanism: stopping the chain reaction created by the abnormal pacemaker cells. During episodes of arrhythmias, they deliver an electric shock that depolarises all the cardiac cells simultaneously, thereby halting the progression of the arrhythmia. The primary purpose of ICDs is thus to end life-threatening ventricular arrhythmias and reduce SCD or arrhythmia-related complications. We can therefore only expect a relevant reduction in mortality rate in subgroups of patients with heart failure with high incidence of sustained ventricular arrhythmias leading to cardiac arrest if not terminated.

In people with non-ischaemic cardiomyopathy, currents that are abnormally generated in the ventricle can be immediately stopped through the delivery of a therapeutic dose of electric energy from an ICD device.

Why it is important to do this review

Several studies have assessed the efficacy of ICD treatment in people with non-ischaemic cardiomyopathy (NICM), however these studies had conflicting results, with some finding significant improvement in primary outcome (e.g. COMPANION) and others finding no benefit (e.g. CAT and AMIOVIRT trials)

The ACC and European Society of Cardiology (ESC) guidelines for device-based therapy give Class IA recommendation for ICD implantation in people with non-ischaemic heart failure with LVEF $\leq$ 35% (Ponikowski 2016; Al-Khatib 2017b).

The results of a recently published large randomised controlled trial, the DANISH study, appear to be inconsistent with current guidelines and recent systematic reviews, suggesting that ICD use in NICM patients does not reduce the all-cause mortality rate.

While a number of systematic reviews have been published on this topic since the publication of the DANISH results (Golwala 2016; Akel 2017; Akinapelli 2017; Barakat 2017; Kolodziejczak 2017; Luni 2017; Masri 2017; Narayanan 2017; Omar 2017; Romero 2017; Shah 2017; Shun-Shin 2017; Singh 2017; Stavrakis 2017; Turagam 2017; Wolff 2017; Xing 2017; Al-Khatib 2017a; Alba 2018; Beggs 2018), none of them assessed the adverse events of ICD implantation, its impact on quality of life, and associated costs. Hence, the purpose of this Cochrane Review was to systematically assess the benefit and harms of ICD use in people with non-ischaemic cardiomyopathy, and thus provide a framework for future guideline updates.

OBJECTIVES

To evaluate the benefits and harms of using compared to not using ICD for primary prevention in people with non-ischaemic cardiomyopathy receiving optimal medical therapy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered cluster-randomised controlled trials (cluster-RCTs), parallel randomised controlled trials (RCTs), and economic evaluation studies that focused on the primary prevention of SCD in people with non-ischaemic cardiomyopathy published after 1975 in any language. The first ICD was implanted in February 1980 at Johns Hopkins Hospital by Dr Levi Watkins (Mirowski 1980). All RCT and economic evaluation studies were therefore supposedly published after this date. However, we allowed a safety margin of five years (1975). We included studies reported either as full-text or as abstracts, in addition to unpublished studies.

Types of participants

We included all adults (aged 18 years or older) with a diagnosis of chronic non-ischaemic cardiomyopathy due to a left ventricular systolic dysfunction and with ejection fraction $\leq$ 35% (NYHA type I-IV).

Left ventricular dysfunction includes both systolic and diastolic ventricular dysfunctions. The left ventricular systolic dysfunction is defined by an LVEF, whereas the left ventricular diastolic

dysfunction is defined by an abnormal filling of left ventricle accompanied by an elevated filling pressure (Wu 2007).

Many published studies include both ischaemic and non-ischaemic participants. In such situations, we contacted the authors of the studies for data on the non-ischaemic participants. If we could not obtain this information, we extracted data from both ischaemic and non-ischaemic participants when the percentage of participants with ischaemic cardiomyopathy constituted less than 25% of the total population for the following outcomes: adverse events, health-related quality of life, and cost.

Types of interventions

Intervention

The intervention of interest is implantable cardioverter-defibrillator (ICD) or cardiac resynchronisation therapy-defibrillator (CRT-D), in addition to optimal medical therapy.

Control

The control of interest is optimal medical therapy alone for studies with ICD as the intervention, or optimal medical therapy with cardiac resynchronisation therapy-pacemaker (CRT-P) for studies with CRT-D as the intervention.

We included CRT trials that include a defibrillator arm (CRT-D) (intervention group) and a cardiac resynchronisation pacing-only arm (CRT-P) (control group) since the control group (CRT-P) is appropriately balanced for the antiarrhythmic effect of CRTs. We excluded studies that compared CRT-D to ICD since both treatment arms will have ICDs. We also excluded studies that compared CRT-D to no device.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Cardiovascular mortality.
- Sudden cardiac death (SCD).
- Adverse events of using CRT-D or ICD (adverse events included serious device infection, pneumothorax, haemothorax, inappropriate shocks, lead displacement, dissection and tamponade, lead-failure/fracture).

Secondary outcomes

- Non-cardiovascular death.
- Health-related quality of life (measured on any validated scale such as the Chronic Heart Failure Questionnaire (Guyatt 1989), Quality of Life Questionnaire for Severe Heart Failure (Wiklund 1987), the Kansas City Cardiomyopathy Questionnaire (Green 2000), the Left Ventricular Dysfunction questionnaire (O'Leary 2000), and the Minnesota Living with Heart Failure Questionnaire (Rector 1987)).
- Cost-effectiveness (measured by quality-adjusted life-year (QALYs), disability-adjusted life-years (DALYs), life-year saved (LYS)).
- Heart failure hospitalisation.
- First ICD-related hospitalisation.

We included studies with a follow-up time of at least 12 months, since only long-term trials can obtain sufficient and reliable results

for the mortality-related outcomes of interest (e.g. SCD, all-cause mortality). Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion of the review.

Search methods for identification of studies

Electronic searches

We searched the following bibliographic databases on 10 October 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 9 of 12, 2018).
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid, 1946 to 9 October 2018).
- Embase (Ovid, 1980 to 2018 week 41).
- Web of Science Core Collection (Thomson Reuters, 1900 to 10 October 2018).

We adapted the search strategy developed for MEDLINE (Ovid) for use in the other databases (Appendix 1). We applied the Cochrane sensitivity-maximising RCT filter to MEDLINE (Ovid) and adaptations of it to the other databases except CENTRAL (Lefebvre 2011).

We also searched the following clinical trial registries for ongoing or unpublished trials on 12 October 2018.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).
- ISRCTN registry (www.isrctn.com/).

We used the following keywords when searching the clinical trials registers: non-ischaemic cardiomyopathy, implantable cardioverter defibrillator, implantable defibrillator and ICD.

We searched all databases starting 1975, as the first ICD was implanted in February 1980 at Johns Hopkins Hospital by Dr Levi Watkins, therefore all RCTs were likely to be published after this date (Mirowski 1980). However, we allowed a five-year safety margin by searching from 1975. We then set a weekly search alert for MEDLINE to capture subsequent publications. We imposed no restriction on language of publication or publication status.

We conducted a separate search of the NHS Economic Evaluation Database in the Cochrane Library (from 1975 to 31 March 2015) to identify economic evaluation studies. As this database has not been updated since 2015, we also searched MEDLINE (Ovid) and Embase (Ovid) from 2015 to October 2018. We adapted the review search strategy, removing the RCT filter and applying an adaptation of the Centre for Reviews and Dissemination economics evaluation search filter instead to MEDLINE (Ovid) (Appendix 1) (Centre for Reviews and Dissemination).

Finally, we used the European Association for Grey Literature Exploitation (EAGLE) and National Technical Information Service (NTIS) databases (October 2018) to search the grey literature using the following strategy: '(non-ischemic OR non-ischaemic OR nonischemic OR nonischaemic) AND (cardiomyopathy OR heart failure)' (Appendix 1).

We did not perform a separate search for adverse events of interventions used for the treatment of non-ischaemic heart failure. We considered the adverse effects described in the included studies only.

Searching other resources

We checked reference lists of all included studies and any relevant systematic reviews identified for additional references to trials. We also examined any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

Two review authors (ME, JN) screened in duplicate and independently the titles and abstracts of all citations identified by the search for potential eligibility (eligible or unclear eligibility). We retrieved the full texts of citations judged as potentially eligible by at least one of the two review authors. The two review authors (ME, JN) screened in duplicate and independently the full texts for eligibility. Any disagreements were resolved through discussion or with the help of a content expert (MR) when necessary.

We identified and excluded duplicate articles and collated reports that related to the same study. Each study, rather than each report, was the unit of interest in the review. We completed a PRISMA flow diagram to record the selection process. We also completed a 'Characteristics of excluded studies' table to record the reasons for exclusion of the ineligible studies.

Data extraction and management

Two review authors (JN, ME) extracted independently and in duplicate data regarding study characteristics from the included studies. We developed and pilot tested a data collection form for study characteristics and outcome data. Any disagreements were resolved through discussion or with the help of a content expert (MR) when necessary.

We extracted data of the following study characteristics.

- **Methods:** study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
- **Participants:** inclusion and exclusion criteria, number of participants randomised, number of participants lost to follow-up/withdrawn, number of participants analysed, and general characteristics (e.g. age, gender, LVEF, NYHA class, diagnostic criteria).
- **Interventions:** intervention, comparison, concomitant medications, and excluded medications.
- **Outcomes:** primary and secondary outcomes reported, and time points specified.
- **Notes:** funding for trial, reported conflicts of interest of trial authors.

Many published studies included both ischaemic and non-ischaemic participants. In such situations, we contacted the authors of the studies for data on the non-ischaemic participants.

For survival data, we abstracted the log (hazard ratio (HR)) and its variance from trial reports (and when not available, the data

needed to calculate them). The COMPANION study did not report the HR explicitly (COMPANION). We used the indirect and mixed-treatment method to extract the HR with its 95% confidence interval (CI) (Salanti 2012). For dichotomous data, we extracted data needed to calculate the risk ratio (RR). We contacted the study authors for incompletely reported data.

Health-related quality of life data was presented as a continuous variable. We extracted for each scale and at each follow-up time the reported statistic (e.g. mean/median score $\pm$ standard deviation (SD), mean change from baseline and its SD, or per cent difference in means value from baseline and its 95% CI). For cost, we extracted the lifetime cost of each arm of the study and the QALY and the "dollars per life-year saved" (LYS) provided by the studies.

One review author (ME) transferred data into the Review Manager 5 file (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the forest plot with the study reports. A second review author (JN) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (ME, JN) assessed independently and in duplicate the risk of bias for each included study. Any disagreements were resolved by discussion or by consulting a third review author (GI) when necessary.

We assessed risk of bias using the following criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of data collectors and outcome adjudicators.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as low, high, or unclear and provided a quote from the study report, together with a justification for our judgement, in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trial author, we noted this in the 'Risk of bias' table.

When considering treatment effects, we considered the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to its published protocol and have reported any deviations from it in the [Differences between protocol and review](#) section of the review.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RR) and time-to-event data as hazard ratios (HR), with 95% confidence intervals (CIs). When data were available for both RR and HR, we ran analyses for the two effect measures. For continuous data, we had planned to use the mean difference (MD) when pooling data from studies

that used the same tool to assess the outcome of interest, and the standardised mean difference (SMD) when pooling data from studies that used different tools. The only outcome reported as a continuous variable by the included studies was quality of life. Since these studies reported quality of life in different ways (e.g. mean score $\pm$ SD, median, change from baseline) and at different time points, we decided against the pooling of data. We instead extracted relevant data for each scale and at different follow-up times and reported them in a summary table (Table 1).

Unit of analysis issues

Had we identified any cluster-RCTs that did not make adjustments for correlation between cluster participants and that met the inclusion criteria, we would have contacted the corresponding authors of such studies for information about the correlation between participants of the individual clusters.

Dealing with missing data

We attempted to contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data (e.g. when we identified a study as an abstract only). When this was not possible, and we considered that the missing data introduced serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis (Akl 2013; Ebrahim 2013; Ebrahim 2014).

COMPANION suffered from high risk of attrition bias due to missing participant data. We planned to conduct a sensitivity analysis to explore the impact of missing data on the results using worst-case assumption (i.e. all missing participants in the intervention group died and none of the missing participants in control group died). If the sensitivity analysis showed no change in the results, we would conclude that missing data is not associated with an appreciable risk of bias. If there was a significant change in the results, we would move to more plausible and less extreme assumptions (Akl 2013). As we could not extract the number of events for non-ischaemic participants from the study, we could not perform such an analysis. We instead assumed that missing data from COMPANION introduced a serious risk of bias, and we performed a sensitivity analysis excluding this trial to explore how it impacted the overall assessment of our results.

For trials reporting no loss to follow-up for the primary outcome (all-cause mortality in most trials), we considered that there was also no loss to follow-up for other mortality-related outcomes (e.g. cardiovascular mortality, SCD, and non-cardiovascular mortality).

Assessment of heterogeneity

Clinical heterogeneity

We assessed clinical heterogeneity by comparing the population, experimental intervention, and control intervention.

Statistical heterogeneity

We used the standard Chi^2 test value ($P = 0.1$) and a visual analysis of a forest plot to explore statistical heterogeneity in the included trials. Additionally, we used the I^2 statistic to measure heterogeneity among the trials in each analysis. We considered a statistically significant value for the Chi^2 test along with an I^2 statistic value of $\geq 50\%$ as substantial statistical heterogeneity

(Higgins 2011a). In such cases, we explored possible causes of the heterogeneity by prespecified subgroup analysis.

Methodological heterogeneity

We explored methodological heterogeneity by comparing the quality and study design of the included trials.

Assessment of reporting biases

We planned to create and examine a funnel plot to explore possible small-study biases for the primary outcomes if pooling of more than 10 trials was possible. Otherwise, the power of the tests becomes too low to distinguish chance variation from real asymmetry (Higgins 2011a).

Data synthesis

We undertook meta-analyses only where it was meaningful to do so, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense. We pooled the log (HRs) for time-to-event data using a random-effects model, and the generic inverse variance method in Review Manager 5 (RevMan 2014). For dichotomous data, we calculated the RR separately for each study and pooled them using a random-effects model since the studies differed in the mixes of participants and in the implementations of interventions, etc. For outcomes where both HR and RR were calculated, we considered the analysis with the higher number of participants to be more informative and used it in the 'Summary of findings' table and to derive conclusions. When the number of participants was similar, we considered HR to be more informative than RR since it accounts for time and censorship. We presented all results with the corresponding 95% CIs. We explained the calculations of effect estimates for all-cause mortality in Appendix 2. We conducted all analyses according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* and with the statistical components of Review Manager 5 (Higgins 2011a; RevMan 2014). We included outcome measures only if it was the intention of the study to perform the necessary assessments in all included participants (i.e. not an optional outcome or only performed in some centres).

For adverse events, we performed a separate analysis for each reported complication. We reported the number of inappropriate shocks and less serious complications descriptively in the text.

