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The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review

J Bryant, H Brodin, E Loveman, E Payne and A Clegg

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The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review

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Abstract

The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review

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Objectives: To consider the clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators (ICDs) for arrhythmias.

Data sources: Electronic databases. Manufacturer submissions.

Review methods: A systematic review of the literature on clinical and cost-effectiveness was undertaken. The quality of selected randomised controlled trials (RCTs) was assessed using the Jadad criteria, and of selected systematic reviews using criteria developed by the NHS Centre for Reviews and Dissemination. Economic evaluations were quality assessed by their internal validity (i.e. the methods used) using a series of relevant questions, and external validity (i.e. generalisability of the economic study to the population of interest) by modified standard criteria. The clinical effectiveness and cost-effectiveness of ICDs for arrhythmias were synthesised through a narrative review with full tabulation of results of all included studies.

Results: Eight RCTs, two systematic reviews and a meta-analysis met the inclusion criteria of the review. The RCTs were of variable quality, with most trials having a Jadad quality score of 1/5 or 2/5, owing to the nature of comparing a device with drug therapy and the impossibility of double-blinding. The outcome measure of interest was mortality, which was reported as all-cause mortality in most trials and sudden cardiac death in some trials. Eleven economic evaluations of ICDs for arrhythmias were identified. None were shown to have high internal and external validity. One unpublished study relevant to the UK was identified. The evidence suggests that ICDs reduce mortality in patients with previous ventricular arrest or symptomatic sustained ventricular arrhythmias, in patients who have not had a previous sudden cardiac episode or previous ventricular arrhythmia but have reduced left ventricular function due to coronary artery disease with asymptomatic non-sustained ventricular arrhythmia and sustained tachycardia that could be induced electrophysiologically, and in some patients with severe left ventricular dysfunction (ejection fraction $\leq$ 30%) after myocardial infarction. QoL data are inconsistent but suggest that there is impaired QoL in patients who received numerous shocks from implanted devices. Studies show that ICDs improve survival compared with drug treatment, but with considerably increased cost. Incremental cost per life-year gained ranges from US$27,000 to Can$213,543 and incremental cost per quality-adjusted life-year from US$71,700 to US$558,000 in the published literature.

Conclusions: The use of ICDs in the UK is increasing, but the technology is still under-utilised compared with other developed countries. Extending the current indications to patients with prior myocardial infarction and depressed heart function would impact on costs and service provision. Further research is needed on the risk stratification of patients in whom ICDs are most likely to be clinically and cost-effective. An evaluation of shock frequency on QoL is also required.

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List of abbreviations

AA	anti-arrhythmic
AAD	anti-arrhythmic drug
ACE	angiotensin-converting enzyme
ARR	absolute risk reduction
AVID	Anti-arrhythmic Versus Implantable Defibrillator trial
CABG	coronary artery bypass graft
CABG-Patch	Coronary Artery Bypass Graft Patch trial
CASH	Cardiac Arrest Study Hamburg
CAT	Cardiomyopathy Trial
CI	confidence interval
CIDS	Canadian Implantable Defibrillator Study
CRD	Centre for Reviews and Dissemination
DCM	dilated cardiomyopathy
ECG	electrocardiogram
EF	ejection fraction
EGT	electrophysiological-guided therapy
EP	electrophysiologic
EPS	electrophysiological study
HR	hazard ratio
HRQoL	health-related quality of life
ICD	implantable cardioverter defibrillator
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
LV	left ventricular
LVEF	left ventricular ejection fraction
LYG	life-year gained
MADIT	Multicentre Automatic Defibrillator Implantation Trial
MCS	mental component summary score
MHI	Mental Health Inventory
MI	myocardial infarction
MUSTT	Multicentre Unsustained Tachycardia Trial
NHP	Nottingham Health Profile
NICE	National Institute for Health and Clinical Excellence
NS	not significant
PCC	Patient Concerns Checklist
PCS	physical component summary score
PES	programmed electrical stimulation
PTSD	post-traumatic stress disorder
QALY	quality-adjusted life-year
QoL	quality of life

continued

List of abbreviations *continued*

RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
SCD	sudden cardiac death
SF-36	Short Form with 36 Items
SHTAC	Southampton Health Technology Assessment Centre
VF	ventricular fibrillation
VT	ventricular tachycardia

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Sudden cardiac death occurs in approximately 100,000 people annually in the UK and is usually due to ventricular tachyarrhythmia. Increasing numbers of people are surviving a first episode of ventricular tachyarrhythmia and are at high risk of further episodes. Other risk factors for sudden cardiac death are prior myocardial infarction, coronary heart disease, genetic factors, poor cardiac function and heart failure. Treatments are aimed at either suppressing (anti-arrhythmic drug therapy) or terminating (implantable cardioverter defibrillator) the arrhythmia.

Objectives

This review considers the clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators (ICDs) for arrhythmias.

Methods

A systematic review of the literature on clinical and cost-effectiveness was undertaken.

Data sources

The main electronic databases were searched with English language limits for periods up to November 2003. Bibliographies of related papers were assessed for relevant studies and experts were contacted for advice and peer review and also to identify additional published and unpublished references. Manufacturer submissions to the National Institute for Health and Clinical Excellence were reviewed.

Study selection

Studies were included if they fulfilled the following criteria, which were applied independently by two reviewers, with any disagreements resolved through discussion:

- Intervention was implantable cardioverter defibrillators (ICDs).
- Participants were people at risk of sudden cardiac death due to arrhythmias, in secondary and primary prevention categories.
- Primary outcome was mortality, with quality of life (QoL) as the secondary outcome.
- Designs were systematic reviews of randomised controlled trials (RCTs), or individual RCTs, that assessed the effects of ICDs compared with anti-arrhythmic drug therapy.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. The quality of RCTs was assessed using the Jadad criteria and the quality of systematic reviews was assessed using criteria developed by the NHS Centre for Reviews and Dissemination. The quality of economic evaluations was assessed by their internal validity (i.e. the methods used) using a series of relevant questions, and external validity (i.e. generalisability of the economic study to the population of interest) by modified standard criteria.

Data synthesis

The clinical effectiveness and cost-effectiveness of ICDs for arrhythmias were synthesised through a narrative review with full tabulation of results of all included studies.

Results

Number and quality of studies

Eight RCTs, two systematic reviews and a meta-analysis met the inclusion criteria of the review. The RCTs were of variable quality, with most trials having a Jadad quality score of 1/5 or 2/5, owing to the nature of comparing a device with drug therapy and the impossibility of double-blinding. The outcome measure of interest was mortality, which was reported as all-cause mortality in most trials and sudden cardiac death in some trials.

Eleven economic evaluations of ICDs for arrhythmias were identified. None were shown to have high internal and external validity. One unpublished study relevant to the UK was identified.

Summary of benefits

The evidence suggests that ICDs reduce mortality in patients with previous ventricular arrest or symptomatic sustained ventricular arrhythmias, in patients who have not had a previous sudden cardiac episode or previous ventricular arrhythmia but have reduced left ventricular function due to coronary artery disease with asymptomatic non-sustained ventricular arrhythmia and sustained tachycardia that could be induced electrophysiologically, and in some patients with severe left ventricular dysfunction (ejection fraction <30%) after myocardial infarction.

QoL data are inconsistent but suggest that there is impaired QoL in patients who received numerous shocks from implanted devices.

Costs and cost-effectiveness

Studies show that ICDs improve survival compared with drug treatment, but with considerably increased cost. Incremental cost per life-year gained ranges from US$27,000 to Can$213,543 and incremental cost per quality-adjusted life-year from US$71,700 to US$558,000 in the published literature.

Implications

The use of ICDs in the UK is increasing, but the technology is still under-utilised compared with other developed countries. Extending the current indications to patients with prior myocardial infarction and depressed heart function would impact on costs and service provision.

Research recommendations

Further research is needed on the risk stratification of patients in whom ICDs are most likely to be clinically and cost-effective and the evaluation of shock frequency on QoL.

Chapter 1

Aim of the review

The aim of the review is to provide a systematic review of the clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators (ICDs) compared with anti-arrhythmic (AA) drug therapy in people at risk of sudden cardiac death (SCD) due to arrhythmias.