For quality of life, we grouped the scales into three broad categories: quality of life, functional status, and psychological well-being. We were not able to perform a meta-analysis since the outcome was reported differently across studies (one study reporting the mean change from baseline versus another reporting the total score at each follow-up time). We instead extracted the data as described in the [Data extraction and management](#) section, tabulated it in a summary table, and provided a narrative synthesis of the findings. We then counted the number of studies reporting a significant difference in quality of life between intervention and control and those that did not. When we found statistical significance, we checked the minimal clinically important difference (MCID) of the scale involved and compared it to the difference between both groups (ICD and placebo) to judge its clinical significance (Guyatt 2002).

Given that pooling of results was not possible, we summarised the results for costs descriptively.

We reported our findings using the language suggested by Glenton and colleagues, focusing on the size of the effect and its clinical significance in relation to the certainty of the evidence on which the result is based (including the precision of the effect) (see [Appendix 3](#)) ([Glenton 2010](#)).

'Summary of findings' table

We created a GRADE 'Summary of findings' table using the following outcomes: all-cause mortality, cardiovascular mortality, SCD, adverse effects of using CRT-D or ICD, non-cardiovascular death, health-related quality of life, and first ICD-related hospitalisations.

For outcomes where both HR and RR were calculated, we reported the analysis that pooled the highest number of participants. If the number of participants was equal, we reported the HR since it is more informative, accounting for time and censorship.

We assessed the certainty of evidence based on the following factors: study limitations, consistency of effect, imprecision, indirectness, and publication bias ([Balshem 2011](#); [Guyatt 2011a](#); [Guyatt 2011b](#); [Guyatt 2011c](#); [Guyatt 2011d](#); [Guyatt 2011e](#); [Guyatt 2011f](#); [Guyatt 2013a](#); [Guyatt 2013b](#); [Guyatt 2013c](#)). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2011](#); [Higgins 2011b](#)), employing GRADEpro software ([GRADEpro GDT 2015](#)). We justified all decisions to downgrade the certainty of evidence using footnotes and made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses for the primary outcome.

- Mean age (< 65 years versus ≥ 65 years).
- CRT therapy (yes versus no).
- NYHA functional class (NYHA I-II versus III-IV).
- Gender (male versus female).
- Mean baseline LVEF (measured by echocardiography) (LVEF ≥ 25% versus LVEF < 25%).
- Mean heart failure duration (< 18 months versus ≥ 18 months).
- Follow-up duration of studies (< 24 months versus 24 to 36 months versus > 36 months).
- Year of publication of RCT (studies published before or in 2003 versus studies published from 2004 onwards).

The paradigm of heart failure treatment has shifted over time, and the introduction of beta-blockers to the optimal medical therapy regimen is largely due to the publication of large RCTs in the early 2000s that showed reduction in mortality rate with the use of these drugs. Since recruitment of participants in ICD trials usually takes two to three years, we considered 2003 as the relevant time cut-off. We expect trials published after 2004 to have most participants taking beta-blocker, now considered an essential pillar in the treatment of cardiomyopathy (ischaemic and non-ischaemic), but not trials published before 2003. The benefit of ICD therapy might differ depending on the medications included under 'optimal medical therapy'. Hence, we conducted a subgroup analysis based on whether trials were published before or in 2003 versus from 2004 onwards.

We performed a subgroup analysis based on whether the intervention included a CRT or not for the outcome of adverse events, since the presence of a CRT is a potential effect modifier. We attempted to contact the corresponding authors of studies for information about subgroups whenever they were not well defined and data were not available separately. We used the formal test for subgroup interactions in Review Manager 5 ([RevMan 2014](#)).

We performed a post hoc meta-regression analysis on Stata ([Stata 2013](#)) using residual maximum likelihood (REML) to estimate the between-study variance with Knapp-Hartung modification.

Sensitivity analysis

We performed a sensitivity analysis to assess the potential impact of bias by excluding all studies at high risk of bias ([Higgins 2011a](#)). We included only studies at low and unclear risk of bias.

The nature of the intervention makes it difficult to blind participants and healthcare personnel. Some trials that studied the effect of device therapy, though not necessarily ICD, versus pharmacological therapy blinded participants with regard to the treatment received by having the device switched on or switched off ([Young 2003](#)). Also, in some studies that compared CRT-Ds to CRT-Ps, participants were blinded to the type of device received ([Higgins 2003](#)). However, blinding was either not clear or not performed in the RCTs included in this review. Hence, we did not perform a sensitivity analysis that excluded trials with high risk of bias for blinding of participants and personnel for the hard outcomes such as mortality. Trials that had a high risk of bias for any of the other 'Risk of bias' domains (random sequence generation, allocation concealment, blinding of data collectors and outcome adjudicators, incomplete outcome data, selective outcome reporting, and other bias) were excluded from the analysis.

We also planned to perform a sensitivity analysis to assess the potential impact of missing data using recent GRADE guidance ([Guyatt 2017](#)).

The [AMIOVIRT](#) study compared ICD to amiodarone, a Class III antiarrhythmic medication. We thus conducted a sensitivity analysis excluding [AMIOVIRT](#) in order to assess the impact of this study on our results.

For the outcomes of health-related quality of life and adverse events, we had planned to pool data from trials with mixed populations when the percentage of participants with ischaemic cardiomyopathy was less than 25% of the total population. We planned to then perform a sensitivity analysis excluding trials with mixed population. However, as we did not encounter any such trials we did not perform this analysis.

Reaching conclusions

We based our conclusions only on findings from the quantitative and narrative syntheses of included studies. When both HR and RR were reported for an outcome, we derived our conclusions based on the most informative analysis that pooled the most participants. When the number of participants was equal, we used HR since it is more informative, accounting for time and censorship. We avoided making recommendations for practice, and our implications for research suggest priorities for future research and outline what the remaining uncertainties are in the area.

RESULTS

Description of studies

Results of the search

The study flow diagram is depicted in [Figure 1](#). Our searches identified 16,662 records via bibliographic databases, six studies via

clinical trial registries, 310 via economic evaluation databases, and nine via the grey literature. We identified a total of 11,136 unique citations.

Figure 1. Study flow diagram.

Title and abstract screening resulted in 99 potentially relevant studies. Full-text screening of these articles identified 53 reports for six eligible RCTs ([AMIOVIRT](#); [CAT](#); [COMPANION](#); [DANISH](#); [DEFINITE](#); [SCD-HeFT](#)). We did not encounter any cluster-RCTs.

Included studies

We included data from six RCTs in this meta-analysis, the characteristics of which are summarised in the [Characteristics of included studies](#) tables.

Setting

The trials included data from centres in the USA ([AMIOVIRT](#); [COMPANION](#); [DEFINITE](#); [SCD-HeFT](#)), Germany ([CAT](#)), Denmark ([DANISH](#)), Israel ([DEFINITE](#)), Canada, and New Zealand ([SCD-HeFT](#)). There is a gap of nearly 15 years between the time of publication of the first trial, [CAT](#), and the last trial, [DANISH](#). Five of the six trials were published in the early to mid-2000s ([AMIOVIRT](#); [CAT](#); [COMPANION](#); [DEFINITE](#); [SCD-HeFT](#)), however the [DANISH](#) study was published a decade later, in 2016.

Participants

The six trials recruited a total of 3128 participants with non-ischaemic cardiomyopathy. The studies focused on adult patients, and excluded all patients less than 18 years old. The mean age of participants ranged from 52, in [CAT](#), to 68, in [COMPANION](#). The mean LVEF was similar across trials, ranging from 21.4%, in [DEFINITE](#), to 25%, in [DANISH](#). The [SCD-HeFT](#) study did not report the mean LVEF value; the median LVEF was reported and was equal to 25%. All studies included patients with NYHA III. The [COMPANION](#) trial was the only study that included patients with NYHA IV, as well as the only one not to include patients with NYHA II. [AMIOVIRT](#) and [DEFINITE](#) included patients with NYHA I. The number of events among non-ischaemic participants in the experimental and control group was only available in four RCTs ([AMIOVIRT](#); [CAT](#); [DANISH](#); [DEFINITE](#)). We only used the reported HR for the remaining two RCTs ([COMPANION](#); [SCD-HeFT](#)).

Interventions

Of the six included RCTs, five used ICD plus optimal medical therapy as the intervention and optimal medical therapy alone as the control ([AMIOVIRT](#); [CAT](#); [DANISH](#); [DEFINITE](#); [SCD-HeFT](#)), and one used CRT-D as the intervention and CRT-P as the control ([COMPANION](#)). More than half of the participants of the [DANISH](#) study received a CRT (58% in both groups).

Outcomes

The outcome all-cause mortality was studied in all the included trials, and was the primary endpoint in all but one study ([AMIOVIRT](#); [CAT](#); [DANISH](#); [DEFINITE](#); [SCD-HeFT](#)). The primary endpoint of the [COMPANION](#) trial was a composite of death from any cause or hospitalisation from any cause; death from any cause was a secondary endpoint. Other mortality-related outcomes such as SCD and deaths from cardiovascular causes were assessed in the [AMIOVIRT](#), [CAT](#), [COMPANION](#), [DANISH](#), and [DEFINITE](#) trials. For non-mortality related outcomes, the [AMIOVIRT](#), [COMPANION](#), [DEFINITE](#), and [SCD-HeFT](#) trials compared the quality of life of participants from both groups, and the [AMIOVIRT](#), [DEFINITE](#), and [SCD-HeFT](#) studied the cost-effectiveness of the intervention. Although the [DANISH](#) study did not publish data on quality of life, the outcome is nonetheless listed in the methods section, implying that it will be published in future manuscripts.

Only [DANISH](#) and [DEFINITE](#) provided clear definitions of outcomes and details of how they were assessed. The [DEFINITE](#) trial used the definitions set forth in the paper 'Classification of death in antiarrhythmia trials' ([Epstein 1996](#)). [DANISH](#) defined cardiovascular death as death due to heart failure, sudden presumed cardiac death (witnessed and unwitnessed), death due to other cardiovascular causes (e.g. pulmonary embolus, stroke), and presumed cardiovascular death. Sudden presumed cardiac death was defined as death that occurs unexpectedly in a previously stable patient (witnessed and unwitnessed). Non-cardiovascular death was defined as any death not covered by cardiac death or vascular death (e.g. renal failure, pneumonia, sepsis, malignancy, etc.).

The [AMIOVIRT](#) and [SCD-HeFT](#) trials did not define any of the outcomes of interest in this review. The [CAT](#) study only defined cardiovascular mortality as including SCD and non-SCD deaths. The [COMPANION](#) trial only defined adverse events as any undesirable clinical outcome, which included device-related events as well as events related to the participants' general condition.

Trial duration

All trials had a duration of follow-up of at least 12 months for all-cause mortality.

Source of funding

All six trials received industry funding. The [SCD-HeFT](#) study received additional government funding (National Heart, Lung, and Blood Institute and US National Institutes of Health), while the [DANISH](#) study received additional funding from a non-governmental organisation (the Danish Heart Foundation).

Excluded studies

We excluded full-text articles for the following reasons:

- not intervention of interest:
 - * ICD for secondary prevention (6 studies), CRT versus optimal medical therapy (5 studies), CRT-D versus optimal medical therapy (1 study);
- not comparison of interest: right ventricular versus biventricular CRT (2 studies), univentricular pacing versus no pacing (1 study), ICD + CRT versus CRT (3 studies), CRT-on versus CRT-off (5 studies);
- not design of interest: not RCT (11 studies);
- not population of interest: people with ischaemic cardiomyopathy (12 studies) (see [Characteristics of excluded studies](#)).

Risk of bias in included studies

'Risk of bias' judgements are summarised in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AMIOVIRT	?	?	-	+	+	?	+
CAT	+	+	?	+	?	+	+
COMPANION	?	?	-	+	-	+	-
DANISH	+	+	-	+	+	+	+
DEFINITE	?	?	-	+	+	+	+
SCD-HeFT	?	+	?	?	+	+	?

Allocation

The method of sequence generation was adequate for only two studies (CAT; DANISH), and unclear for the remaining four studies (AMIOVIRT; COMPANION; DEFINITE; SCD-HeFT).

Allocation was adequately concealed in three studies (CAT; DANISH; SCD-HeFT). It was unclear whether it was adequately concealed in the remaining three studies (AMIOVIRT; COMPANION; DEFINITE).

Blinding

Blinding of participants and personnel (performance bias)

We judged participants and personnel to be unblinded in four studies (AMIOVIRT; COMPANION; DANISH; DEFINITE); it was unclear whether participants were blinded in the remaining two studies (CAT; SCD-HeFT).

Blinking of outcome assessment (detection bias)

We judged outcome assessors to be blinded in five studies (AMIOVIRT; CAT; COMPANION; DANISH; DEFINITE); it was unclear if outcome assessors were blinded in one study (SCD-HeFT).

Incomplete outcome data

Only one study reported a high attrition rate (COMPANION), and was considered to be at high risk for attrition bias. The risk of attrition bias was unclear for one study that did not report withdrawal rate or missing participant data (CAT). The remaining studies reported no loss to follow-up and were therefore judged as at low risk of bias (AMIOVIRT; DANISH; DEFINITE; SCD-HeFT).

Selective reporting

Five of the six studies had a protocol published prior to the publication of the main paper (CAT; COMPANION; DANISH; DEFINITE; SCD-HeFT), and one study had its protocol published after the publication of the main article (AMIOVIRT). All of the prespecified outcomes in the protocol were reported in either the main paper of each study or in subsequent publications. We judged the AMIOVIRT study to be at unclear risk of reporting bias since a protocol published after the manuscript does not offer any indication of whether or not there was selective reporting.

We did not have access to the protocol of one study (SCD-HeFT), however all the specified outcomes in the methods section of the manuscript were reported.

Other potential sources of bias

One study reported a statistically significant difference in the use of beta-blockers at the time of the last follow-up visit between the intervention and the control groups ($P < 0.001$) (SCD-HeFT). One study excluded people with a history of non-compliance with oral heart failure therapy (COMPANION).

Effects of interventions

See: [Summary of findings for the main comparison ICD plus optimal medical therapy compared to optimal medical therapy alone for people with non-ischaemic cardiomyopathy](#)

We contacted the authors of the COMPANION, DEFINITE, and SCD-HeFT studies for information on study design (e.g. allocation concealment, random sequence generation) and data on participants with non-ischaemic cardiomyopathy (e.g. number of events in each group, HR of mortality-related outcomes). None of the authors were able to provide us with the requested information.

The CAT trial reported the number of deaths from any cause after one year and after long-term follow-up. The remaining outcomes (i.e. SCD, cardiac and non-cardiac deaths) were only reported after one-year follow-up. We conducted the all-cause mortality analysis using the number of events reported after the long-term follow-up. For the SCD, cardiovascular and non-cardiovascular mortality analyses, we used the number of events reported after one-year follow-up.

All-cause mortality

A meta-analysis that pooled hazard ratios (HRs) from the six RCTs with 3128 participants found that the use of ICD in addition to optimal medical therapy compared to optimal medical therapy

alone decreases all-cause mortality (HR 0.78, 95% confidence interval (CI) 0.66 to 0.92; participants = 3128; studies = 6; high-certainty evidence) (see [Analysis 1.1](#); [Summary of findings for the main comparison](#); [Appendix 2](#)) (AMIOVIRT; CAT; COMPANION; DANISH; DEFINITE; SCD-HeFT). An average of 24 patients need to be implanted with an ICD to prevent one additional mortality from any cause (number needed to treat for an additional beneficial outcome (NNTB) = 24). A meta-analysis of the relative risk of only four of the six RCTs including 1781 participants suggested that using ICD in addition to optimal medical therapy probably decreases all-cause mortality rate slightly compared to optimal medical therapy alone (risk ratio (RR) 0.87, 95% CI 0.72 to 1.05; participants = 1781; studies = 4; moderate-certainty evidence) (possibility of both plausible benefit and no effect) (see [Analysis 1.2](#)) (AMIOVIRT; CAT; DANISH; DEFINITE). We downgraded the certainty of evidence to moderate due to imprecision, since the CI of the absolute effect includes values suggesting clinically significant benefit and values suggesting no effect (28 fewer per 1000, 95% CI from 61 fewer to 11 more). We could not retrieve the number of events in the non-ischaemic subgroup from the SCD-HeFT and COMPANION trials. Hence, these trials, which carry a significant weight in the analysis due to their high number of participants, could not be pooled in the RR analysis. Since the number of participants pooled was higher for HR than for RR, we reported HR in the 'Summary of findings' table and based our conclusion on this analysis ([Summary of findings for the main comparison](#)).

The I^2 value, which indicates that the percentage of the variability in effect estimates is due to heterogeneity rather than sampling error (chance), was absent ($I^2 = 0\%$) for the comparison of ICD plus optimal medical therapy versus optimal medical therapy alone. Due to the relatively few trials to permit an accurate assessment, we did not create and examine an inverted funnel plot.

Since the primary meta-analysis found a statistically significant effect (HR 0.78, 95% CI 0.66 to 0.92; participants = 3128; studies = 6; high-certainty evidence), we conducted a sensitivity analysis in which the COMPANION study, which was found to have a high risk of overall bias, was excluded. The results did not change, and the use of ICD in addition to optimal medical therapy was shown to decrease all-cause mortality compared to optimal medical therapy alone (HR 0.79, 95% CI 0.67 to 0.95; participants = 2573; studies = 5; high-certainty evidence) (see [Analysis 1.3](#)).

We could not conduct a sensitivity analysis to explore the impact of missing outcome data. Indeed, four trials reported complete follow-up for all participants (AMIOVIRT; DANISH; DEFINITE; SCD-HeFT). The CAT study did not report missing participant data. Finally, the COMPANION trial suffered from significant attrition rate. However, we derived the effect estimate using the indirect method (see [Appendix 2](#)), and we did not have the number of events in each group to conduct such an analysis.

We conducted a sensitivity analysis excluding AMIOVIRT, since the participants randomised to the control group of this trial received amiodarone, an antiarrhythmic medication. The results did not change, and the use of ICD in addition to medical therapy was shown to decrease all-cause mortality compared to medical therapy alone (HR 0.78, 95% CI 0.65 to 0.92; participants = 3025; studies = 5; high-certainty evidence) (see [Analysis 1.4](#)).

Only the DANISH study reported outcomes for the subgroups age, NYHA functional class, gender, baseline LVEF, CRT, and mean heart

failure duration. We performed a subgroup analysis in the [DEFINITE](#) trial, and the risk ratios of 95% confidence intervals are plotted in Figure 2 of the manuscript, however the numbers are not displayed, and we could not extract the data. We could not pool subgroup data from the [SCD-HeFT](#) and [COMPANION](#) trials since they included both ischaemic and non-ischaemic cardiomyopathy patients.

We conducted the subgroup meta-analyses listed in the [Methods](#) section. The test for subgroup effect was only statistically significant for age ($P = 0.05$, $I^2 = 74.4\%$). Our results suggest that ICD, when added to optimal medical therapy, may decrease the rate of death from any cause in patients who are younger than 65 years of age (HR 0.51, 95% CI 0.29 to 0.91; participants = 348; studies = 1; high-certainty evidence), but probably has little or no effect on patients who are 65 years of age or older (HR 0.98, 95% CI 0.73 to 1.31; participants = 768; studies = 1; moderate-certainty evidence)

(possibility of both plausible benefit and no effect). An average of 10 patients younger than 65 years of age need to be treated with an ICD to prevent one additional death from any cause (NNTB = 10). The remaining tests were not statistically significant (gender: $P = 0.57$, $I^2 = 0\%$; CRT: $P = 0.86$, $I^2 = 0\%$; NYHA class: $P = 0.62$, $I^2 = 0\%$; heart failure duration: $P = 0.77$, $I^2 = 0\%$; LVEF: $P = 0.71$, $I^2 = 0\%$; year of publication of study: $P = 0.84$, $I^2 = 0\%$; mean follow-up time: $P = 0.53$, $I^2 = 0\%$) (see [Analysis 1.5](#); [Analysis 1.6](#); [Analysis 1.7](#); [Analysis 1.8](#); [Analysis 1.9](#); [Analysis 1.10](#); [Analysis 1.11](#); [Analysis 1.12](#)).

We performed a post hoc meta-regression based on the number of patients included per centre per year. The values we used to perform this are reported in [Table 2](#). While there seems to be a tendency for lower beneficial effect of ICD when the inclusion rate is higher, the results were not statistically significant ($P = 0.30$) (see [Figure 4](#)).

Figure 4. Inclusion rate meta-regression.

Cardiovascular mortality

A meta-analysis that pooled the HR from two RCTs with 1219 participants showed that use of ICD plus optimal medical therapy probably decreases cardiovascular mortality compared to optimal medical therapy alone (HR 0.78, 95% CI 0.58 to 1.05; participants = 1219; studies = 2; moderate-certainty evidence) (possibility of both plausible benefit and no effect) (see [Analysis 1.13](#)) ([AMIOVIRT](#); [DANISH](#)). We downgraded the certainty of evidence to moderate due to imprecision, since the CI of the absolute effect

includes values suggesting clinically significant benefit and values suggesting no effect (33 fewer per 1000, 95% CI from 64 fewer to 7 more).

Another meta-analysis that pooled the RR from four RCTs with 1781 participants also showed that the use of ICD in addition to optimal medical therapy probably decreases cardiovascular mortality compared to optimal medical therapy alone (RR 0.75, 95% CI 0.46 to 1.21; participants = 1781; studies = 4; moderate-certainty evidence) (possibility of both plausible benefit and no effect) (see

Analysis 1.14 ([AMIOVIRT](#); [CAT](#); [DANISH](#); [DEFINITE](#)). We downgraded the certainty of evidence to moderate due to imprecision, since the CI of the absolute effect includes values suggesting clinically significant benefit and values suggesting no effect (35 fewer per 1000, 95% CI from 77 fewer to 30 more). Since the number of participants pooled was higher for RR than for HR, we reported RR in the 'Summary of findings' table and based our conclusion on this analysis ([Summary of findings for the main comparison](#)).

The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent low heterogeneity ($I^2 = 39\%$).

Sudden cardiac death

Four studies compared the effect of adding versus not adding ICD to optimal medical therapy on SCD ([AMIOVIRT](#); [CAT](#); [DANISH](#); [DEFINITE](#)). There were no reported sudden cardiac deaths in the ICD and control groups of the [CAT](#) trial. A meta-analysis on the other three trials including data from 1677 participants showed that the use of ICD in addition to optimal medical therapy decreases SCD compared to optimal medical therapy alone (HR 0.45, 95% CI 0.29 to 0.70; participants = 1677; studies = 3; high-certainty evidence) (see [Analysis 1.15](#)). An average of 25 patients need to be treated with an ICD to prevent one additional SCD (NNTB = 25). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) was absent ($I^2 = 0\%$). The certainty of the evidence was high (see [Summary of findings for the main comparison](#)).

Another analysis that pooled the RR of these three trials with the same number of participants ($n = 1677$) also showed that the use of ICD in addition to optimal medical therapy decreases SCD compared to optimal medical therapy alone (RR 0.47, 95% CI 0.30 to 0.73; participants = 1677; studies = 3; high-certainty evidence) (see [Analysis 1.16](#)) ([AMIOVIRT](#); [DANISH](#); [DEFINITE](#)). Since the number of participants pooled was higher for HR than for RR, we reported HR in the 'Summary of findings' table and based our conclusion on this analysis (see [Summary of findings for the main comparison](#)).

Adverse events

The [COMPANION](#) and [DANISH](#) trials included data for adverse events. We did not pool data from the [COMPANION](#) trial since 55% of the participants had ischaemic cardiomyopathy.

The adverse events reported were: device infection, serious device infection, bleeding requiring intervention, and pneumothorax. An analysis of the [DANISH](#) trial including 1116 participants suggested that using ICD in addition to optimal medical therapy probably increases the risk for device infection (RR 1.36, 95% CI 0.77 to 2.40; participants = 1116; studies = 1; moderate-certainty evidence) (possibility of both plausible harm and benefit) and pneumothorax (RR 1.85, 95% CI 0.69 to 4.96; participants = 1116; studies = 1; moderate-certainty evidence) (possibility of both plausible harm and benefit) compared to optimal medical therapy alone (see [Analysis 1.17](#); [Analysis 1.18](#)). We downgraded the certainty of evidence to moderate, since the CI of the absolute effect includes values suggesting clinically significant benefit and values suggesting no effect (device infection: 13 more per 1000, 95% CI from 8 fewer to 50 more; pneumothorax: 9 more per 1000, 95% CI from 3 fewer to 42 more). Results from the analysis also suggest that adding ICD to optimal medical therapy probably slightly increases the risk for serious device infection compared to not adding ICD (RR

1.16, 95% CI 0.56 to 2.42; participants = 1116; studies = 1; moderate-certainty evidence) (possibility of both plausible harm and benefit) (see [Analysis 1.19](#)). We downgraded the certainty of evidence to moderate, since the CI of the absolute effect includes values suggesting clinically significant benefit and values suggesting no effect (4 more per 1000, 95% CI from 10 fewer to 33 more). Finally, adding ICD to optimal medical therapy may increase the risk for bleeding requiring intervention compared to not adding it (RR 3.02, 95% CI 0.12 to 74.01; participants = 1116; studies = 1; low-certainty evidence) (possibility of both plausible harm and benefit) (see [Analysis 1.20](#)). The analysis suffered from very serious imprecision, and the certainty of evidence was downgraded to low since the CI of the effect estimate was very wide.

In the [CAT](#) study, 10 complications occurred in 7 participants: dislocation of electrode and sensing/isolation defect (7), device infection and replacement (2), and perforation (1).

Two studies reported the number of inappropriate shocks in the ICD group: in the [DANISH](#) study, 33 participants (5.9%) had inappropriate shocks, while in the [DEFINITE](#) study, 49 participants had inappropriate shocks. The [AMIOVIRT](#) study did not report the number of inappropriate shocks and adverse events.

Subgroup analysis

We performed a subgroup analysis based on CRT for device infection and serious device infection (see [Analysis 1.21](#); [Analysis 1.22](#)). The test for subgroup effect was only statistically significant for device infection ($P = 0.02$, $I^2 = 0\%$). Our results suggest that using ICD in addition to optimal medical therapy increases the risk for device infection in patients with no CRT compared to not using ICD (RR 6.08, 95% CI 1.38 to 26.86; participants = 471; studies = 1; high-certainty evidence), but probably has little or no effect in patients with a CRT (RR 0.82, 95% CI 0.34 to 1.95; participants = 645; studies = 1; moderate-certainty evidence) (possibility of both plausible harm and benefit). For [DANISH](#), we did not pool pneumothorax and bleeding events in our analysis since we did not know which participants had a CRT and which ones did not.

Non-cardiovascular death

A meta-analysis that pooled the HR of two RCTs with 1219 participants showed that adding ICD to optimal medical therapy probably has little or no effect on non-cardiovascular mortality compared to not adding it (HR 1.11, 95% CI 0.72 to 1.71; participants = 1219; studies = 2; moderate-certainty evidence) (possibility of both plausible benefit and no effect) (see [Analysis 1.23](#)) ([AMIOVIRT](#); [DANISH](#)). We downgraded the certainty of evidence to moderate due to imprecision, since the CI of absolute effect includes values suggesting clinically significant benefit and values suggesting no effect (7 more per 1000, 95% CI from 17 fewer to 42 more).

A meta-analysis that pooled the RR from four RCTs with 1781 participants also showed that the use of ICD in addition to optimal medical therapy probably has little or no effect on non-cardiovascular mortality compared to optimal medical therapy alone (RR 1.17, 95% CI 0.81 to 1.68; participants = 1781; studies = 4; moderate-certainty evidence) (possibility of both plausible benefit and no effect) (see [Analysis 1.24](#)) ([AMIOVIRT](#); [CAT](#); [DANISH](#); [DEFINITE](#)). We downgraded the certainty of evidence to moderate due to imprecision, since the CI of absolute effect includes values suggesting clinically significant benefit and values suggesting no effect (10 more per 1000, 95% CI from 11 fewer to 39 more)

(see [Summary of findings for the main comparison](#)). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) was absent ($I^2 = 0\%$). Since the number of participants pooled was higher for RR than for HR, we reported RR in the 'Summary of findings' table and based our conclusion on this analysis (see [Summary of findings for the main comparison](#)).

Health-related quality of life

Two studies with a total of 561 participants evaluated the health-related quality of life of participants using four different scales: Quality of Well-Being Schedule ($n = 1$), Minnesota Living With Heart Failure Questionnaire (MLHFQ) ($n = 1$), 12-Item Short Form Health Survey (SF-12) ($n = 1$), and State-Trait Anxiety Inventory ($n = 1$) ([Table 1](#)) ([AMIOVIRT](#); [DEFINITE](#)). We did not include data from [COMPANION](#) and [SCD-HeFT](#), since the percentage of participants with ischaemic cardiomyopathy in these trials was more than 25% (55% and 52%, respectively).

There was no difference in quality of life score between the ICD and the control group, suggesting that ICD probably has little or no effect on patient quality of life. We downgraded the certainty of the evidence to moderate due to high risk of bias, since lack of blinding can influence the results of a subjective outcome ([Summary of findings for the main comparison](#)). We did not perform a sensitivity analysis excluding trials with mixed populations (participants with ischaemic cardiomyopathy < 25% of total population), since we did not encounter any such trials.

One study assessed the impact of shocks on quality of life ([DEFINITE](#)). Health-related quality of life scores between shocked and non-shocked participants was not significantly different. However, an analysis of the pre-shock and postshock quality of life of individuals receiving a discharge found a decline in the mental and emotional components of the MLHFQ. These changes represented small changes in the overall score.