This is an update of a previous technology assessment review[1] and also includes the assessment of ICDs in additional patient groups.

Chapter 2
Background

Description of underlying health problem

SCD has been defined as death from cardiac causes occurring unexpectedly within 1 hour of onset of symptoms.[2] About 80% of SCD events are due to ventricular tachyarrhythmia[3] (abnormal heart rate in the ventricles), that is, ventricular tachycardia (VT) and ventricular fibrillation (VF). The remaining 20% consists of a number of conditions, including cardiomyopathies (10–15%), other structural heart defects (<5%) and bradycardia (slow heartbeats).

SCD occurs in approximately 75,000–100,000 people annually in the UK and represents the largest proportion of the deaths attributable to coronary heart disease[4,5] (*Table 1*). Approximately 85–90% of SCD is due to a first arrhythmic event, the remaining 10–15% being due to recurrent events. Prevention of SCD is either primary, defined as prevention of a first life-threatening arrhythmic event, or secondary, which refers to the prevention of an additional life-threatening event in survivors of sudden cardiac events or patients with recurrent unstable rhythms.

Survival rates for out-of-hospital sudden cardiac episodes are generally poor (about 3–10% survive in most studies), and those people who survive a first episode of a life-threatening ventricular arrhythmia are at high risk of further episodes. Half will be re-hospitalised within 1 year[6,7] and 40% will die within 2 years.[8] In the UK, fewer than 5% of people survive the initial cardiac arrest (Morgan J, Southampton University Hospitals Trust: personal communication, 2000). However, some survivors live for many years without treatment.

Apart from a previous sudden cardiac event, risk factors for SCD include previous VT, a prior myocardial infarction (MI), coronary artery disease, genetic factors such as family history of SCD and familial cardiac conditions (e.g. long QT syndrome), poor cardiac function [low left ventricular ejection fraction (EF)] and heart failure. Transient risk factors are drugs, electrolyte imbalance and ischaemia.[9,10]

Subgroups of patients with the highest relative risk for SCD (survivors of cardiac arrest, low left ventricular EF) are a small proportion of the total population burden of SCD. Identifying patients at risk of a first life-threatening sudden cardiac event due to arrhythmias that could potentially most benefit from ICD is difficult.[11,12] The risk of SCD in the adult population is 2 per 1000 (see *Table 1*) and identifying people at risk is difficult. Risk stratification using techniques such as electrophysiological study (EPS), signal-averaged ECGs and heart rate variability have been used, although the evidence base for these is often not strong.[10,13]

Current service provision

For patients presenting with tachyarrhythmias with or without symptoms, the main treatments are anti-arrhythmic drug (AAD) therapy and implantation of ICDs (see the next section). Patients with tachyarrhythmias may experience a wide range of outcomes with some being well controlled and others not.

TABLE 1 *Deaths in England and Wales, 2002*

	Males	Females	Total
Coronary heart disease[14]	58,512	47,383	105,893
Sudden cardiac death[a]	29,000–38,000	23,000–31,000	52,000–69,000
Ventricular tachyarrhythmia[a]	21,000–29,000	17,000–23,000	39,000–52,000
Myocardial infarction with depressed heart function[14]	3,820	6,573	10,402
Dilated cardiomyopathy[14]	400	167	567

[a] Data for sudden cardiac death and ventricular tachyarrhythmia have been estimated from the data in the previous technology assessment report and updated data for coronary heart disease.[1]

The majority of patients will be treated with AAD therapy. AADs are divided into Classes I–IV, and the most commonly used for long-term management of ventricular arrhythmias is amiodarone, a Class III drug. Chronic prophylactic AAD therapy is aimed at suppressing the development of arrhythmias in patients at high risk of SCD.

ICDs can actively sense and terminate life-threatening arrhythmias. National Institute for Health and Clinical Excellence (NICE) guidance[15] has recommended that the use of ICDs should be routinely considered for patients in the following categories:

1. Secondary prevention, i.e for patients who present, in the absence of a treatable cause, with:
   (a) Cardiac arrest due to VT or VF.
   (b) Spontaneous sustained VT causing syncope (fainting) or significant haemodynamic compromise.
   (c) Sustained VT without syncope/cardiac arrest, and who have an associated reduction in EF (<35%) but are no worse than Class III of the New York Heart Association classification of heart failure.
2. Primary prevention for patients who do not have a previous SCD episode or previous VT, with:
   (a) A history of previous MI and all of the following: non-sustained VT on Holter (24-hour ECG) monitoring, inducible VT on electrophysiological testing and left ventricular dysfunction with an EF <35% who are no worse than Class III of the New York Heart Association functional classification of heart failure.
   (b) A familial cardiac condition with a high risk of SCD, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia and following repair of tetralogy of Fallot.

Since the first ICD was implanted in 1980,[16] more than 240,000 ICDs have been implanted worldwide. It has been estimated that by 2002, a total of 2321 patients in the UK have received an ICD.[17]

There have been no agreed UK guidelines for use of ICDs. NICE issued guidance on the use of ICDs in the management of arrhythmias in 2000 and there is a national directive to implement this guidance. It was estimated by NICE that following the issuing of its guidance, the level of ICD implantation should rise to 50 devices per million population. Despite a steady increase in implantations, the total rate of implantations in 2002 was 20 per million population, which is still less than half the NICE expected rate.[17] This practice is lower than in other European countries and North America (see *Table 2*). Additionally, there are variations across regions of the UK. Industry estimates for the UK in 2002–03 are 35 implantations per million population.[18]

Provision of electrophysiologists, who are involved with the therapeutic use of electric currents, is also different in North America and the UK. The rate of electrophysiologists to the population in the USA is 1:263,690, in Canada 1:750,000 and in the UK 1:2,800,000.[19] This has implications for the service provision should the rate of implantation of ICD increase in the UK, and adds to the debate on the present service provision for arrhythmia management in the UK and the optimum number of cardiologists who may be required to provide the service.

There is an increasing demand for the service within cardiology, with wider indications including

TABLE 2 *Frequency and number of ICDs implanted (1999–2000 data[17])*

Region/country	Estimated number of ICDs inserted	Approximate ratio of ICDs inserted to population (per million)
USA	50,100	184
Germany	n/a	67
Denmark	239	47
Canada	n/a	35
Italy	n/a	25
Spain	n/a	19
UK	961	15.2
France	n/a	13

n/a, Not available.

people who have a history of MI and depressed heart function (EF ≤0.30) and those with non-ischaemic (dilated) cardiomyopathy (DCM) with arrhythmia at high risk of SCD, making the cost-effectiveness of ICDs a continuing local, regional and national issue.

Description of the interventions

ICDs are battery-powered, fully implantable devices capable of monitoring heart rhythm and delivering an electric shock to restore normal sinus rhythm when a potentially life-threatening arrhythmia is detected. They consist of a pulse generator, similar in size to a pacemaker (30–40 cm^3 in capacity), weigh <80 g and have one or more leads. Early devices were implanted by the trans-thoracic method but current ICDs are placed under the skin in the pectoral region with the leads into the heart inserted via a vein (trans-venous) whilst under local anaesthesia.

The latest devices offer graded responses to a sensed ventricular arrhythmia. Antitachycardia pacing, low-energy synchronised cardioversion and high-energy defibrillation shocks can be delivered via a single transvenous lead, terminating a potentially life-threatening arrhythmia. Antibradycardia systems are now included as standard. Devices last from 5 to 8 years before replacement is required. Device longevity is gradually being extended with advances in technology. Battery life is about 6–7 years depending on the number of shocks delivered. Electrocardiogram storage provides a retrievable record of the onset and termination of the arrhythmia. Further details can be found in Appendix 1.

EPS is sometimes used to identify the origins of an arrhythmia and programmed electrical stimulation (PES) of the heart may be used in stimulating the heart to induce the arrhythmia. EPS may be used prior to implantation of ICD in order to confirm the need for ICD or diagnostic work-up.

Of the antiarrhythmic agents, Class III drugs, such as amiodarone, have been shown to have the best efficacy profile and are very commonly used. A meta-analysis of the effects of amiodarone showed that it reduced total mortality by 10–19% [95% confidence interval (CI): 6 to 30%, $p < 0.01$], in patients at risk for SCD.[20] Amiodarone reduced risk similarly in patients after MI, with heart failure or with clinically evident arrhythmia. In a population of patients post-MI or post-chronic cardiac failure, an additional meta-analysis has shown that prophylactic amiodarone gives a 13% reduction in total mortality (95% CI: 1 to 22%, $p = 0.3$) and a 29% reduction in arrhythmic deaths (95% CI: 15 to 41%, $p = 0.0003$).[21] However, typically around 25% of patients have needed to withdraw from treatment because of side-effects. Most of these are not fatal, but an excess risk of potentially fatal pulmonary toxicity of 1% has been reported.[21]

Chapter 3
Methods

Methods for reviewing effectiveness

The *a priori* methods used for the review are outlined in the research protocol (see Appendix 2). This was sent to members of the advisory group for the review for expert comments (see Acknowledgements, p. 39). Helpful comments were received relating to the general content of the research protocol; there were none that identified specific problems with the methods of the review.

Some changes, additions or points of clarification were made to the methods discussed in the original protocol.

- This systematic review is an update of a systematic review completed in 2000. Searches were conducted for the period since the original systematic review. The original general inclusion/exclusion criteria have been retained, although these have been applied more strictly than in the original systematic review to meet more closely the needs of NICE. All data extraction and quality assessment of studies was done specifically for the current systematic review for consistency of approach. The current systematic review has two additional indications for ICDs: people with a prior MI and advanced ventricular dysfunction, and people with DCM and advanced ventricular dysfunction.
- Since the original systematic review in 2000, the NHS R&D HTA Programme has commissioned a systematic review and economic evaluation to assess the cost-effectiveness of ICDs versus AAD (Project Number 99/23/04),[17] which was to inform the current update technology assessment. The results of this project were unpublished at the time of writing, but the current systematic review team were kindly given access to the pre-final draft report, which has been used as a source of data and for checking completeness of searches.
- The economic evaluation outlined in the research protocol was undertaken. However, the economic model was populated with data from the unpublished report mentioned above, which supplied relevant UK information. As such, this section of the review contains academic-in-confidence data which prevent its publication in advance of the original source. Therefore, this report is limited to the systematic review of the literature on the clinical and cost-effectiveness of ICDs.

Sources of information, including databases searched and key search terms, can be found in Appendix 3.

Studies identified by the search strategy were assessed for inclusion through three stages (*Figure 1* in Appendix 3). Titles and abstracts of studies were screened independently for inclusion by two reviewers. The full text of studies included at this stage were examined for inclusion by two reviewers. Data extraction and quality assessment of included studies were undertaken by one reviewer and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion.

Randomised controlled trials (RCTs) were quality assessed using the Jadad scale[22] (Appendix 4) and systematic reviews were assessed for quality using the criteria developed by the NHS Centre for Reviews and Dissemination (CRD)[23] (see Appendix 5). Published economic evaluations were assessed for internal[24] and external validity.[25]

Chapter 4

Clinical effectiveness

Results

Quantity and quality of research available

Two systematic reviews, one meta-analysis and eight RCTs met the inclusion criteria for the review and are shown in Table 3 and Appendices 6 and 7. Three RCTs were secondary prevention trials and the remainder were primary prevention trials. The systematic reviews and meta-analysis have been published since the original technology assessment report, as have the final results for one secondary prevention trial (CASH[26,27]), for which only preliminary results were available at the time of the original review. Two primary prevention trials (MADIT II[28] and CAT[29]) relate to the additional indications for this update review (for abbreviations, see footnote to *Table 3*).

Secondary research

The systematic review by Ezekowitz and colleagues[30] was of very good quality (CRD quality score 4/5), clearly stating its research question, search strategy, inclusion/exclusion criteria, details of included studies and appropriately summarising the data, but did not provide details of the assessment of the validity of included studies. It included the three secondary prevention trials that were included in the original technology assessment report (AVID,[33] CASH,[27] CIDS[35]) and also assessed the research relating to primary prevention and included five RCTs[28,29,37,39,41] which compare ICD with alternative treatment.

The systematic review by Lee and colleagues[32] was also of very good quality (CRD quality score 4/5), clearly stating its research question, search strategy, inclusion/exclusion criteria, details of included studies and appropriately summarising the data, but did not provide details of the assessment of the validity of included studies. In addition to the three secondary prevention trials included in the systematic review by Ezekowitz (AVID,[33] CASH,[27] CIDS[35]), it also included the trial by Wever (see Appendix 9, excluded studies). It also assessed the research relating to primary prevention and included the five RCTs[28,29,37,39,41] which compare ICD with alternative treatment.

The meta-analysis[31] used pooled raw data from the same three secondary trials presented in the systematic review by Ezekowitz and colleagues[30] and original technology assessment report (that is, AVID,[33] CASH,[27] CIDS[35]).

TABLE 3 *Clinical effectiveness studies*

Study name	Publication date of main results	Subsequent included publications
Systematic reviews/meta-analyses		
Ezekowitz	2003[30]	None
Connolly	2000[31]	None
Lee	2003[32]	None
Secondary prevention trials		
AVID	1997[33]	2002 QoL[34]
Siebels/Kuck (CASH)	2000[26,27]	None
Connolly (CIDS)	2000[35]	2002 QoL[36]
Primary prevention trials		
Moss (MADIT I)	1996[37]	2001 subgroup analysis[38]
CABG-Patch	1997[39]	1999 QoL[40]
Buxton (MUSTT)	1999[41]	None
Moss (MADIT II)	2002[28]	None
Bänsch (CAT)	2002[29]	None

AVID, Anti-arrhythmic Versus Implantable Defibrillator trial; CABG-Patch, Coronary Artery Bypass Graft Patch trial; CASH, Cardiac Arrest Study Hamburg; CAT, Cardiomyopathy Trial; CIDS, Canadian Implantable Defibrillator Study; MADIT, Multicentre Automatic Defibrillator Implications Trial; MUSTT, Multicentre Unsustained Tachycardia Trial; QoL, quality of life.

Primary research

Secondary prevention trials

The three secondary prevention trials (AVID,[33] CASH,[27] CIDS[35]) had quality scores of 1/5, 1/5 and 2/5, respectively, when assessed using the Jadad method. They were described as randomised, but none gave the methods of randomisation used. Blinding was not possible within the context of these studies which involved the comparison of a drug (subject to compliance issues) and a device (whose interaction with the patient is involuntary and requires removal which is more easily measurable than compliance). However, blinding of outcome assessors could have been possible but there was no reporting of this. Only one trial reported details of drop-outs/sample attrition (CIDS[35]).

All three trials were controlled, comparing ICD with either initial amiodarone or sotalol (AVID[33]); amiodarone or metoprolol or propafenone (CASH[27]), where the propafenone arm was discontinued after 11 months; or amiodarone (CIDS[35]). Overall crossover rates were reported for two trials, 20% (AVID[33]) and 6% (CASH[27]). Concomitant therapies occurred in both ICD and control groups in all three trials, and included AAD therapy in the ICD group in AVID and CIDS and the use of amiodarone in AVID. In only one trial did the ICD group not receive either anti-arrhythmic drugs or beta-blockers (CASH[27]).

Participants in all three trials were survivors of cardiac arrest, although details differed slightly between the studies. People with either VF or symptomatic, sustained VT were included in two trials (AVID,[33] CIDS[35]) with left ventricular ejection fraction (LVEF) ≤40% (AVID[33]) and LVEF <35% (CIDS[35]). Additionally patients with unmonitored syncope who were shown to have VT were also included in one trial (CIDS[35]). Only one study included patients with previously documented VF (CASH[27]).

All three trials reported all-cause mortality as the primary outcome. Secondary outcomes included arrhythmic death, cardiac mortality, adverse events, costs and QoL. Mean length of follow-up was 18 months (AVID[33]), 4.5 years (CASH[27]) and 3 years (CIDS[35]). The sample sizes randomised were 1016 (AVID[33]), 191 (CASH[27]) and 659 patients (CIDS[35]).