Cost-effectiveness

We identified one study that assessed the cost and/or cost-effectiveness of ICD therapy in people with non-ischaemic cardiomyopathy ([AMIOVIRT](#); [SCD-HeFT](#)). The [COMPANION](#) study assessed the cost-effectiveness of ICD therapy in participants with ischaemic and non-ischaemic cardiomyopathy and was thus not included in the analysis.

The [SCD-HeFT](#) study showed that the incremental cost per life-year added for ICD therapy in participants with non-ischaemic cardiomyopathy was USD 32,100 per life-year saved when undiscounted, and USD 38,557 when discounted at 3%. The results were highly sensitive to how long the benefits of ICD persist, with efficiency increasing with longer follow-up time ([SCD-HeFT](#)).

The [AMIOVIRT](#) study showed that the cost of therapy in the ICD group was USD 22,079 +/- USD 22,039, while the cost in the amiodarone group was USD 8879 +/- USD 27,614 in the first year after entry into the study ($P = 0.1$).

Other

None of the included studies assessed the outcomes of heart failure hospitalisation or first ICD-related hospitalisation.

DISCUSSION

Summary of main results

Our findings suggest that the use of ICD therapy in addition to optimal medical treatment decreases all-cause mortality and sudden cardiac deaths compared to optimal medical therapy alone. There is moderate-certainty evidence showing that the use of ICDs in addition to optimal medical therapy probably decreases cardiovascular mortality compared to optimal medical therapy alone.

The results of the [DANISH](#) trial show that there was an age-related effect for ICD therapy. In fact, ICD therapy decreases mortality rate in patients who are younger than 65 years of age, but probably has little or no effect on patients who are 65 years old or more. Unfortunately, there were no sub-analyses allowing confirmation of those results in the remaining trials. The main role of ICD is to decrease mortality by preventing SCD. Older participants were more likely to die of causes other than SCD compared to younger participants, which might be why ICDs have little or no benefit in older participants ([Elming 2017](#)).

Some reviews have chosen to exclude the [COMPANION](#) trial from their analysis due to concomitant CRT in all participants (see [Table 3](#); [Table 4](#)). We are currently living in an era in which CRT is part of the armamentarium used to treat non-ischaemic cardiomyopathy with wide QRS (especially with left bundle branch block morphology) who remain in NYHA functional class II, III, and ambulatory IV despite adequate medical therapy. This trend is mirrored in the [DANISH](#) trial, where more participants than not had a concomitant CRT device (58% of all participants had a CRT). Its use has been shown to improve symptoms and quality of life, and decrease adverse events in patients with heart failure and cardiac dyssynchrony. This is achieved through reverse left ventricular remodelling ([Cleland 2005](#)). The investigators of the [DANISH](#) trial conducted a subgroup analysis to determine whether participants with a CRT would derive different benefits from ICD treatment than participants without a CRT. The test for CRT subgroup effect failed to reach significance for all-cause mortality. This suggests that there is no real effect difference between patients with and without a CRT. We included the [COMPANION](#) trial in the all-cause mortality analysis. Based on the [DANISH](#) trial, it was unlikely that CRT would affect our results. In fact, we performed a sensitivity analysis where we excluded the [COMPANION](#) trial, and the results did not change significantly: using ICDs in addition to optimal medical therapy decreases all-cause mortality compared to optimal medical therapy alone. Furthermore, we performed a subgroup analysis pooling data from the six trials (3128 participants) to determine whether concomitant CRT therapy affected our results. The test of subgroup effect showed no difference in effect between participants with and without a CRT. Finally, other systematic reviews have included the [COMPANION](#) trial. However, in contrast to other reviews which compared CRT-D to optimal medical therapy, we compared CRT-D to CRT-P, thereby properly balancing the effect of CRT in both groups.

Our findings suggest that adding an ICD to optimal medical therapy probably increases the risk of adverse events. In fact, the use of this device probably increases the risk of device infection and pneumothorax compared to no such use. A subgroup analysis showed that ICD, when added to optimal medical therapy in

participants with no previous CRT, increases the risk for device infection, but probably has little or no effect in participants with a previous CRT. We also showed that ICD probably slightly increases the risk of serious device infection. Finally, using ICD in addition to optimal medical therapy may increase the risk of bleeding requiring intervention compared to optimal medical therapy alone, however the evidence supporting this finding was of low certainty since the results suffered from very serious imprecision. Data from a large registry involving 5918 patients and published in 2013 showed that around 1 in 10 patients implanted with any cardiovascular device experienced at least one complication (Kirkfeldt 2014). The improvement of implantation techniques, from thoracotomy in the 1990s to transcatheter procedure today, was associated with a reduction in complication rate (Ezzat 2005). Nevertheless, limitations in current techniques such as subclavian puncture without the use of ultrasound guidance contributes to a higher rate of adverse events in patients undergoing device implantation.

Our results showed that adding ICDs to optimal medical therapy probably has little or no effect on non-cardiovascular mortality compared to not adding them. The evidence supporting this finding was of moderate certainty due to imprecision. This is not surprising given the mechanism by which ICDs work. These high-energy devices were designed to deliver an electric shock that terminates potentially fatal arrhythmic events. Hence, besides reducing arrhythmic deaths, they have no other obvious benefits.

Factors other than mortality rate come into consideration when deciding whether or not to implant a patient with an ICD, notably the quality of life that accompanies device therapy. While an improvement in quality of life was not expected, the risk accompanying ICD therapy such as inappropriate shocks and complications were of concern since they could affect the patient's psychological well-being and the quality of life (Mark 2008). The currently available evidence suggests that adding ICD therapy probably has little or no effect on quality of life when compared to no ICD therapy (see [Summary of findings for the main comparison](#)). The evidence supporting this finding was of moderate certainty, since participants were not blinded to the treatment received, which introduces a serious risk of bias for this subjective outcome. One study showed that while there was no difference in the quality of life of participants who received a shock and those who did not receive a shock, participants who experienced a shock had a deterioration in their emotional and mental well-being (DEFINITE). However, the data were limited due to the lack of blinding of participants to the treatment received.

The lifetime cost of ICD therapy is significantly higher than that of medical therapy. The literature still lacks strong evidence of the cost-effectiveness of ICD therapy. Most RCTs were not designed to assess the cost-effectiveness of ICD intervention, as the majority were performed over a relatively short period of time, and a short follow-up period will not be able to reveal the full benefit of such a high-cost intervention.

We found no studies that looked at heart failure hospitalisation or first ICD-related hospitalisation.

Overall completeness and applicability of evidence

This Cochrane Review includes six RCTs that found that the use of ICDs in addition to optimal medical therapy decreases all-cause mortality and SCD compared to optimal medical therapy alone. The

clinical, statistical, and methodological heterogeneity across the pooled studies was low. Our results showed that ICD in addition to optimal medical therapy probably decreases cardiovascular mortality compared to optimal medical therapy alone.

The mainstay of heart failure treatment has shifted over time, and therapies that are now considered essential in treating heart failure were once considered counterintuitive. This is especially the case of beta-blockers, which were less commonly used in older studies (e.g. CAT; MADIT) compared to newer studies (e.g. DANISH; SCD-HeFT). Medications that have been shown to reduce mortality from heart failure (angiotensin converting enzyme inhibitors, beta-blockers, spironolactone) were used much more in the DANISH study than in any other trial. One could argue that this change in standard of care may explain why the benefit of ICD appears lower in the DANISH compared to older trials.

Our results suggest that ICD therapy probably increases adverse events, and probably has little or no effect on quality of life when compared to no ICD therapy. However, the number of events was low, which lowered the precision of our findings.

Our results are in agreement with the latest American College of Cardiology (ACC) guidelines, which give a Class Ia recommendation for ICD implantation in people with non-ischaemic cardiomyopathy (NYHA II-III and LVEF < 35%) (Al-Khatib 2017b).

Certainty of the evidence

For the comparison of ICD plus optimal medical therapy to optimal medical therapy alone, we judged the certainty of evidence as high for all-cause mortality and sudden cardiac deaths. We downgraded the certainty of evidence to moderate for cardiovascular mortality, non-cardiovascular mortality, and adverse events (pneumothorax and device infection) due to imprecision. We downgraded the certainty of evidence to moderate for health-related quality of life due to serious risk of bias ([Summary of findings for the main comparison](#)).

Potential biases in the review process

The major weakness of this review was the discrepancy between pooled RR and HR analyses for all-cause mortality, which was due to the inconsistent reporting of number of events in the non-ischaemic participants across the studies. We could not pool two large-scale trials in the RR analysis since they did not report the number of events in the non-ischaemic subgroups (COMPANION; SCD-HeFT). Other systematic reviews attempted to compensate for this problem by pooling RR and HR into a single meta-analysis. However, we refrained from pooling time-to-event and dichotomous data as other reviews did.

Our systematic approach to searching, study selection, and data extraction should have minimised the likelihood of missing relevant studies or relevant data.

Agreements and disagreements with other studies or reviews

Our searching strategy, last updated in April 2018, has identified 20 published systematic reviews and meta-analyses on this topic (Golwala 2016; Akel 2017; Akinapelli 2017; Barakat 2017; Kolodziejczak 2017; Luni 2017; Masri 2017; Narayanan 2017; Omar 2017; Romero 2017; Shah 2017; Shun-Shin 2017; Singh 2017;

Stavrakis 2017; Turagam 2017; Wolff 2017; Xing 2017; Al-Khatib 2017a; Alba 2018; Beggs 2018). Despite this large number, there are many differences between these studies and our study. We grouped the major differences under the following four categories: outcomes, analysis, 'Risk of bias' assessment, and certainty of evidence assessment. We have included a table that displays some of the differences between the reviews (see Table 3; Table 4).

Outcomes

Our paper is the only review to include non-mortality-related outcomes. We are the only study to address quality of life, adverse events, and cost-effectiveness. While Wolff and colleagues reported the device-related complications for each trial, they did not conduct an analysis to determine whether participants in the ICD arm were more likely to experience adverse events than participants in the control arm (Wolff 2017).

Analysis

We are the only review to perform both RR and HR meta-analyses for all mortality-related outcomes. While Alba and colleagues conducted a meta-analysis on all-cause mortality using HR and RR, they did not do so for other outcomes (Alba 2018). By employing this approach, we were able to maximise the amount of data that could be used in the analysis. For some outcomes, more data were available for HR than for RR, and more studies could be pooled for HR. For other outcomes, more data were available for RR than for HR, and more studies could be pooled for RR.

The pooled effect estimates for all-cause mortality were consistent among all studies, ranging from 0.75 (95% CI 0.61 to 0.93), Al-Khatib 2017a, to 0.87 (95% CI 0.67 to 0.96), Akeel 2017. To our knowledge, our review is the first to pool the HR from all six identified RCTs for the primary analysis. Other reviews that included the six RCTs pooled HR and RR into a single analysis, especially when the HR was not explicitly displayed (AMIOVIRT; CAT), or when data for the non-ischaemic subgroup could not be extracted from the COMPANION and SCD-HeFT studies. The SCD-HeFT study provides the HR for all-cause mortality in participants with non-ischaemic cardiomyopathy with a 97.5% CI. Only two reviews beside ours converted this number to a 95% CI (Shun-Shin 2017; Al-Khatib 2017a). The remaining reviews pooled the HR and its 97.5% CI with the HRs and their 95% CI of other studies.

Most studies did not include the COMPANION trial. Of the studies that did, five included the HR of CRT-D versus optimal medical therapy (Golwala 2016; Luni 2017; Masri 2017; Stavrakis 2017; Beggs 2018), and two others included the HR of CRT-D versus CRT-P of ischaemic and non-ischaemic participants combined (Singh 2017; Turagam 2017). Only one study included COMPANION and had the same effect estimate as ours, however it is unclear how they derived its 95% CI (Shun-Shin 2017).

'Risk of bias' assessment

Several studies conducted a 'Risk of bias' assessment for the included trials. Our review was the only one to include an explanation for each judgement in the 'Risk of bias' table. Shun-Shin and colleagues provided an elaborate table on risk of bias assessment, however not all judgements were justified (Shun-Shin 2017).

Certainty of evidence assessment

Two studies reported using the GRADE methodology to assess the certainty of the evidence of the outcomes included (Barakat 2017; Alba 2018); only one of these studies included a 'Summary of findings' table (Alba 2018). This study reported using the random-effects model in their meta-analysis. However, the RR (and its 95% CI) of cardiovascular mortality displayed in the 'Summary of findings' table suggests that they conducted their analysis using the fixed-effect model. The CI interval was subsequently narrowed to the point that it did not cross 1, therefore they considered the outcome not to be imprecise and assessed the certainty of evidence as high. We conducted a similar analysis for this outcome using the random-effects model. The 95% CI crossed 1, and we downgraded the certainty of evidence to moderate due to imprecision.

Finally, we used GRADE to assess the certainty of evidence for all outcomes, not only those reported in our 'Summary of findings' table.

We are in the process of drafting a paper that further explores the differences between all the reviews.

AUTHORS' CONCLUSIONS

Implications for practice

Data from randomised controlled trials have demonstrated that the use of implantable cardioverter-defibrillators (ICDs) in addition to medical therapy reduces all-cause mortality and sudden cardiac deaths compared to medical therapy alone. Our review suggests a probable increase in adverse events in participants with ICD compared to no ICD. Adding ICD to optimal medical therapy probably has little or no effect on patient's quality of life. Our findings suggest that ICD should be implemented for primary prevention in people with non-ischaemic cardiomyopathy.

Implications for research

The high number of patients with non-ischaemic cardiomyopathy needed to prevent one sudden cardiac death (25 patients), reinforces the need of finding better ways of risk stratifying patients with non-ischaemic cardiomyopathy, as based on current guidelines, the large majority of these patients (> 90%) will not have their lives saved by the device. Age may be an important variable to be used for this purpose, but the interesting results observed in the DANISH trial need to be confirmed in further trials.