Primary prevention trials

Five primary prevention trials met the inclusion criteria for the review, three of which were reported in the original technology assessment report (MADIT I,[37] MUSTT[41] and CABG-Patch[39]) and two which have been published since on the additional indications for this update review (MADIT II[37] and CAT[29]). Quality assessment using the Jadad quality assessment score was 2/5 (MADIT I[37] and MADIT II[37]) and 1/5 (MUSTT,[41] CABG-Patch[39] and CAT[29]). All trials were described as randomised but none gave details of the method of randomisation used, none was described as double blind (difficult within the context of a trial comparing a device and drug therapy, as mentioned before) and only two trials (MADIT I[37] and MADIT II[28]) gave details of withdrawals and drop-outs.

All five trials were controlled, with ICDs compared with conventional medical therapy at the discretion of the physician (MADIT I[37] and MADIT II[28]); no anti-arrhythmic therapy or electrophysiologic (EP)-guided AAD therapy (MUSTT[41]); no ICD after CABG (CABG-Patch[39]); and usual care (CAT[29]). Co-interventions were reported in all trials but there were no significant differences between the randomised arms, except in one trial where beta-blocker use was significantly higher in the no-therapy group (MUSTT[41]).

Participants were similar in two trials (MADIT I[37] and MUSTT[41]). They included patients who had had an MI with LVEF ≤35%, non-sustained VT and inducible VT not suppressible by procainamide (MADIT I[37]) and non-sustained VT and LVEF <40% (MUSTT[41]). Patients undergoing CABG surgery with LVEF ≤35% and who had an abnormal signal-averaged ECG were enrolled in one trial (CABG-Patch[39]). Participants in the other two trials met the criteria for the new indications under consideration in this review. People with a history of previous MI and depressed heart function (LVEF ≤30%) were enrolled in one study (MADIT II[28]) and those with DCM and LVEF ≤30%, with no history of VT and VF, in the other (CAT[29]).

The primary end-points were all-cause mortality (MADIT I,[37] CABG Patch,[39] MADIT II[28] and CAT[29]), cardiac arrest or death from arrhythmias (MUSTT[41]) and QoL (CABG-Patch[39]). Average duration of follow-up was 27 months (MADIT I[37]), 31 months (CABG[39]), 20 months (MADIT II[28]) and 22 months (CAT[29]) and median 39 months (MUSTT[41]).

Assessment of effectiveness

Secondary prevention

Tables 4 and *5* summarise the clinical effectiveness of the included secondary prevention studies.

TABLE 4 *Included systematic reviews and meta-analysis of secondary prevention trials*

Trial details	Outcomes	
Study: Ezekowitz *et al.*, 2003[30]	**Fixed effects meta-analysis**	**Summary RR**
Design: systematic review and meta-analysis	SCD	0.50 (95% CI: 0.38 to 0.66)
Intervention: ICD vs placebo; or ICD vs antiarrhythmic therapy	All-cause mortality	0.76 (95% CI: 0.65 to 0.89)
Patients: 4909 patients randomised (numbers for groups not reported)	**Random effects meta-analysis**	**Summary RR**
Age: not reported	All-cause mortality	0.77 (95% CI: 0.65 to 0.91)
Males: not reported		
Quality assessment: CRD 4/5		
Study: Lee *et al.*, 2003[32]	**Meta-analysis**	**Summary RR**
Design: systematic review and meta-analysis	Arrhythmic death	0.50 (95% CI: 0.34 to 0.62)
Intervention: ICD vs medical therapy	All-cause mortality	0.75 (95% CI: 0.64 to 0.87)
Patients: >5000 patients randomised, numbers for groups not reported		
Age: not reported		
Males: not reported		
Quality assessment: CRD 4/5		
Study: Connolly *et al.*, 2000[31]	**Meta-analysis**	**Fixed effects HR**
Design: meta-analysis of individual patient data	Arrhythmic death	0.50 (95% CI: 0.37 to 0.67)
Intervention: ICD vs amiodarone	Total mortality	0.72 (95% CI: 0.60 to 0.87)
Patients: ICD n = 934; Amiodarone n = 932	Survival extended by 4.4 months by ICD over 6 years	
Age: ICD 63±11; amiodarone 64 ± 10 years		
Males (%): ICD 81; amiodarone 82		
Quality assessment: CRD: not applicable		

HR, hazard ratio; RR, relative risk.

Sudden cardiac death

Both systematic reviews[30,32] and the meta-analysis[31] report that ICDs are highly efficacious in preventing SCD. Arrhythmic death was reduced with an RRR of 50% in favour of ICD compared with AAD therapy, that is, the summary RR for SCD was 0.50 (95% CI: 0.38 to 0.66, $p < 0.001$),[30] 0.50 (95% CI: 0.34 to 0.62, $p < 0.00001$)[32] and 0.50 (95% CI: 0.37 to 0.67, $p < 0.001$).[31] The meta-analysis[31] also reported that the results of the three secondary prevention trials are consistent with one another, and that two trials (AVID[33] and CASH[27]) demonstrated a significant reduction in arrhythmic death with ICD, whereas the third trial (CIDS[35]) showed a non-significant benefit.

Crude SCD rates were 13% (95% CI: 7.9 to 19.6) in the ICD arm and 33% (95% CI: 27.2 to 41.1) in the AAD therapy arm in one trial (CASH[27]). This study also reported that survival free of sudden death was significantly higher in patients assigned to ICD than those assigned to drug therapy (HR 0.423, $p = 0.005$). One trial (CIDS[35]) reported a non-significant reduction in the risk of arrhythmic death with ICD therapy compared with amiodarone, from 4.5% to 3.0% per year, with an RR of 32.8% (95% CI: –7.2 to 57.8%; $p = 0.094$).

Total mortality

Both systematic reviews[30,32] and the meta-analysis[31] reported a statistically significant survival benefit in ICD-treated patients, with a summary RR of all-cause mortality of 0.76 (95% CI: 0.65 to 0.89, $p = 0.0006$),[30] 0.75 (95% CI: 0.64 to 0.87, $p = 0.0002$)[32] and 0.72 (95% CI: 0.60 to 0.87; $p = 0.0006$),[31] which is an RRR between 24 and 27%. This reduction was mainly due to the 50% reduction in arrhythmic deaths. The absolute risk reduction due to ICD was reported as 7%

TABLE 5 *Included RCTs of secondary prevention*

Trial details	Survival outcomes				
Study: AVID investigators, 1997[33] (and Schron *et al*., 2002[34]) *Study name:* AVID *Design:* multicentre RCT *Intervention:* ICD vs AAD *Patients:* ICD *n* = 507; AAD *n* = 509 Age: ICD 65 ± 11; AAD 65 ± 10 years Males (%): ICD 78; AAD 81 *Quality assessment:* 1/5		**ICD**	**AAD**		***p*-Value**
	Crude death rates over mean follow-up (%)	15.8 ± 3.2	24.0 ± 3.7		
	Overall survival (%) 1 year (overall n = 644) 2 years (overall *n* = 333) 3 years (overall *n* = 104)	 89.3 81.6 75.4	 82.3 74.7 64.1		$p < 0.02$ (adjusted for repeated analysis, *n* = 6)
	Reduction in mortality with ICD 1 year 2 year 3 year	 39 ± 20% 27 ± 21% 31 ± 21%			
Study: Connolly *et al*., 2000[35] (and Irvine *et al*., 2002[36]) *Study name:* CIDS *Design:* multicentre RCT *Intervention:* ICD vs amiodarone *Patients:* ICD *n* = 328; amiodarone *n* = 331 Age: ICD 63.3 ± 9.2; amiodarone 63.8 ± 9.9 years Males (%): ICD 85.4; amiodarone 83.7 *Quality assessment:* 2/5		**ICD**		**Amiodarone**	**Adjusted treatment effect (95% CI)**
	Survival	**No. of events**	**Rate/ year (%)**	**No. of events**	**Rate/ year (%)**
	Arrhythmic death	30	3.0	43	4.5	RRR 32.8% (95% CI: –7.2 to 57.8), $p = 0.094$
	All-cause mortality	83	8.3	98	10.2	RRR 19.7% (95% CI: –7.7 to 40.0), $p = 0.142$
Study: Siebels *et al*., (1993)[27] and Kuck *et al*., (2000)[26] *Study name:* CASH (Cardiac Arrest Study Hamburg) *Design:* RCT *Intervention:* ICD vs AAD *Patients:* ICD *n* = 99; AAD *n* = 92; Age: ICD 58±11; AAD 59±10: Male: ICD 79; AAD 82 *Quality assessment:* 1/5		**ICD**	**Amiodarone**		***p*-Value**
	Crude sudden death rate	13.0% (95% CI: 7.9 to 19.6%)	33.0% (95% CI: 27.2 to 41.8%)		$p = 0.005$, HR 0.423 (97.5% CI: upper bound 0.721)
	Crude death rate	36.4% (95% CI: 26.9 to 46.6%)	44.4% (95% CI: 37.2 to 51.8%)		$p = 0.081$, HR 0.766 (97.5% CI: upper bound 1.112)
	Crude rates of non-fatal cardiac arrest	11.1% (95% CI: 6.9 to 16.5%)	19.5% (95% CI: 12.2 to 25.6)		$p = 0.072$, HR 0.481 (97.5% CI: upper bound 1.338)

RRR, relative risk reduction.

(95% CI: 4 to 11%)[32] and 3.5% per year.[31] Prolongation of life by an ICD over amiodarone was 2.1 months at 3 years and 4.4 months at 6 years.[31] The meta-analysis also showed that patients with LVEF >35% had significantly less benefit than those with LVEF of ≤35% ($p = 0.011$).[31]

Overall survival was greater with ICD with estimates of 89.3% compared with 82.3% in the AAD group at 1 year, 81.6% versus 74.7% at 2 years and 75.4% versus 64.1% at 3 years ($p < 0.02$) (AVID[33]). The corresponding reduction in total mortality with ICDs was 39% ± 20%, 27% ± 21% and 31% ± 21%. Over a mean follow-up of 18.2 ± 12.2 months, the crude death rates were 15.8% ± 3.2% in the ICD group and 24.0% ± 3.7% in the AAD group (AVID[33]). The average unadjusted length of additional life associated with ICD was 2.7 months at 3 years (AVID[33]).

TABLE 6 *Included systematic reviews of primary prevention trials*

Trial details	Outcomes	
Study: Ezekowitz *et al*., 2003[30]	**Fixed effects meta-analysis**	**Summary RR**
Design: systematic review and meta-analysis	Sudden cardiac death	0.37 (95% CI: 0.27 to 0.50)
Intervention: ICD vs placebo; or ICD vs antiarrhythmic therapy	All-cause mortality	0.72 (95% CI: 0.63 to 0.84)
Patients: 4909 patients randomised, numbers for groups not reported	**Random effects meta-analysis**	**Summary RR**
Age: not reported	All cause mortality	0.69 (95% CI: 0.46 to 1.03)
Males: not reported	Substantial heterogeneity in total mortality was observed between primary prevention trials enrolling high-risk patients and those enrolling moderate-risk patients ($p < 0.001$)	
Quality assessment: CRD 4/5		
Study: Lee *et al*., 2003[32]	**Meta-analysis**	**Summary RR**
Design: systematic review and meta-analysis	Arrhythmic death	0.34 (95% CI: 0.23 to 0.50)
Intervention: ICD vs medical therapy	All-cause mortality	0.66 (95% CI: 0.46 to 0.96)
Patients: >5000 patients randomised, numbers for groups not reported	Non-arrhythmic death	0.95 (95% CI: 0.74 to 1.21)
Age: not reported	There was significant heterogeneity in the all-cause mortality and arrhythmic mortality estimates	
Males: not reported		
Quality assessment: CRD 4/5		

Crude death rates were 36.4% (95% CI: 26.9 to 46.6) in the ICD arm and 44% (95% CI: 37.2 to 51.8) in the AAD arm over a mean follow-up of 57 ± 34 months (CASH[27]). Overall survival was higher, although not significantly, in patients assigned to ICD than those assigned to AAD therapy (HR 0.766, $p = 0.081$).[27]

The third trial (CIDS[35]) reported a non-significant reduction in the risk of death with ICD, from 10.2 to 8.3% per year, which is a 19.7% RRR (95% CI: –7.7 to 40%, $p = 0.142$).

Primary prevention

Tables 6 and *7* summarise the clinical effectiveness of the included primary prevention studies.

Sudden cardiac death

The systematic reviews[30,32] reported that ICDs are highly efficacious in preventing SCD as primary prevention with RRs of 0.37 (95% CI: 0.27 to 0.50)[30] and 0.34 (95% CI: 0.23 to 0.50, $p < 0.00001$).[32] Although no appreciable heterogeneity was reported among trials, these results should be interpreted with caution as pooling data from different patients groups may not be appropriate. In particular, no sudden cardiac deaths occurred in either study group on one trial (CAT[29]) because lower risk patients had been recruited.

The risk of death from cardiac arrest or arrhythmia was significantly reduced in patients who received an ICD compared with those with EP-guided therapy without a defibrillator, RR 0.24 (95% CI: 0.13 to 0.43, $p < 0.001$) and compared with patients with no therapy, RR 0.28 (95% CI: 0.16 to 0.49, $p < 0.001$) (MUSTT[41]). The 5-year rate of cardiac arrest or death from arrhythmia was 9% among those with EP-guided defibrillator therapy compared with 37% among those who did not receive an ICD ($p < 0.001$) (MUSTT[41]).

There were no deaths from sudden cardiac causes in either the ICD group or the control group in the study looking at prophylactic use of ICD in DCM (CAT[29]).

The other primary prevention trials reported all-cause mortality only.

Total mortality

The systematic reviews[30,32] reported a survival benefit in ICD-treated patients. A summary RR of 0.72 (95% CI: 0.63 to 0.84) was reported from pooling data from the five primary prevention studies in one[30] and an RRR of death from any cause of 0.66 (95% CI: 0.46 to 0.96, $p = 0.03$) in the other.[32] However, substantial heterogeneity in total mortality was observed between trials enrolling high-risk patients (MADIT I,[37]

TABLE 7 *Included RCTs of primary prevention*

Trial details	Survival outcomes			
Study: Moss *et al*., 2002[28] *Study name:* MADIT II *Design:* multicentre RCT *Intervention:* ICD vs medical therapy *Patients:* ICD $n = 742$; medical $n = 490$. Age: ICD 64 ± 10; medical 65 ± 10 years Males (%): ICD 84; medical 85 *Quality assessment:* 2/5	**Survival**	**ICD**	**Medical**	***p*-Value**
	Number of deaths (%)	105 (14.2)	97 (19.8)	HR 0.69 (95% CI: 0.51 to 0.93), $p = 0.016$
	Survival (Kaplan–Meier) at 12 months	503 (0.91)	329 (0.90)	Reduction of 12% (95% CI: –27 to 40)
	Survival (Kaplan–Meier) at 24 months	274 (0.84)	170 (0.78)	Reduction of 28% (95% CI: 4 to 46)
	Survival (Kaplan–Meier) at 36 months	110 (0.78)	65 (0.69)	Reduction of 28% (95% CI: 5 to 46)
Study: Bigger, 1997[39] *Study name:* CABG-Patch *Design:* multicentre RCT *Intervention:* ICD vs control (not defined) *Patients:* ICD $n = 446$; control $n = 454$ Age: ICD 64 ± 9; control 63 ± 9 years Gender (M/F): ICD 386/60; control 373/81 *Quality assessment:* 1/5	**Survival**	**ICD**	**Comparison**	***p*-Value**
	30-day mortality	24	20	$p = 0.60$
	Mortality during average follow-up	101 (71 cardiac cause)	95 (72 cardiac cause)	HR 1.07 (95% CI: 0.81 to 1.42)
	Kaplan–Meier cumulative mortality (% estimated from figure)			At 48 months $p = 0.64$
	12 months	14 ($n = 384$)	12 ($n = 399$)	
	24 months	16 ($n = 313$)	16 ($n = 308$)	
	36 months	21 ($n = 213$)	20 ($n = 199$)	
	48 months	27 ($n = 61$)	24 ($n = 57$)	
Study: Buxton *et al*., 1999[41] *Study name:* MUSTT *Design:* multicentre RCT *Intervention:* EGT (included ICDs) vs. no antiarrhythmic therapy (no therapy) *Patients:* EGT $n = 351$; no therapy $n = 353$ Age: EGT 67 (60–72); no therapy 66 (58–72) years Males (%): EGT 90, no therapy 90 *Quality assessment:* 1/5	**Subgroup analyses**	**ICD subgroup of EGT**	**No ICD subgroup of EGT**	***p*-Value**
	NB: subgroups of those with ICDs only is not a randomised comparison			
	Five-year rate of cardiac arrest or death from arrhythmia (Kaplan–Meier) (%)	9	37	$p < 0.001$
	Five-year rate of overall mortality (Kaplan–Meier) (%)	24	55	$p < 0.001$
	Cardiac arrest or death from arrhythmia (number of events)	12	56	Unadjusted RR 0.24 (95% CI: 0.13 to 0.43), adjusted RR 0.24 (95% CI: 0.13 to 0.45), $p < 0.001$
	Death from all causes (number of events)	35	97	Unadjusted RR 0.42 (95% CI: 0.29 to 0.61), adjusted RR 0.40 (95% CI: 0.27 to 0.59) $p < 0.001$