Additional research is required to elucidate the effect of ICD on quality of life and hospitalisation in people with non-ischaemic cardiomyopathy. Further large-scale studies with longer follow-up periods are needed to investigate adverse events associated with ICD implantation and the complications that follow. These trials should also take into consideration the advancements in cardiac therapy as well as in diagnostic modalities that are able to classify participants as low-, moderate-, or high-risk patients.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

AMIOVIRT

Methods	<ul style="list-style-type: none"> Unblinded randomised controlled trial Study conducted at 10 medical centres in the USA, from August 1996 to June 2001. Randomisation was stratified by centre. Study duration: 5 years
Participants	<p>103 participants who:</p> <ul style="list-style-type: none"> 18 years or older; non-ischaemic dilated cardiomyopathy (NIDCM); LVEF $\leq$ 35%; asymptomatic non-sustained VT (3 consecutive ventricular premature depolarisations with a rate 100 beats/min, lasting 30 s and not associated with symptoms of cerebral hypoperfusion); NYHA class I to III. <p>Exclusion criteria: syncope, pregnancy, a contraindication to amiodarone or defibrillator therapy, or concomitant therapy with a Class I antiarrhythmic drug.</p> <p>Mean age 59 years, 70% males, mean LVEF 23%, mean duration of NIDCM 3.2 years, NYHA II-III 83%, NSVT 155 beats/min, mean follow-up time 24 months.</p> <p>No participants were lost to follow-up/withdrawn.</p>
Interventions	<p>Intervention: ICD</p> <p>Control: amiodarone (initiated at 800 mg/day and decreased to 400 mg/day after 7 days and to 300 mg/day after 1 year)</p> <p>Co-intervention: optimal medical therapy with ACE inhibitors (85% of participants), beta-blockers (52% of participants), potassium-sparing diuretics (20% of participants)</p>
Outcomes	<p>Participants were followed up from time of enrolment to the time of discontinue (due to inability of the study to demonstrate statistical significance) with mean follow-up time being 24 months.</p> <ul style="list-style-type: none"> Total mortality (primary outcome) SCD Non-SCD death Non-cardiac death Syncope Arrhythmia-free survival (freedom from death, syncope, appropriate ICD therapy, and sustained VT or VF) Quality of life (measured using Quality of Well-Being Schedule and State-Trait Anxiety Inventory) Cost <p>The definition of outcomes was not provided in the paper.</p>
Notes	<ul style="list-style-type: none"> Funding: Guidant

AMIOVIRT (Continued)

- Ethical approval: "Ten centres participated in this trial (see Appendix), and the institutional review boards approved the study protocol"
- Conflict of interest: not reported
- Intention-to-treat analysis: "All analyses were based on intention-to-treat"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported; authors did not mention how randomisation was performed
Allocation concealment (selection bias)	Unclear risk	Not reported; allocation concealment was not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "AMIOVIRT was an unblinded randomised trial..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Each of the three members of the events committee independently evaluated all information... To assure a blinded review, all references to amiodarone or ICD therapy were removed from the reviewed documents"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patients were lost to follow up"
Selective reporting (reporting bias)	Unclear risk	The study protocol was published after the publication of the original manuscript.
Other bias	Low risk	The study appears to be free from other sources of bias.

CAT

Methods	<ul style="list-style-type: none"> • Randomised controlled trial • Participants enrolled at 15 German centres between July 1991 and March 1997 • A blinded interim analysis after the inclusion of 100 participants was done at 1 year of follow-up (pilot phase). • A survival analysis of all participants with at least 1 year of follow-up was performed at the end of the study period.
Participants	<p>104 participants who:</p> <ul style="list-style-type: none"> • between 18 and 70 years of age; • symptomatic DCM for ≤ 9 months; • LVEF $\leq 30\%$ by LV angiography; • NYHA class II or III; • no history of symptomatic bradycardia, VT or VF; • CAD excluded by angiography; • no excessive alcohol consumption; • not listed for heart transplantation at time of presentation. <p>Exclusion criteria:</p>

CAT (Continued)

- Documented cardiac arrest or VT
- Symptoms such as dizziness or syncope that could be related to a ventricular arrhythmia
- Organic heart disease (valvular heart disease, hypertrophic cardiomyopathy, or coronary artery stenosis > 70%)
- Heart transplant expected within 6 months

Mean age 52 years, 78.9% males, mean ejection fraction 24%, NYHA II 65.3%, mean QRS width 108 msec, mean follow-up time 5.5 years

Interventions	Intervention: ICD Control: no intervention Co-intervention: conventional medical therapy (diuretics, ACE inhibitors, digitalis)	
Outcomes	Protocol: participants are to be followed up every 3 months for 2 years. Paper: participants were followed up every 3 months for mean duration of 5.5 years. <ul style="list-style-type: none">• All-cause mortality at 1 year (primary outcome)• All-cause mortality (reported at 1, 2, 3, 4, 5, 6, and 7 years)• Heart transplantation• Cardiac mortality (SCD and non-SCD)• Sustained VT (adequate ICD therapy)• Symptomatic tachyarrhythmias requiring antiarrhythmic treatment The definition of outcomes was not provided in the paper.	
Notes	<ul style="list-style-type: none">• Funding: Guidant• Ethical approval: "The protocol was approved by the institutional review board in Freiburg, Germany, and by the review boards at each clinical center"• Conflict of interest: not reported	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment was performed centrally"
Allocation concealment (selection bias)	Low risk	Quote: "Closed envelopes with the assigned study group were sent to each centre ... envelopes were opened when a patient was enrolled"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "it was decided to perform a blinded interim analysis after the inclusion of 100 patients at 1 year of follow-up (pilot phase)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing participant data not reported
Selective reporting (reporting bias)	Low risk	All prespecified outcomes in the protocol were reported in the trial's paper.

CAT (Continued)

Other bias	Low risk	The study appears to be free from other sources of bias.
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COMPANION

Methods	<ul style="list-style-type: none"> • Open-label, prospective, multicentre, randomised clinical trial • Duration of study: January 2000 to December 2002 • Date of study: 3 years • Country: USA (128 centres involved)
Participants	<p>1520 participants who:</p> <ul style="list-style-type: none"> • 18 years or older; • NYHA class III or IV; • ischaemic or non-ischaemic cardiomyopathy; • LVEF $\leq$ 35%; • QRS $\geq$ 120 msec; • PR interval $\geq$ 150 msec; • sinus rhythm; • no clinical indication for a pacemaker or implantable defibrillator; • heart failure hospitalisation in the preceding 12 months. <p>People with history of non-compliance with oral heart failure therapy were excluded from the study.</p> <p>Withdrawal rates:</p> <ul style="list-style-type: none"> • 26% of participants in the pharmacologic-therapy group • 6% of participants in the pacemaker group • 7% of participants in the pacemaker-defibrillator group <p>For participants who had not reached a primary endpoint at the time of withdrawal:</p> <ul style="list-style-type: none"> • 13% in pharmacologic-therapy group • 2% in pacemaker group • 2% in pacemaker-defibrillator group <p>Mean age 68 years, 69% males, NYHA III 82%, mean LVEF 22%, mean duration of heart failure 3.6 years, mean QRS interval 158 msec, mean LVED dimension 67 mm, mean HR 72 beats/min, mean blood pressure: 112 (systolic)/64 (diastolic), distance walked 6 min 244 m, non-ischaemic cardiomyopathy 41%, diabetes 45%, LBBB 70%, RBBB 9%</p>
Interventions	<p>The number of participants with non-ischaemic cardiomyopathy was 682.</p> <p>Intervention 1 (n = 285): optimal pharmacologic therapy plus cardiac resynchronisation therapy with a pacemaker (CRT-P)</p> <p>Intervention 2 (n = 270): optimal pharmacologic therapy plus cardiac resynchronisation therapy with a pacemaker-defibrillator (CRT-D)</p> <p>Control (n = 127): optimal pharmacologic therapy alone</p> <p>The pharmacologic therapy used in all groups consisted of all of the following, unless 1 or more of the below treatments were not tolerated: diuretics, ACE inhibitors (or ARBs), beta-blockers, and spironolactone. Digoxin and other medications used to treat heart failure could be given at the investigator's discretion.</p>

COMPANION (Continued)

Outcomes

Participants were followed up from the time of enrolment to the time of the completion of the study (median duration of follow-up was 16.5 months in the CRT-P group, and 16.0 months in the CRT-D group).

- Combination of all-cause mortality or all-cause hospitalisation the time of randomisation to the time of the first event (primary outcome)
- All-cause mortality (secondary outcome)
- Death from or hospitalisation for cardiovascular causes
- Adverse events
- 6-minute walk test
- Quality of life
- Changes in NYHA class

The definition of outcomes was not provided in the paper.

Notes

- Funding: Guidant
- Ethical approval: "The research protocol was approved by the IRB of each centre"
- Intention-to-treat analysis: "All analyses were conducted according to the intention to treat"
- Conflict of interest: SK reports having received lecture fees from Guidant. DK, AF, JB, LS, TD, and MB are consultants to and report having received lecture fees from Guidant. BW and DD are under contract to Guidant, and BW holds equity in Guidant. WD is an employee of Guidant, and LD is an employee of Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients, physicians, independent statisticians, and members of the data-management group and the data safety and monitoring board were not blinded to the treatment assignments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "steering committee and endpoint committee were unaware of the treatment assignments"
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Quote: "26% of patients in the pharmacologic-therapy group withdrew, as compared with 6% of those in the pacemaker group and 7% of those in the pacemaker-defibrillator group"</p> <p>"To mitigate the withdrawal rate, the independent statistical group recommended ... a policy of asking patients who had withdrawn ... to consent to the collection of data on vital status and hospitalizations for the duration of the study."</p> <p>"Data on patients who withdrew before reaching an end point who were not known to have died and for whom complete post-withdrawal information on hospitalisation could not be obtained by this means were censored at the time of elective hospitalisation for device implantation or on the date of the last contact. For the mortality endpoint analysis, data on patients whose vital status was not known at the end of the study were censored on the date of the last known contact."</p>

COMPANION (Continued)

Selective reporting (reporting bias)	Low risk	All prespecified outcomes in the protocol of the trial were reported in the original manuscript.
Other bias	High risk	Patients with history of non-compliance with oral heart failure therapy were excluded from the study.

DANISH

Methods	<ul style="list-style-type: none"> Randomised, unblinded, controlled, parallel, 2-group trial Study date: December 2007 to June 2016 Study duration: 8 years Stratification by centre and by whether or not patients were scheduled to receive CRT Study involves 5 centres in Denmark
Participants	<p>1116 participants</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Clinical heart failure Non-ischaemic aetiology Optimal medical treatment NYHA II-III (patients in NYHA class IV could be included if planned for CRT) LVEF $\leq$ 35% NT-proBNP above 200 pg/mL (23.6 pmol/L) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Dysregulated permanent atrial fibrillation (resting heart rate above 100 beats/min) Uncorrected congenital heart disease or valve obstruction, obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, untreated hypothyroidism or hyperthyroidism, adrenal insufficiency, active vasculitis due to collagen vascular disease On the urgent waiting list for a heart transplant (UNOS category 1A or 1B, or equivalent) Recipient of any major organ transplant Receiving or having received cytotoxic or cytostatic chemotherapy and/or radiation therapy for treatment of a malignancy within 6 months before randomisation or clinical evidence of current malignancy, with the following exceptions: basal or squamous cell carcinoma of the skin, cervical intraepithelial neoplasia, prostate cancer (if stable localised disease, with a life expectancy of > 2.5 years in the opinion of the investigator) Known to be HIV positive with an expected survival < 5 years due to HIV Renal failure treated with dialysis Recent (within 3 months) history of alcohol or illicit drug abuse disorder, based on self report Any condition (e.g. psychiatric illness) or situation that, in the investigator's opinion, could put the person at significant risk, confound the study results, or interfere significantly with the person's participation in the study Lack of informed consent <p>No participants were lost to follow-up for the primary outcome.</p> <p>Mean age: 63 years, 72% males, mean duration of heart failure 1.5 years, 58% CRT, 22% atrial fibrillation, 19% diabetes mellitus, mean LVEF 25%, mean QRS 146 msec, 53% NYHA II, 45% NYHA III, 1% NYHA IV</p>
Interventions	<p>Intervention: ICD plus optimal medical therapy</p> <p>Control: optimal medical therapy alone</p>

DANISH (Continued)

Optimal medical therapy consists of ACE inhibitors or angiotensin II receptor blockers, beta-blockers, and an aldosterone antagonist (if tolerated).

Outcomes	<p>All participants were followed up initially for 2 months and every subsequent 6 months thereafter. Participants who received an ICD underwent regular follow-up by the implantation centre (median follow-up time was 67.6 months).</p> <ul style="list-style-type: none"> Time to death from any cause (primary outcome) Time to sudden cardiac death (sudden presumed cardiac death was defined as death that occurs unexpectedly in a previously stable patient (witnessed and unwitnessed)) Time to cardiovascular death (defined as death due to heart failure, sudden presumed cardiac death (witnessed and unwitnessed), death due to other cardiovascular causes (e.g. pulmonary embolus, stroke) and presumed cardiovascular death) Time to resuscitated cardiac arrest or sustained ventricular tachycardia Non-cardiovascular death (defined as any death not covered by cardiac death or vascular death (e.g. renal failure, pneumonia, sepsis, malignancy, etc.)) Change in quality of life from baseline (assessed by the Minnesota Living with Heart Failure Questionnaire)
Notes	<ul style="list-style-type: none"> Funding: Medtronic, St Jude Medical, TrygFonden, and the Danish Heart Foundation Ethical approval: "The trial protocol, available at NEJM.org, was approved by the regional scientific ethics committee for the Capital Region of Denmark and the Danish Data Protection Agency." Intention-to-treat analysis: all analyses were performed in the intention-to-treat population. Conflict of interest: JCN reports speakers' fees from Biotronik and Biosense Webster and consultants' fees from Boston Scientific. NEB reports speakers' fees from Biotronik. AB reports consulting fees/honoraria from Bayer, Boehringer Ingelheim, and Pfizer. JHS reports research grants and personal fees from Medtronic and research grants and personal fees from Biotronik in relation to the submitted work, in addition to research grant from Gilead and personal fees from Boehringer Ingelheim outside the submitted work. CTP has functioned as a consultant for Biotronik.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with the use of a Web-based system, in permuted blocks, with block sizes ranging from 2 to 6 patients, and was stratified according to centre and according to whether patients were scheduled to receive CRT"
Allocation concealment (selection bias)	Low risk	Participants and investigators enrolling participants could not foresee assignment because a web-based allocation system was used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "There is no blinding in this study, but data on the primary outcome (mortality) and secondary clinical outcomes by treatment group is only viewed by the independent Data Monitoring"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Endpoint classification committee, the members of which were unaware of the treatment assignments, used prespecified criteria to adjudicate all prespecified clinical outcomes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patients were lost to follow-up for the primary outcome."
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported in the study.