continued

TABLE 7 *Included RCTs of primary prevention (cont'd)*

Trial details	Survival outcomes			
		ICD subgroup of EGT	**No therapy group**	
	Cardiac arrest or death from arrhythmia (number of events)	12 (as before)	90	Unadjusted RR 0.28 (95% CI: 0.16 to 0.49), adjusted RR 0.27 (95% CI: 0.15 to 0.47), $p < 0.001$
	Death from all causes (number of events)	35 (as before)	158	Unadjusted RR 0.49 (95% CI: 0.35 to 0.69), adjusted RR 0.45 (95% CI: 0.32 to 0.63), $p < 0.001$
Study: Moss *et al*., 1996[37] and Moss *et al*., 2001[38]	**Survival**	**ICD**	**Medical**	***p*-Value**
Study name: MADIT	Five-year overall mortality (average follow-up 27 months)	15	39	HR 0.46 (95% CI: 0.26 to 0.82), $p = 0.0009$
Design: multicentre RCT				
Intervention: ICD vs conventional medical therapy	**Risk factors**	**Number of patients**	**Risk factor HR**	**ICD: non-ICD HR**
Patients: ICD $n = 95$; medical $n = 101$	EF < 0.26, QRS ≥ 0.12 s, history of congestive heart failure requiring treatment	38	4.33	0.20
Age: ICD 62 ± 9; medical 64 ± 9 years				
Gender (M/F): ICD 92/8; medical 92/8				
Quality assessment: 2/5				
Study: Bänsch *et al*., 2002[29]	**Survival**	**ICD**	**Control**	***p*-Value**
Study name: CAT	Mortality during 1st year of follow-up	4 deaths (all cardiac)	2 deaths (non-cardiac)	NS
Design: multicentre RCT	Mortality during follow-up (mean 5.5 ± 2.2 years)	13	17	NS
Intervention: ICD vs control	Cumulative survival (%)			
Patients: ICD $n = 50$; control $n = 54$	2 years	92	93	Log-rank, $p = 0.554$
Age: ICD 52 ± 12; control 52 ± 10 years	4 years	86	80	
Gender (M/F): ICD 43/7; control 40/14	6 years	73	68	
Quality assessment: 1/5				

NS, not significant.

MUSTT,[41] MADIT II[28]) and those enrolling moderate-risk patients (CABG-Patch,[39] CAT[29]) ($p < 0.001$).[30] No survival benefit with ICD was demonstrated in the latter trials. Substantial survival benefit was only shown in the three high-risk trials which recruited patients with known coronary artery disease and reduced LVEF, and also inducible ventricular arrhythmias on EP testing in two (MADIT I[37] and MUSTT[41]).[30] Primary prevention findings were also found to be sensitive to the contributions of individual trials in the other review.[32] When these three trials (MADIT I,[37] MUSTT,[41] MADIT II[28]) were combined, there was a reduction in RR of death from any cause of 0.53 (95% CI: 0.37 to 0.76, $p < 0.001$).[32]

One trial found a significant reduction in overall mortality associated with implantation of an ICD in patients with prior MI at high risk for VT, with

an HR of 0.46 (95% CI: 0.26 to 0.82, $p = 0.009$) (MADIT I[37]), a 54% reduction in mortality. This study further analysed survival benefit from ICD in relation to severity of the mortality risk. ICD was associated with a significant reduction ($p = 0.002$) in mortality only in high-risk subsets with EF <0.26, QRS duration ≥ 0.12 seconds, and a history of heart failure requiring treatment. Patients at the highest mortality risk (all three risk factors; HR 4.33) achieved the largest mortality reduction (HR 0.20) from ICD therapy.

Death from all causes was significantly reduced in the ICD group compared with EP-guided therapy without a defibrillator, RR 0.42 (95% CI 0.29 to 0.61, $p < 0.001$) and compared with no therapy, RR 0.49 (95% CI 0.35 to 0.69, $p < 0.001$) (MUSTT[41]). The overall mortality rates at 5 years were 24% among patients who received a defibrillator and 55% among those who did not.

Actuarial mortality rates by 4 years of follow-up in one trial (CABG-Patch[39]) were 24% in the control group and 27% in the group assigned an ICD. The HR for death from any cause was 1.07 (95% CI 0.81 to 1.42, $p = 0.64$). This lack of evidence of improved survival with ICD was among patients with coronary heart disease, depressed LVEF and abnormal signal-averaged ECG in whom ICD was implanted at the time of coronary bypass surgery.[39]

In patients with a prior MI and advanced left ventricular (LV) dysfunction, prophylactic implantation of an ICD was shown to improve survival (MADIT II[28]). Mortality rates were 14.2% in the ICD group and 19.8% in the medical group.[28] The relative risk of death from any cause in the ICD group compared with the medical therapy group was 0.69 (95% CI: 0.51 to 0.93, $p = 0.016$), a 31% reduction in risk of death at any interval. Kaplan–Meier survival at 3 years showed a 28% reduction in death in the ICD group.

All-cause mortality rates were not different between the ICD treatment and control group after 1 year or during long-term follow-up in one trial (CAT[29]). This study considered the prophylactic use of ICD in patients with DCM of recent onset and impaired LVEF (≤30%). All four deaths in the ICD group were due to cardiac causes, whereas both deaths in the control group were due to non-cardiac causes after 1 year. Cumulative survival was 92, 86 and 73% in the ICD group compared with 93, 80 and 68% in the control group after 2, 4 and 6 years, respectively ($p = 0.554$).

Quality of life

Three trials reported QoL outcomes, two secondary prevention studies (AVID,[33] CIDS[35]) and one primary prevention trial (CABG-Patch[39]).

Quality of life – secondary prevention

QoL outcomes in secondary prevention trials are shown in *Table 8*.

In one study (AVID[33]), three self-administered instruments were used: the generic Medical Outcome Short Form with 36 Items questionnaire (SF-36) with subsets for physical component summary (PCS) score and mental component summary (MCS) score; the Patient Concerns Checklist (PCC), which evaluates disease specific aspects of QoL relevant to patients with VF or VT; and the Cardiac version of QoL Index (Cardiac QoL), which assesses issues relevant to people with heart disease. Generalised linear models were used to assess the relationships between self-perceived QoL and treatment and adverse symptoms and ICD shocks. The other secondary prevention trial reporting QoL issues (CIDS[35]) used the Rand Corporation 38-item Mental Health Inventory (MHI) to assess emotional functioning and the Nottingham Health Profile (NHP) to assess health-related quality of life (HRQoL).

The AVID study[33] demonstrated that ICD and AAD therapy are associated with similar effects on self-perceived QoL in patients with ventricular arrhythmia over 1 year of follow-up. The development of adverse symptoms is associated with significant impairment in QoL, in both groups, and the occurrence of sporadic shocks in ICD recipients.