DANISH (Continued)

Other bias	Low risk	The study appears to be free from other sources of bias.
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DEFINITE

Methods	<ul style="list-style-type: none"> Prospective, randomised, investigator-initiated study based on observational data 48 centres in the USA and Israel Total duration of study: 3 years Date of study: 2002 to 2004
Participants	<p>458 participants who:</p> <ul style="list-style-type: none"> age 21 to 80 years; non-ischaemic cardiomyopathy with LVEF $\leq$ 35% (by any technique including radionuclide angiography, echocardiogram, or left ventriculogram); history of symptomatic heart failure; non-sustained VT (3 to 15 beats) or > 10 PVCs per hour on Holter monitor or telemetry within the past 6 months. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Symptomatic ventricular arrhythmias Unexplained syncope within the past 6 months Prior cardiac arrest, sustained VT/VF NYHA IV at time of enrolment Absence of coronary artery disease Familial cardiomyopathy Permanent pacemaker Electrophysiology study within the past 3 months Patients with imminent cardiac transplantation <p>No reported loss to follow-up.</p> <p>Mean age 58 years, 71.2% males, 22.9% diabetes mellitus, 24.5% atrial fibrillation, mean duration of heart failure 2.83 years, 21.6% NYHA I, 57.4% NYHA II, 21% NYHA III, mean QRS interval 115.1 msec, 19.7% LBBB, 3.3% RBBB, mean LVEF 21.4%, mean distance walked in 6 min 319.4 m, 22.5% NSVT only, 9.4% PVCs only, NSVT and PVCs 68.1%</p>
Interventions	<p>Intervention: single-chamber ICD with standard medical therapy</p> <p>Control: standard medical therapy</p> <p>Standard medical therapy was ACE inhibitors and beta-blockers (carvedilol) unless they were contraindicated. Participants unable to tolerate ACE inhibitors received hydralazine or nitrates or ARBs. Digoxin and diuretics were used when necessary to manage clinical symptoms. Some participants who had symptomatic atrial fibrillation or supraventricular arrhythmias were treated with amiodarone.</p>
Outcomes	<p>The duration of follow-up was computed from the time of randomisation to death for participants who died, and to the date of the 68th death for participants who did not die. All participants were evaluated at 3-month intervals (mean duration of follow-up was 29.0 $\pm$ 14.4 months).</p> <ul style="list-style-type: none"> Death from any cause (primary outcome) Arrhythmic mortality (secondary outcome) Quality of life (assessed at each follow-up visit using SF-12 and Minnesota Living with Heart Failure Questionnaire) Cost-effectiveness

DEFINITE (Continued)

Used the outcomes definition set forth by Epstein and colleagues (Epstein 1996)

Notes	<ul style="list-style-type: none">• Funding: St Jude Medical• Ethical approval: "The trial received annual approval from the institutional review board of North-western University as well as each of the study centers"• Intention-to-treat: "all analyses were conducted according to the intention to treat"• Conflict of interest: not reported	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote : "Randomization was stratified by centre and for the use of anti-arrhythmic drugs for supraventricular arrhythmias"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The blinding process included editing any information from progress notes or laboratory reports that could have identified the presence of an ICD"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The cause of death was determined by an events committee (see the Appendix) whose members were unaware of patients' treatment assignments" "The blinding process included editing any information from progress notes or laboratory reports that could have identified the presence of an ICD"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported loss to follow-up. Participants assigned to the ICD group who were not successfully implanted or who had their ICD explanted were included in the ICD group according to intention-to-treat.
Selective reporting (reporting bias)	Low risk	The study protocol was available, and all of the study's prespecified outcomes (primary and secondary) that were of interest in the review have been reported.
Other bias	Low risk	The study appears to be free from other sources of bias.

SCD-HeFT

Methods	<ul style="list-style-type: none"> Prospective, randomised, primary prevention clinical trial 148 centres in Canada, New Zealand, and the USA Study duration: 5 years Date of study: September 1997 to July 2001
Participants	2521 participants who: <ul style="list-style-type: none"> ≥ 18 years and < 90 years; NYHA II or III; stable congestive heart failure due to ischaemic or non-ischaemic causes; LVEF ≤ 35%; no history of prior VF/VT. <p>Exclusion criteria:</p>

SCD-HeFT (Continued)

- Asymptomatic patients with LV dysfunction
- NYHA Class I or IV
- Class I ICD indications
- Pacemaker indications
- < 18 years of age
- Death expected $\leq$ 1 year due to cardiac causes
- Amiodarone or other antiarrhythmic drugs contraindicated
- Current Class I or II antiarrhythmic drugs
- Unexplained syncope $\leq$ 5 years
- Atrial fibrillation patients requiring catheter ablation or amiodarone
- Myocardial infarction $\leq$ 30 days
- CABG or PTCA $\leq$ 30 days

No participants were lost to follow-up.

Mean age 60 years, 77% males, median ejection fraction 25%, diabetes mellitus 29%, pulmonary disease 17%, hypercholesterolaemia 52%, hypertension 56%, atrial fibrillation 15%, non-sustained VT 23%, syncope 6%, median weight 190 lbs, median systolic BP 118 mmHg, median diastolic BP 70 mmHg, median heart rate 72, 48% non-ischaemic heart failure, 70% NYHA II, mean QRS duration 112 msec, mean follow-up time 45.5 months

Interventions

A total of 1211 participants had non-ischaemic cardiomyopathy.

Intervention 1 (n = 419): amiodarone loading dose of 800 mg daily for 1 week and 400 mg daily for 3 weeks. Participants > 200 lbs received 400 mg daily; participants 150 to 200 lbs received 300 mg daily; and participants < 150 lbs received 200 mg daily.

Intervention 2 (n = 398): single-chamber ICD programmed to shock-only mode

Control (n = 394): placebo (administered in same manner as amiodarone)

Co-intervention: all arms received conventional medical therapy (beta-blocker and an angiotensin-converting-enzyme inhibitor, as well as aldosterone, aspirin, and statins, when appropriate).

Outcomes

Surviving participants were followed at least 2 years (minimum duration of follow-up: 2.5 years, mean follow-up time: 45.5 months) until completion of study.

Primary outcome:

- Overall mortality

Secondary outcomes:

- Mortality: ischaemic vs non-ischaemic
- Mortality: NYHA Class II vs III
- Mortality by subgroups: age, gender, LVEF, MI history, time of MI, QRS width
- Cause-specific death
- Heart failure morbidity and mortality
- Quality of life
- Cost of care and cost-effectiveness

Notes

- Funding: National Heart, Lung, and Blood Institute, US National Institutes of Health, Medtronic, Wyeth-Ayerst Laboratories, and Knoll Pharmaceuticals
- Ethical approval: "The study was approved by the human subjects' committee of each participating institution"
- Intention-to-treat analysis was performed.
- Conflict of interest: Mark D received grant support and speaking fees from Medtronic. Poole J and Packer D received speaking fees from Guidant and Medtronic. Fishbein D received research support

SCD-HeFT (Continued)

from Medtronic and speaking fees from Guidant and Medtronic. Ip J is a consultant for St Jude Medical and holds equity in Guidant.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Allocation was concealed. (ebm.bmj.com/content/ebmed/10/4/109.full.pdf)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Placebo and amiodarone were administered in a double-blind fashion". However, there is no indication of blinding for ICD participants, hence it was probably not done due to the inherent difficulty of blinding such an intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes evaluated by the independent and safety monitoring board.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were followed until October 31, 2003."
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported.
Other bias	Unclear risk	Quote: "There were no significant differences among the three groups, except in the use of beta-blockers at the time of the last follow-up visit ($P<0.001$)."

ACE: angiotensin converting enzyme
ARB: angiotensin receptor blocker
BP: blood pressure
CABG: coronary artery bypass graft
CAD: coronary artery disease
CRT: cardiac resynchronization therapy
DCM: dilated cardiomyopathy
HR: hazard ratio
ICD: implantable cardioverter defibrillator
LBBB: left bundle branch block
LV: left ventricle
LVED: left ventricle end-diastolic
LVEF: left ventricle ejection fraction
MI: myocardial infarction
NSVT: non-sustained ventricular tachycardia
NT-proBNP: N-terminal pro b-type natriuretic peptide
NYHA: New York Heart Association
PTCA: percutaneous transluminal coronary angioplasty
PVC: premature ventricular contractions
RBBB: right bundle branch block
SCD: sudden cardiac death
SF-12: 12-item Short Form Health Survey
UNOS: United Network for Organ Sharing
VF: ventricular fibrillation
VT: ventricular tachycardia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aidelsburger 2008	Not comparison of interest: CRT-D vs optimal medical therapy
Amara 2018	Not design of interest (observational study)
AVID	This study compares the use of ICD vs no ICD for secondary prevention in heart failure patients. We were only interested in primary prevention studies.
Barra 2018	Not study design of interest (systematic review)
Biton 2018	Not population of interest (based on Multicenter Automatic Defibrillator Implantation Trial (MADIT), which randomised participants with ischaemic cardiomyopathy)
BLOCK-HF	Not the intervention of interest (compares biventricular pacing to standard right ventricular pacing)
Bond 2009	Not population of interest: did not specify the type of cardiomyopathy (ischaemic vs non-ischaemic)
Boriani 2012	Not the intervention of interest (cost-effectiveness of CRT)
Bryant 2007	Not study design of interest (systematic review)
Calvert 2010	Not study design of interest (editorial material)
CIDS	Not the population of interest: this study compares ICD vs amiodarone in people resuscitated from VT or VF, hence it compares the use of ICD for secondary prevention. We were only interested in primary prevention studies.
Cowie 2009	Not population of interest: included people with ischaemic and non-ischaemic cardiomyopathy (ischaemic > 25% of total population)
DEBUT	Not the population of interest: this study evaluates the use of ICD for secondary prevention in survivors of SUDS. We were only interested in primary prevention studies.
Doring 2018	Not study design of interest (retrospective study)
Drozd 2017	Not study design of interest (non-randomised, prospective cohort)
Hua 2012	Not a randomised controlled trial, but rather a prospective multicentre trial
IMPROVE-HF	Not a randomised controlled trial, but rather a prospective cohort study
Kutyifa 2014	Not a randomised controlled trial, but rather a retrospective chart review
Kutyifa 2018	Not intervention of interest (compares CRT-D to ICD)
MADIT	Not population of interest: ischaemic heart failure patients. We were interested in ICD use in non-ischaemic heart failure.
MADIT II	Not population of interest: ischaemic heart failure patients. We were interested in ICD use in non-ischaemic heart failure.

Study	Reason for exclusion
Mealing 2016	Not population of interest: ischaemic heart failure patients. We were interested in ICD use in non-ischaemic heart failure.
MIRACLE	Not intervention of interest: compares CRT to optimal medical therapy
PATCH-CHF II	Not comparison of interest: compares active univentricular pacing to no pacing
RAFT	Not intervention of interest: study compares ICD + CRT vs ICD (CRT is the comparator)
REVERSE	Not comparison of interest: participants were assigned to either CRT-on or CRT-off
Ribeiro 2010	Not population of interest: included people with ischaemic and non-ischaemic cardiomyopathy (ischaemic > 25% of total population)
Richardson 2018	Not population of interest: included people with ischaemic and non-ischaemic cardiomyopathy (ischaemic > 25% of total population)
Wang 2018	Not study design of interest (retrospective study)
Yao 2006	Not population of interest: mixed ischaemic and non-ischaemic patients (based on CARE-HF study where ischaemic patients > 25% of total participants)

CARE-HF: Cardiac Resynchronisation in Heart Failure Study

CRT-D: cardiac resynchronisation therapy defibrillator

ICD: implantable cardioverter-defibrillator

SUDS: sudden unexplained death syndrome

VF: ventricular fibrillation

VT: ventricular tachycardia

DATA AND ANALYSES

Comparison 1. ICD plus optimal medical therapy compared to optimal medical therapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (HR) - main analysis	6	3128	Hazard Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
2 All-cause mortality (RR)	4	1781	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.05]
3 All-cause mortality (HR) - 'Risk of bias' sensitivity analysis	5	2573	Hazard Ratio (Random, 95% CI)	0.79 [0.67, 0.95]
4 All-cause mortality (HR) - amiodarone sensitivity analysis	5	3025	Hazard Ratio (Random, 95% CI)	0.78 [0.65, 0.92]
5 All-cause mortality (HR) - subgroup analysis (age)	1	1116	Hazard Ratio (Random, 95% CI)	0.74 [0.40, 1.40]
5.1 Age ≥ 65	1	768	Hazard Ratio (Random, 95% CI)	0.98 [0.73, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Age < 65	1	348	Hazard Ratio (Random, 95% CI)	0.51 [0.29, 0.91]
6 All-cause mortality (HR) - subgroup analysis (gender)	1	1116	Hazard Ratio (Random, 95% CI)	0.88 [0.68, 1.13]
6.1 Male	1	809	Hazard Ratio (Random, 95% CI)	0.85 [0.64, 1.12]
6.2 Female	1	307	Hazard Ratio (Random, 95% CI)	1.03 [0.57, 1.87]
7 All-cause mortality (HR) - subgroup analysis (CRT)	6	3128	Hazard Ratio (Random, 95% CI)	0.78 [0.65, 0.92]
7.1 CRT	2	1200	Hazard Ratio (Random, 95% CI)	0.79 [0.51, 1.23]
7.2 No CRT	5	1928	Hazard Ratio (Random, 95% CI)	0.76 [0.62, 0.93]
8 All-cause mortality (HR) - subgroup analysis (NYHA)	1	1116	Hazard Ratio (Random, 95% CI)	0.86 [0.67, 1.10]
8.1 NYHA I-II	1	597	Hazard Ratio (Random, 95% CI)	0.92 [0.63, 1.35]
8.2 NYHA III-IV	1	519	Hazard Ratio (Random, 95% CI)	0.81 [0.58, 1.13]
9 All-cause mortality (HR) - subgroup analysis (heart failure duration)	1	1115	Hazard Ratio (Random, 95% CI)	0.83 [0.65, 1.06]
9.1 Heart failure duration < 18 months	1	531	Hazard Ratio (Random, 95% CI)	0.88 [0.54, 1.43]
9.2 Heart failure duration ≥ 18 months	1	584	Hazard Ratio (Random, 95% CI)	0.81 [0.61, 1.08]
10 All-cause mortality (HR) - subgroup analysis (LVEF)	1	1116	Hazard Ratio (Random, 95% CI)	0.83 [0.65, 1.07]
10.1 LVEF < 25%	1	506	Hazard Ratio (Random, 95% CI)	0.87 [0.62, 1.22]
10.2 LVEF ≥ 25%	1	610	Hazard Ratio (Random, 95% CI)	0.79 [0.55, 1.14]
11 All-cause mortality (HR) - subgroup analysis (year of publication)	6		Hazard Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
11.1 Year of publication before 2003	2		Hazard Ratio (Random, 95% CI)	0.82 [0.45, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Year of publication 2004 or after	4		Hazard Ratio (Random, 95% CI)	0.77 [0.65, 0.93]
12 All-cause mortality (HR) - subgroup analysis (mean follow-up time)	6		Hazard Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
12.1 Mean follow-up time < 36 months	2		Hazard Ratio (Random, 95% CI)	0.68 [0.44, 1.06]
12.2 Mean follow-up time ≥ 36 months	4		Hazard Ratio (Random, 95% CI)	0.80 [0.66, 0.96]
13 Cardiovascular mortality (HR)	2	1219	Hazard Ratio (Random, 95% CI)	0.78 [0.58, 1.05]
14 Cardiovascular mortality (RR)	4	1781	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.46, 1.21]
15 Sudden cardiac death (HR)	3	1677	Hazard Ratio (Random, 95% CI)	0.45 [0.29, 0.70]
16 Sudden cardiac death (RR)	3	1677	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.30, 0.73]
17 Adverse events - device infection (RR)	1	1116	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.77, 2.40]
18 Adverse events - pneumothorax (RR)	1	1116	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.69, 4.96]
19 Adverse events - serious device infection (RR)	1	1116	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.56, 2.42]
20 Adverse events - bleeding requiring intervention (RR)	1	1116	Risk Ratio (M-H, Random, 95% CI)	3.02 [0.12, 74.01]
21 Device infection subgroup analysis (RR)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 CRT	1	645	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.43, 1.63]
21.2 No CRT	1	471	Risk Ratio (M-H, Random, 95% CI)	6.08 [1.38, 26.86]
22 Serious device infection subgroup analysis (RR)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 CRT	1	645	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.34, 1.95]
22.2 No CRT	1	471	Risk Ratio (M-H, Random, 95% CI)	3.04 [0.62, 14.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Non-cardiovascular mortality (HR)	2	1219	Hazard Ratio (Random, 95% CI)	1.11 [0.72, 1.71]
24 Non-cardiovascular mortality (RR)	4	1781	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.81, 1.68]

Analysis 1.1. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 1 All-cause mortality (HR) - main analysis.