In the CIDS study,[35] emotional and physical health were shown to improve significantly in the ICD group and were either unchanged (emotional health) or deteriorated (energy and physical mobility) in the amiodarone group. The benefits of ICD on QoL were not evident in participants who received five or more ICD shocks. Differences among ICD subgroups were observed only on emotional health scales, which suggests that the deleterious effects of receiving numerous ICD shocks appears to be specific to emotional functioning.

Quality of life – primary prevention

QoL outcomes in one primary prevention trial are shown in *Table 9*.

The primary prevention trial (CABG-Patch[39]) assessed QoL using the SF-36 and reported health

TABLE 8 *QOL in secondary prevention trials*

Study: AVID[33]	**ICD**	**AAD**	***p*-Value**
SF-36 – PCS and MCS (higher score indicates better QoL)			
Mean PCS	37.4 ± 10.9	36.5 ± 11.2	
PCS change over time (estimated from figure)	Baseline: 38 3 months: 39 6 months: 39 12 months: 40	Baseline: 36 3 months: 37 6 months: 37 12 months: 37	Baseline scores $p = 0.3$, increased over time ($p = 0.01$) but similarly $p = 0.03$
Mean MCS	45.9 ± 11.8	47.5 ± 11.5	
MCS change over time (estimated from figure)	Baseline: 45 3 months: 46 6 months: 47 12 months: 47	Baseline: 49 3 months: 47 6 months: 48 12 months: 47	Baseline scores lower in ICD group ($p = 0.006$). Time trend NS ($p = 0.27$)
PCC (higher score indicates poorer QoL)			
Mean PCC	15.9 ± 8.6	16.2 ± 8.9	
PCC change over time	No data	No data	Baseline scores $p = 0.6$, during follow-up ($p = 0.1$) but scores declined as a group ($p = 0.001$)
QoL index (cardiac) (higher score indicates better QoL)			
Mean QoL index	22.1 ± 4.9	21.9 ± 5.0	
QoL index change over time	No data	No data	Baseline and follow-up scores similar, and scores did not change over time
Impact of adverse symptoms on QOL (any vs none)			
SF-36 PCS	–2.25 (–3.32, –1.18), $p < 0.001$	–1.64 (–2.89, –0.41), $p = 0.009$	Not tested
SF-36 MCS	–2.32 (–3.76, –0.88), $p = 0.002$	–0.51 (–1.97, 0.94) $p = 0.5$	Not tested
PCC	1.84 (0.91, 2.76), $p < 0.001$	0.91 (0.07, 1.75), $p = 0.03$	Not tested
Automatic pacing or shocks in ICD group (cumulative percentage of patients with any activation)	For those with VT: 36% at 3 months 68% at 1 y 81% at 2y 85% at 3 y For those with VF: 15% at 3 months 39% at 1 y 53% at 2 y 69% at 3 y		($p < 0.001$ for those with VT vs those with VF)
Impact of shocks on QoL (any vs none)			
SF-36 PCS	–1.45 (–2.74, –0.18), $p = 0.03$		Not tested
SF-36 MCS	–1.82 (–3.56, –0.08), $p = 0.04$		Not tested
PCC	2.15 (1.07, 3.23), $p < 0.001$		Not tested
Study: CID[35]	**ICD (*n* = 86)**	**Amiodarone (*n* = 92)**	**Time × group *p*-Value**
QoL MHI			
Total index[a]			
Baseline	173.2 ± 25.5	180.4 ± 27.8	
6 months	183.1±30.2[c]	180.2 ± 31.1	
12 months	184.3±27.9[d]	178.3 ± 28.7	0.001

continued

TABLE 8 *QOL in secondary prevention trials (cont'd)*

Study: CID[35]	**ICD (*n* = 86)**	**Amiodarone (*n* = 92)**	**Time × group *p*-Value**
Psychological distress[b]			
Baseline	51.3 ± 14.1	47.8 ± 16.5	
6 months	45.1 ± 17.6[c]	47.6 ± 18.3	
12 months	43.4 ± 15.9[d]	48.8 ±16.8	0.001
Psychological well-being[a]			
Baseline	58.5 ± 12.7	62.2 ± 12.3	
6 months	62.2 ± 13.4[c]	61.8 ± 14.1	
12 months	61.7 ± 13.2[d]	61.1 ± 13.1	0.03
QoL NHP[a]			
Energy level (n)	83	88	
Baseline	27.5 ± 32.2	24.4 ± 32.4	
6 months	18.6± 30.1[c]	27.8 ± 32.1	
12 months	17.7 ± 26.1[d]	36.8 ± 37.3[d]	0.0001
Physical mobility (n)	84	90	
Baseline	10.9 ± 12.0	13.2 ± 20.5	
6 months	10.5 ± 13.7	15.1 ± 19.2	
12 months	9.1 ± 13.6	17.7 ± 19.2[d]	0.002
Social interaction (n)	81	88	
Baseline	8.5 ± 15.4	9.9 ± 17.7	
6 months	9.8 ± 18.6	12.2 ± 22.4	
12 months	8.5 ± 18.4	11.1 ± 22.6	0.9
Emotional reactions (n)	76	86	
Baseline	17.3 ± 18.1	14.3 ± 20.1	
6 months	11.1 ± 18.2[c]	15.3 ± 22.4	
12 months	8.3 ± 16.6[d]	14.5 ± 19.6	0.002
Pain (n)	83	90	
Baseline	4.4 ± 7.9	7.5 ± 15.1	
6 months	7.5 ± 17.1	6.3 ± 13.6	
12 months	4.5 ± 9.9	8.2 ± 15.4	0.52
Sleep disturbance (n)	78	88	
Baseline	31.4 ± 27.4	29.6 ± 31.5	
6 months	25.0 ± 29.7[c]	30.8 ± 31.0	
12 months	23.9 ± 29.4[d]	30.2 ± 32.4	0.02
Lifestyle impairment (n)	78	83	
Baseline	2.0 ± 1.9	1.6 ± 1.7	
6 months	1.6 ± 1.8	1.9 ± 1.9	
12 months	1.6 ± 1.3[d]	1.8 ± 1.9	0.005
Impact of ICD shocks on QoL			

ICD shocks and QoL MHI (mean ± SD)	**ICD, no shocks (*n* = 66)**	**ICD, 1–4 shocks (*n* = 27)**	**ICD, ≥ 5 shocks (*n* = 15)**	**Amiodarone (*n* = 95)**	***p*-Value between groups**
Total index					
Baseline	175.3 ± 26.5	171.7 ± 22.7	171.2 ± 32.0	177.9 ± 27.1	
12 months	186.2 ± 26.9[c,d]	186.6 ± 21.7[c,d]	168.8 ± 41.2	175.6 ± 29.2	
Within-group *p*-Value	0.001	0.001	0.725		0.001