Analysis 1.2. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 2 All-cause mortality (RR).

Analysis 1.3. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 3 All-cause mortality (HR) - 'Risk of bias' sensitivity analysis.

Analysis 1.4. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 4 All-cause mortality (HR) - amiodarone sensitivity analysis.

Analysis 1.5. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 5 All-cause mortality (HR) - subgroup analysis (age).

Analysis 1.6. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 6 All-cause mortality (HR) - subgroup analysis (gender).

Analysis 1.7. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 7 All-cause mortality (HR) - subgroup analysis (CRT).

Analysis 1.8. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 8 All-cause mortality (HR) - subgroup analysis (NYHA).

Analysis 1.9. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 9 All-cause mortality (HR) - subgroup analysis (heart failure duration).

Analysis 1.10. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 10 All-cause mortality (HR) - subgroup analysis (LVEF).

Analysis 1.11. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 11 All-cause mortality (HR) - subgroup analysis (year of publication).

Analysis 1.12. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 12 All-cause mortality (HR) - subgroup analysis (mean follow-up time).

Analysis 1.13. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 13 Cardiovascular mortality (HR).

Analysis 1.14. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 14 Cardiovascular mortality (RR).

Analysis 1.15. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 15 Sudden cardiac death (HR).

Analysis 1.16. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 16 Sudden cardiac death (RR).

Analysis 1.17. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 17 Adverse events - device infection (RR).

Analysis 1.18. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 18 Adverse events - pneumothorax (RR).

Analysis 1.19. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 19 Adverse events - serious device infection (RR).

Analysis 1.20. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 20 Adverse events - bleeding requiring intervention (RR).

Analysis 1.21. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 21 Device infection subgroup analysis (RR).

Analysis 1.22. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 22 Serious device infection subgroup analysis (RR).

Analysis 1.23. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 23 Non-cardiovascular mortality (HR).

Analysis 1.24. Comparison 1 ICD plus optimal medical therapy compared to optimal medical therapy alone, Outcome 24 Non-cardiovascular mortality (RR).

ADDITIONAL TABLES

Table 1. Health-related quality of life

Study	Questionnaire		Total number of participants	Measure	Baseline score	Score/change at 3 months	Score/change at 6 months	Score/change at 12 months	Score/change at 30 months	Notes
AMIOVIRT	Quality of Well-Being Schedule		103	Baseline vs 1 year (mean ± SD)	Amiodarone: 70 ± 17 ICD: 67 ± 15	N/A	N/A	Amio-darone: 70 ± 22 ICD: 74 ± 19	N/A	Scores were not significantly different at 1 year between ICD and amiodarone groups (P > 0.05).
	State-Trait Anxiety Inventory				Amiodarone: 79 ± 21 ICD: 75 ± 25			Amio-darone: 67 ± 20 ICD: 61 ± 17		
DEFINITE	MLHFQ	Physical	458	Change in quality of life (mean ± SD per month)	Placebo: 20 ± 12 ICD: 20 ± 12	Placebo: -0.7 ± 0.1/month ICD: -0.8 ± 0.1/month	N/A	Placebo: 0.7 ± 0.3/year ICD: 0.6 ± 0.2/year		No significant difference in long-term MLHFQ scores between ICD and control groups
		Emotional			Placebo: 10 ± 8 ICD: 11 ± 8			Placebo: -1.6 ± 0.2/month ICD: -1.5 ± 0.2/month		
	SF-12	Physical (PCS)			Placebo: 38 ± 10 ICD: 37 ± 11	Placebo: +1.0 ± 0.2/month ICD: +1.2 ± 0.2/month		Placebo: -0.4 ± 0.3/year ICD: -0.2 ± 0.2/year	No significant difference in long-term PCS scores between ICD and placebo groups	
		Mental (MCS)			Placebo: 47 ± 11 ICD: 45 ± 11	Placebo: 0.3 ± 0.2/month ICD: 1.0 ± 0.2/month		Placebo: -1.8 ± 0.3/year ICD: -0.7 ± 0.3/year P = 0.89	No significant difference in long-term MCS scores between ICD and placebo groups (P = 0.89)	

Abbreviations: ICD: implantable cardioverter-defibrillator; MCS: mental component summary; MLHFQ: Minnesota Living With Heart Failure Questionnaire; N/A: not available; PCS: physical component summary; SD: standard deviation; SF-12: 12-item Short Form Health Survey

¹95% confidence intervals for difference in mean values for continuous variables.

Table 2. Values used for inclusion rate meta-regression

Study	Start year	End year	Duration	Country	Number of participants	Number of centres	Number of patients included per hospital per year
AMIOVIRT	1996	2001	4 years 10 months	USA	103	10	2.13
CAT	1991	1997	5 years 9 months	Germany	104	15	1.21
COMPANION	2000	2002	3 years	USA	555	128	1.45
DANISH	2007	2016	8 years 7 months	Denmark	1116	5	26
DEFINITE	2002	2004	3 years	USA/Israel	458	48	3.18
SCD-HeFT	1997	2001	3 years 10 months	Canada/New Zealand/USA	792	148	1.40

Table 3. Comparison of reviews

		Our study	Akel 2017	Akinapelli 2017	Alba 2018	Al-Khatib 2017a	Barakat 2017	Beggs 2018	Golwala 2016	Kołodziejczak 2017	Luni 2017										
Out-comes	All-cause mortality	Yes	0.78 (0.66, 0.92)	Yes	0.8 (0.67, 0.96)	Yes	0.88 (0.73, 1.07)	Yes	0.78 (0.66, 0.92)	Yes	0.75 (0.61, 0.93)	Yes	0.79 (0.64, 0.93)	Yes	0.76 (0.65, 0.91)	Yes	0.77 (0.64, 0.91)	Yes	0.81 (0.72, 0.91)	Yes	0.76 (0.64, 0.91)
	Cardiovascular mortality	Yes	0.80 (0.47, 1.35)	No		Yes	0.66 (0.42, 1.03)	Yes	0.77 (0.60, 0.98)	No		No		No		No		Yes	0.80 (0.40, 1.59)	No	
	Sudden cardiac death	Yes	0.45 (0.29, 0.70)	Yes	0.51 (0.34, 0.76)	Yes	0.47 (0.30, 0.73)	Yes	0.45 (0.29, 0.70)	No		Yes	0.47 (0.30, 0.73)	No		No		Yes	0.44 (0.17, 1.12)	No	
	Non-cardiovascular mortality	Yes	1.17 (0.81, 1.68)	No		No		No		No		No		No		No		Yes	1.08 (0.58, 2.02)	No	
	Adverse events	Yes		No		No		No		No		No		No		No		No		No	

Table 3. Comparison of reviews (Continued)

	Cost-effectiveness	Yes	No	No	No	No	No	No	No	No	No
Studies included	COMPANION	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes
	CAT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	AMIOVIRT	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
	DANISH	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	DEFINITE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	SCD-HeFT	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Analysis performed (HR/RR/OR)		HR & HR	HR	RR	HR & RR	HR	HR	RR	HR	HR	OR
GRADE		Yes	No	No	Yes	No	Yes	No	No	No	No
Risk of bias		Yes	No	No	Yes	No	Yes	No	No	Yes	Yes
Subgroup analysis		Yes	No	No	No	No	Yes	No	No	Yes	No

HR: hazard ratio; OR: odds ratio; RR: risk ratio

Table 4. Comparison of reviews 2

		Omar 2017		Romero 2017		Shah 2017		Shun-Shin 2017		Singh 2017		Stavrakis 2017		Turagam 2017		Wolff 2017		Xing 2017		Masri 2017		Narayanan 2017	
Out-comes	All-cause mortality	Yes	0.79 (0.66, 0.91)	Yes	0.84 (0.71, 0.99)	Yes	0.832 (0.712, 0.973)	Yes	0.76 (0.64, 0.90)	Yes	0.79 (0.68, 0.91)	Yes	0.78 (0.66, 0.92)	Yes	0.75 (0.64, 0.89)	Yes	0.77 (0.64, 0.93)	Yes	0.83 (0.71, 0.97)	Yes	0.76 (0.64, 0.91)	Yes	0.76 (0.63, 0.91)
	Cardiovascular mortality	No		No		No		No		No		No		No		Yes	0.83 (0.62, 1.12)	No		Yes	0.75 (0.39, 1.44)	No	
	Sudden cardiac death	No		Yes	0.47 (0.30, 0.73)	No		No		No		Yes	0.46 (0.29, 0.71)	Yes	0.45 (0.28, 0.71)	Yes	0.43 (0.27, 0.69)	Yes	0.54 (0.21, 1.37)	Yes	0.40 (0.18, 0.90)	Yes	0.27 (0.15, 0.50)

Table 4. Comparison of reviews 2 (Continued)

Non-cardiovascular mortality	No	No	No	No	No	No	No	No	Yes	1.18 (0.76, 1.83)	No	No	No
Adverse events	No	No	No	No	No	No	No	No	No	No	No	No	No
Cost-effectiveness	No	No	No	No	No	No	No	No	No	No	No	No	No
Studies included	COM-PANION	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	
	CAT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	AMIOVIRT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	
	DANISH	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	DEFINITE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	SCD-HeFT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Analysis performed (HR/RR/OR)		RR	RR	RR	HR	RR	HR	RR	OR	RR	RR	RR	RR
GRADE		No	No	No	No	No	No	No	No	Yes	No	No	No
Risk of bias		No	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No
Subgroup analysis		No	No	No	No	No	Yes	No	No	No	No	Yes	Yes

HR: hazard ratio; OR: odds ratio; RR: risk ratio

APPENDICES

Appendix 1. Search strategies

CENTRAL

- #1 MeSH descriptor: [Defibrillators] explode all trees
- #2 (defibrillat* or defibrilat*)
- #3 (icd or icds)
- #4 (crt or crts)
- #5 electrover*
- #6 ((resynch* or re-synch*) near/3 (therap* or treatment* or device*))
- #7 (cardiover* or (cardio next ver*) or cardioconver* or (cardio next conver*))
- #8 #1 or #2 or #3 or #4 or #5 or #6 or #7
- #9 MeSH descriptor: [Heart Failure] explode all trees
- #10 ((cardi* or heart* or myocard* or ventricular or systolic) near/2 (fail* or incompet* or insufficien* or decomp* or dysfunction* or overload or over-load))
- #11 MeSH descriptor: [Cardiac Output, Low] this term only
- #12 (output near/2 failure)
- #13 (low near/2 (cardiac or heart or myocardia* or systolic or ventricular) near/2 output)
- #14 MeSH descriptor: [Cardiomyopathies] explode all trees
- #15 cardiomyopath*
- #16 myocardiopath*
- #17 (cardio* next myopathy*)
- #18 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
- #19 #8 and #18 Publication Year from 1975 to 2018

MEDLINE

- 1. exp defibrillators/
- 2. (defibrillat* or defibrilat*).mp.
- 3. (icd or icds).mp.
- 4. (crt or crts).mp.
- 5. electrover*.mp.
- 6. ((resynch* or re-synch*) adj3 (therap* or treatment* or device*)).mp.
- 7. (cardiover* or (cardio adj ver*) or cardioconver* or (cardio adj conver*)).mp.
- 8. 1 or 2 or 3 or 4 or 5 or 6 or 7
- 9. exp Heart Failure/
- 10. ((cardi* or heart* or myocard* or ventricular or systolic) adj2 (fail* or incompet* or insufficien* or decomp* or dysfunction* or overload or over-load)).mp.

11. cardiac output, low/
12. (output adj2 failure).mp.
13. (low adj2 (cardiac or heart or myocardia* or systolic or ventricular) adj2 output).mp.
14. exp cardiomyopathies/
15. cardiomyopath*.mp.
16. myocardiopath*.mp.
17. (cardio* adj myopathy*).mp.
18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 8 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp animals/ not humans.sh.
30. 28 not 29
31. 19 and 30
32. limit 31 to yr=1975-current

Embase

1. exp defibrillator/
2. (defibrillat* or defibrilat*).tw.
3. (icd or icds).tw.
4. (crt or crts).tw.
5. electrover*.tw.
6. ((resynch* or re-synch*) adj3 (therap* or treatment* or device*)).tw.
7. (cardiover* or (cardio adj ver*) or cardioconver* or (cardio adj conver*)).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp heart failure/
10. ((cardi* or heart* or myocardi* or ventricular or systolic) adj2 (fail* or incompet* or insufficien* or decomp* or dysfunction* or overload or over-load)).tw.
11. forward heart failure/

12. (output adj2 failure).tw.
13. (low adj2 (cardiac or heart or myocardia* or systolic or ventricular) adj2 output).tw.
14. exp cardiomyopathy/
15. cardiomyopath*.tw.
16. myocardiopath*.tw.
17. (cardio* adj myopathy*).tw.
18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 8 and 18
20. random\$.tw.
21. factorial\$.tw.
22. crossover\$.tw.
23. cross over\$.tw.
24. cross-over\$.tw.
25. placebo\$.tw.
26. (doubl\$ adj blind\$).tw.
27. (singl\$ adj blind\$).tw.
28. assign\$.tw.
29. allocat\$.tw.
30. volunteer\$.tw.
31. crossover procedure/
32. double blind procedure/
33. randomized controlled trial/
34. single blind procedure/
35. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. (animal/ or nonhuman/) not human/
37. 35 not 36
38. 19 and 37

Web of science core collection

- # 1 TS=(defibrillat* or defibrilat*)
- # 2 TS=(icd or icds)
- # 3 TS=(crt or crts)
- # 4 TS=electrover*
- # 5 TS=((resynch* or re-synch*) near/3 (therap* or treatment* or device*))
- # 6 TS=(cardiover* or (cardio near ver*) or cardioconver* or (cardio near conver*))
- # 7 #6 OR #5 OR #4 OR #3 OR #2 OR #1

8 TS=((cardi* or heart* or myocard* or ventricular or systolic) near/2 (fail* or incompet* or insufficien* or decomp* or dysfunction* or overload or over-load))

9 TS=(output near/2 failure)

10 TS=(low near/2 (cardiac or heart or myocardia* or systolic or ventricular) near/2 output)

11 TS=cardiomyopath*

12 TS=myocardiopath*

13 TS=(cardio* near myopathy*)

14 #13 OR #12 OR #11 OR #10 OR #9 OR #8

15 #14 AND #7

16 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

17 #16 AND #15 (Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1975-2018)

ClinicalTrials.gov

Condition or disease: Non-ischemic cardiomyopathy

Other terms: ICD OR implantable cardioverter defibrillator OR implantable defibrillator

Study type: Interventional Studies (Clinical Trials)

ICTRP register

1. Non-ischemic cardiomyopathy

2. ICD OR implantable cardioverter defibrillator OR implantable defibrillator

3. 1 AND 2

ISRCTN

1. Condition: non-ischemic cardiomyopathy

2. Interventions: ICD OR implantable cardioverter defibrillator OR implantable defibrillator

NHS economic evaluation database

1. MeSH DESCRIPTOR Defibrillators EXPLODE ALL TREES

2. (defibrillat* OR defibrilat*)

3. (icd OR icds)

4. (crt OR crts)

5. (electrover*)

6. ((resynch* OR re-synch*) NEAR3 (therap* OR treatment* OR device*))

7. (cardiover* OR (cardio NEAR ver*) OR cardioconver* OR (cardio NEAR conver*))

8. (electric* NEAR2 card* NEAR2 stimulat*)

9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8

10. MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES

11. ((cardi* OR heart* OR myocard* OR ventricular OR systolic) NEAR2 (fail* OR incompet* OR insufficien* OR decomp* OR dysfunction* OR overload OR over-load))

12. MeSH DESCRIPTOR Cardiac Output, Low IN NHSEED

13. (output NEAR2 failure)

14. (low NEAR2 (cardiac OR heart OR myocardia* OR systolic OR ventricular) NEAR2 output)

15. MeSH DESCRIPTOR Cardiomyopathies EXPLODE ALL TREES

16. (cardiomyopath*)

17. (myocardiopath*)

18. (cardio* NEAR myopathy*)

19. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18

20. 9 AND 19

MEDLINE economics evaluation studies

1. exp defibrillators/
2. (defibrillat* or defibrilat*).mp.
3. (icd or icds).mp.
4. (crt or crts).mp.
5. electrover*.mp.
6. ((resynch* or re-synch*) adj3 (therap* or treatment* or device*)).mp.
7. (cardiover* or (cardio adj ver*) or cardioconver* or (cardio adj conver*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Heart Failure/
10. ((cardi* or heart* or myocard* or ventricular or systolic) adj2 (fail* or incompet* or insufficien* or decomp* or dysfunction* or overload or over-load)).mp.
11. cardiac output, low/
12. (output adj2 failure).mp.
13. (low adj2 (cardiac or heart or myocardia* or systolic or ventricular) adj2 output).mp.
14. exp cardiomyopathies/
15. cardiomyopath*.mp.
16. myocardiopath*.mp.
17. (cardio* adj myopathy*).mp.
18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 8 and 18
20. Economics/
21. exp "costs and cost analysis"/
22. exp economics, hospital/
23. Economics, Medical/
24. Economics, Nursing/
25. Economics, Pharmaceutical/
26. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab.
27. (expenditure\$ not energy).ti,ab.
28. value for money.ti,ab.
29. budget\$.ti,ab.
30. or/20-29
31. ((energy or oxygen) adj cost).ti,ab.
32. (metabolic adj cost).ti,ab.

33. ((energy or oxygen) adj expenditure).ti,ab.

34. or/31-33

35. 30 not 34

36. letter.pt.

37. editorial.pt.

38. historical article.pt.

39. or/36-38

40. 35 not 39

41. exp animals/ not humans/

42. 40 not 41

43. 19 and 42

44. limit 43 to yr=2015-current

Embase economic evaluation studies

1. exp defibrillator/

2. (defibrillat* or defibrilat*).tw.

3. (icd or icds).tw.

4. (crt or crts).tw.

5. electrover*.tw.

6. ((resynch* or re-synch*) adj3 (therap* or treatment* or device*)).tw.

7. (cardiover* or (cardio adj ver*) or cardioconver* or (cardio adj conver*)).tw.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp heart failure/

10. ((cardi* or heart* or myocard* or ventricular or systolic) adj2 (fail* or incompet* or insufficien* or decomp* or dysfunction* or overload or over-load)).tw.

11. forward heart failure/

12. (output adj2 failure).tw.

13. (low adj2 (cardiac or heart or myocardia* or systolic or ventricular) adj2 output).tw.

14. exp cardiomyopathy/

15. cardiomyopath*.tw.

16. myocardiopath*.tw.

17. (cardio* adj myopathy*).tw.

18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 8 and 18

20. Health Economics/
21. exp Economic Evaluation/
22. exp Health Care Cost/
23. pharmacoeconomics/
24. 20 or 21 or 22 or 23
25. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab.
26. (expenditure\$ not energy).ti,ab.
27. (value adj2 money).ti,ab.
28. budget\$.ti,ab.
29. 25 or 26 or 27 or 28
30. 24 or 29
31. letter.pt.
32. editorial.pt.
33. note.pt.
34. 31 or 32 or 33
35. 30 not 34
36. (metabolic adj cost).ti,ab.
37. ((energy or oxygen) adj cost).ti,ab.
38. ((energy or oxygen) adj expenditure).ti,ab.
39. 36 or 37 or 38
40. 35 not 39
41. animal/
42. exp animal experiment/
43. nonhuman/
44. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
45. 41 or 42 or 43 or 44
46. exp human/
47. human experiment/
48. 46 or 47
49. 45 not (45 and 48)
50. 40 not 49
51. conference abstract.pt.
52. 50 not 51
53. 19 and 52
54. limit 53 to yr="2015 -Current"

EAGLE and NTIS

(non-ischemic OR non-ischaemic OR nonischemic OR nonischaemic) AND (cardiomyopathy OR heart failure)

Appendix 2. Effect estimates calculations

Table 1. Number of events for cardiovascular mortality in DEFINITE trial:

	ICD group	Standard therapy group
Arrhythmias	3	14
Heart failure	9	11
Other cardiac causes	0	1
Total cardiac deaths	12	26

Number of events for non-cardiovascular mortality in DEFINITE trial:

	ICD group	Standard therapy group	Total
Non-cardiovascular deaths	X	Y	26
Cardiovascular mortality	12	26	38
Unknown cause	2	2	4
Total mortality	28	40	68

$$X = 28 - 12 - 2 = 14$$

Non-cardiovascular mortality in ICD group = 14

$$Y = 40 - 26 - 2 = 12$$

Non-cardiovascular mortality in control group = 12

Table 2. Calculations of effect estimates for all-cause mortality

Bansch 2002 (CAT)	Using Parmar methodology, we calculated HR of all-cause mortality in 7 years. We used the total number randomised in the ICD arm (50) and control arm (54), total number of events in the ICD arm (13) and control arm (17), and the logrank P value of 0.5539 (Parmar 1998).
Bardy 2005 (SCD-HeFT)	Among the non-ischaemic cardiomyopathy patients, the study reported HR of ICD therapy vs placebo = 0.73 with 97.5% CI (0.50 to 1.07). We calculated the 95% CI as follows: 0.73 (0.52 to 1.02).
Bristow 2004 (COMPANION)	Among participants with non-ischaemic cardiomyopathy, the study reported HR of all-cause mortality of pacemaker-defibrillator vs pharmacological therapy = 0.50 with 95% CI (0.29 to 0.88), and HR of all-cause mortality of pacemaker vs pharmacological therapy = 0.91 with 95% CI (0.55 to

(Continued)

1.49). We derived the indirect estimate from both estimates to get the HR of all-cause mortality defibrillator vs pharmacological therapy (Bucher 1997):

HR_a: OMT vs CRT-P = 0.91 (0.55 to 1.49)

HR_b: OMT vs CRT-D = 0.5 (0.29 to 0.88)

HR_c: CRT-P vs CRT-D

- HR_a = 0.91 (0.55 to 1.49)

$$SE_a = [\ln(\text{upper CI}) - \ln(\text{lower CI})] / (2 * 1.96)$$

$$= [\ln(1.49) - \ln(0.55)] / (3.92) = 0.254$$

- HR_b = 0.5 (0.29 to 0.88)

$$SE_b = [\ln(\text{upper CI}) - \ln(\text{lower CI})] / (2 * 1.96)$$

$$= [\ln(0.88) - \ln(0.29)] / (3.92) = 0.283$$

- HR_c = HR_a / HR_b = 0.5 / 0.91 = 0.55

$$SE_c = \sqrt{(SE_a)^2 + (SE_b)^2} = \sqrt{(0.254)^2 + (0.283)^2} = 0.38$$

HR_c = 0.55 (0.26 to 1.16)

Kadish 2004 (DEFINITE)	The study reported HR for death from any cause in the ICD group vs the standard therapy group = 0.65 with 95% CI (0.40 to 1.06)
Kober 2016 (DANISH)	The study reported HR for death from any cause in the ICD group vs the control group = 0.87 with 95% CI (0.68 to 1.12)
Strickberger 2003 (AMIOVIRT)	Using Parmar methodology, we calculated HR of all-cause mortality. We used the total number randomised in ICD arm (51) and amiodarone arm (52), total number of events in ICD arm (6) and amiodarone arm (7), and the logrank P value of 0.8 (Parmar 1998).

Abbreviations: CI: confidence interval; CRT-D: cardiac resynchronisation therapy defibrillator; CRT-P: cardiac resynchronisation therapy pacemaker; HR: hazard ratio; ICD: implantable cardioverter-defibrillator; OMT: optimal medical therapy; SE: standard error

Appendix 3. GRADE approach to describing results

Table 1. Decision of the clinical importance of effect estimate in relation to its size

	Important benefit or harm	Less important benefit or harm	No important benefit/harm
All-cause mortality	RR/HR < 0.8 (20% decrease in mortality) ¹	RR/HR between 0.8 and 0.9 (10% to 20% decrease in mortality)	RR/HR > 0.9 (less than 10% decrease in mortality)
Cardiovascular mortality	RR/HR < 0.8 (20% decrease in mortality)	RR/HR between 0.8 and 0.9 (10% to 20% decrease in mortality)	RR/HR > 0.9 (less than 10% decrease in mortality)
Sudden cardiac deaths	RR/HR < 0.8 (20% decrease in mortality)	RR/HR between 0.8 and 0.9 (10% to 20% decrease in mortality)	RR/HR > 0.9 (less than 10% decrease in mortality)

(Continued)

Adverse events	RR/HR > 1.25 (25% increase) ²	RR/HR between 1.1 and 1.25	RR/HR < 1.1 (less than 10% increase in adverse events)
Non-cardiac deaths	RR/HR < 0.8 (20% decrease in mortality)	RR/HR between 0.8 and 0.9 (10% to 20% decrease in mortality)	RR/HR > 0.9 (less than 10% decrease in mortality)

Abbreviations: HR: hazard ratio; ICD: implantable cardioverter-defibrillator; RR: risk ratio

¹The [SCD-HeFT](#) trial showed that ICD therapy was associated with a decreased risk of death of 23% (RR 0.77). This was implemented in guidelines and is thus considered clinically important.

²This is the cut-off point for the effect size suggested by GRADE. Risk ratio > 1.25 is considered important by GRADE.

Table 2. Relation of the effect size to the certainty of evidence to describe results^a

	Important benefit or harm	Less important benefit or harm	No important benefit/harm or null effect
High	Improves	Improves slightly	Little or no difference in [outcome]
Moderate	Probably improves	Probably improves slightly	Probably little or no difference in [outcome]
Low	May improve	May improve slightly	May have little or no difference in [outcome]
Very low	We are uncertain whether [intervention] improves [outcome].		
No events or rare events	Use comments in 'Summary of findings' table in a plainer language or summarise the results.		
No studies	No studies were found that looked at [outcome].		

^aTable 2 is based on [Glenton 2010](#).

CONTRIBUTIONS OF AUTHORS

Mohamad El Moheb conceived the review.

Johny Nicolas conceived the review.

Assem Khamis helped with data analysis.

Ghida Iskandarani helped draft the protocol.

Elie A Akl helped draft and revise the review.

Marwan Refaat helped draft the review and revised the review.

DECLARATIONS OF INTEREST

Mohamad El Moheb has no conflict of interest to declare.

Johny Nicolas has no conflict of interest to declare.

Assem Khamis has no conflict of interest to declare.

Ghida Iskandarani has no conflict of interest to declare.

Elie A Akl has no conflict of interest to declare.

Marwan Refaat has no conflict of interest to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were several differences between how we conducted the review and how we planned to do so in the protocol ([El Moheb 2017](#)).

We initially planned to analyse dichotomous data as risk ratio only. However, since more studies reported hazard ratio than risk ratio, and since hazard ratio accounts for time and censorship, we decided to perform an analysis for hazard ratio as well.

In addition to the databases listed in the protocol (i.e. CENTRAL, MEDLINE, Embase, Web of Science), we searched the grey literature using the European Association for Grey Literature Exploitation (EAGLE) and National Technical Information Service (NTIS) databases.

In the protocol, we planned to study the cost of ICD treatment compared to optimal medical therapy as a secondary outcome. We revised the Methods section and decided that it would be more valuable to report data on the cost-effectiveness of ICDs.

In the protocol, we planned to include in our analysis only data from participants with non-ischaemic cardiomyopathy. We found little data for the effect of ICD on adverse events and quality of life in participants with non-ischaemic cardiomyopathy. A number of trials that included participants with ischaemic cardiomyopathy and those with non-ischaemic cardiomyopathy reported adverse events and quality of life for the total population (i.e. participants with ischaemic cardiomyopathy and those with non-ischaemic cardiomyopathy), but not for non-ischaemic participants only. Hence, we pooled data from trials with mixed participants when the percentage of participants with ischaemic cardiomyopathy was less than 25%.

We performed a post hoc meta-regression based on the number of participants included per hospital per year to explore sources of heterogeneity.

We made several modifications with respect to the subgroup analyses. First, we only performed a subgroup analysis for all-cause mortality and adverse events, as the necessary data were lacking for the other outcomes. Moreover, we defined the following subgroups for analysis in our protocol: follow-up duration of studies (< 24 months versus 24 to 36 months versus > 36 months), diabetes (yes versus no), mean estimated glomerular filtration rate (< 60 mL/min/1.73 m² versus ≥ 60 mL/min/1.73 m²), and pre-existing pacemaker (yes versus no). Since no study had a follow-up time of less than 24 months, we have redefined the subgroup in the review as follows: follow-up duration of studies < 36 months versus ≥ 36 months. We did not conduct an analysis on the last three subgroups since it would be unlikely for the differences, if detected, to be real rather than due to residual confounding.

INDEX TERMS

Medical Subject Headings (MeSH)

*Defibrillators, Implantable [adverse effects]; Cardiomyopathies [mortality] [*therapy]; Cause of Death; Death, Sudden, Cardiac [*prevention & control]; Heart Failure; Hospitalization; Numbers Needed To Treat; Quality of Life; Randomized Controlled Trials as Topic; Survival Rate

MeSH check words

Humans