continued

TABLE 8 *QOL in secondary prevention trials (cont'd)*

ICD shocks and QoL MHI (mean ± SD)	**ICD, no shocks (*n* = 66)**	**ICD, 1–4 shocks (*n* = 27)**	**ICD, ≥ 5 shocks (*n* = 15)**	**Amiodarone (*n* = 95)**	***p*-Value between groups**
Psychological distress					
Baseline	50.2 ± 15.2	50.8 ± 12.3	51.9 ± 18.1	49.8 ± 16.3	
12 months	42.5 ± 15.3[c,d]	41.4 ± 11.7[c,d]	52.7 ± 25.2	50.9 ± 17.5	
Within-group *p*-Value	0.001	0.001	0.833		0.001
Psychological well-being					
Baseline	60.1 ± 12.5	56.6 ± 11.6	57.1 ± 15.0	61.7 ± 12.0	
12 months	62.8 ± 13.1	62.1 ± 10.9[c]	55.6 ± 16.8	60.6 ± 13.3	
Within-group *p*-Value	0.074	0.004	0.642		0.02
ICD shocks and QoL NHP (mean ± SD)					
Energy level (n)	64	27	15	90	
Baseline	28.6 ± 32.5	28.5 ± 30.5	22.6 ± 34.2	24.3 ± 30.8	
12 months	19.5 ± 27.1[d]	24.8 ± 33.4[d]	23.5 ± 29.5	37.0 ± 37.6	
Within-group *p*-Value	0.02	0.115	0.859		0.003
Physical mobility (n)	65	27	15	93	
Baseline	13.1 ± 15.0	12.4 ± 10.2	7.1 ± 9.8	13.18 ± 20.1	
12 months	9.3 ± 12.4[d]	15.5 ± 17.3	8.0 ± 13.3	17.2 ± 19.1	
Within-group *p*-Value	0.05	0.638	0.747		0.02
Social isolation (n)	66	27	15	92	
Baseline	10.6 ± 16.7	4.3 ± 9.2	8.9 ± 16.1	11.8 ± 18.5	
12 months	8.8 ± 19.5	6.4 ± 15.5	12.8 ± 23.9	12.5 ± 23.0	
Within-group *p*-Value	0.03	0.991	0.817		0.57
Emotional reactions (n)	61	27	14	90	
Baseline	16.2 ± 17.4	16.3 ± 17.1	21.6 ± 21.1	16.3 ± 19.8	
12 months	7.1 ± 14.6[c,d]	6.8 ± 10.2[d]	22.0 ± 31.0	15.9 ± 20.3	
Within-group *p*-Value	0.001	0.02	0.886		0.001
Pain (n)	66	27	15	92	
Baseline	6.8 ± 11.8	4.0 ± 8.5	5.3 ± 8.3	8.5 ± 15.6	
12 months	6.4 ± 14.7	5.4 ± 11.7	5.5 ± 7.1	7.7 ± 14.5	
Within-group *p*-Value	0.086	0.710	0.721		0.71
Sleep disturbance (n)	62	27	14	89	
Baseline	30.0 ± 26.9	36.3 ± 31.4	27.3 ± 27.1	30.4 ± 30.5	
12 months	22.1 ± 28.1	29.1 ± 33.9	34.6 ± 35.4	30.1 ± 33.6	
Within-group *p*-Value	0.002	0.042	0.680		0.3
Lifestyle impairment (n)	65	26	14	82	
Baseline	2.0 ± 2.0	2.4 ± 1.9	2.2 ± 1.9	1.7 ± 1.6	
12 months	1.3 .± 1.5[d]	1.4 ± 1.5[d]	1.4 ± 1.6	1.9 ± 1.9	
Within-group *p*-Value	0.061	0.033	0.334		0.03

[a] Higher value represents better functioning.
[b] Higher value represents poorer functioning.
[c] Comparisons significant $p < 0.05$ with *post hoc* test from baseline to 6 months.
[d] Comparisons significant $p < 0.05$ with *post hoc* test from baseline to 12 months.

TABLE 9 *QoL in primary prevention trials: QoL at 6 months*

Study: CABG-Patch[39]	ICD (*n* = 262)	Control group (*n* = 228)	*p*-Value
Perception of health			
General health status	54.8 ± 22.9	58.3 ± 23.6	NS
Perception of health transition[a]	2.4 ± 1.2	2.1 ± 1.2	0.030
Physical limitations	41.7 ± 42.3	49.2 ± 42.8	0.055
Bodily pain	57.4 ± 24.6	58.8 ± 24.8	NS
Ability to function			
Employment status	0.25 ± 0.4	0.29 ± 0.5	NS
Physical role functioning	58.3 ± 27.5	61.8 ± 28.3	NS
Emotional role functioning	55.4 ± 43.4	67.3 ± 39.9	0.003
Social functioning	70.5 ± 27.2	70.8 ± 26.4	NS
Psychological well-being			
Mental health	72.5 ± 18.3	77.2 ± 17.0	0.004
Satisfaction with appearance	6.0 ± 1.3	6.3 ± 1.1	0.008
Satisfaction with scar	7.0 ± 1.2	7.2 ± 1.1	0.040

NS, not significant
[a] Lower scores reflect a tendency to rate one's health as better now, relative to 1 year ago. For all other measures, higher scores represent more favourable scores.

transition and additional indicators examining work status and perceptions of body image.

In the CABG-Patch study,[39] which compared QoL 6 months after CABG surgery between patients who received prophylactic ICDs and those who did not at the time of CABG surgery, patients with ICDs had significantly lower scores on scales measuring psychological well-being, perceptions of health and emotional role functioning relative to controls. The greatest differences between the two groups were in the domain of psychological well-being, with significant differences on all three indicators. These differences were more marked for those who had received shocks during the observation period.

Adverse effects of ICD therapy

Tables 10 and *11* summarise adverse events in the secondary and primary prevention trials, respectively.

Generally, serious complications of defibrillator therapy were infrequent in the trials included in the review. These are expressed differently in the studies. For example, they may be reported as any mention of a particular complication, or the number of patients experiencing complications, and as such are difficult to summarise. Complications reported include infection, haematomas and bleeding, lead dislodgement and migration, cardiac perforation, pleural effusion and pneumothorax and device dysfunction/malfunction of generator. Significantly more postoperative infections were noted in the ICD group versus the control group in the CABG-Patch study[39] where both groups received surgery. One study reported a non-significant higher rate of new or worsened heart failure in the ICD group with consequent hospitalisation (MADIT II[28]). An explantation rate of 2.1% was reported in one study (CASH[27]).

Summary of the effectiveness of ICDs

- The evidence suggests that ICDs reduce mortality in patients with a previous SCD episode or previous VT; in patients who have not had a previous SCD episode or previous VT but who have reduced LVEF due to coronary heart disease and unsustained ventricular arrhythmia and sustained tachycardia that could be induced electrophysiologically; and some patients with severe LV dysfunction after MI.

Secondary prevention

- Two systematic reviews and one meta-analysis, using data from three previously reported RCTs, met the inclusion criteria for the review.
- The systematic reviews were of good quality and the meta-analysis pooled raw individual trial data.
- Secondary research suggests that there is a 28% reduction in the RR of death with ICD that is due almost entirely to a 50% reduction in arrhythmic death.
- Three RCTs met the inclusion criteria for the review. All were described as randomised, but none were double blind owing to the nature of the intervention.

TABLE 10 *Adverse events of included RCTs of secondary prevention*

AVID[33]	**ICD**	**AAD**	***p*-Value**
Complications of therapy			
Non-fatal torsade-de-pointes VT		1	
Suspected pulmonary toxicity		3% at 1 year 5% at 2 years	
Thyroid replacement medication	1% at 1 year 1% at 2 years	10% at 1 year 16% at 2 years	
30-day mortality (or by hospital discharge, if later than 30 days)	12 (2.4%)	18 (3.5%)	$p = 0.27$
Bleeding requiring operation or transfusion	6		
Serious haematomas	13		
Infection	10		
Pneumothorax	8		
Cardiac perforation	1		
Early dislodgement or migration of leads	3		
Unsuccessful first attempt at implantation without thoracotomy	5		
Reports of adverse symptoms	All patients: Within 3 months: 49% At 6 months: 36% At 1 year: 54%		The proportions were similar in the 2 treatment groups ($p = 0.8$)
CIDS[35]	**ICD**	**Amiodarone**	***p*-Value**
Adverse events ever reported (%)			
Pulmonary infiltrate		18 (5.7)	Risk 1.9% per year
Visual symptoms (blurred, halo or decreased)		48 (14.5)	
Bradycardia		10 (3.0)	
Skin discoloration		21 (6.3)	
Photosensitivity		34 (10.3)	
Ataxia		97 (17.2)	
Tremor		91 (15.4)	
Insomnia		64 (19.3)	
Peripheral neuropathy		1 (0.3)	
ICD product discomfort	25 (7.6)		
ICD malfunction	2 (0.6)		Rate 1.4% per year
ICD pocket infection	15 (4.6)		
ICD lead dislodgement/fracture	8 (2.4)		
CASH[26,27]	**ICD**	**AAD**	***p*-Value**
Drug-related pulmonary toxicity	n/a	0	
Hyperthyroidism	n/a	3 (3.3%)	
Perioperative death	5 (5.1%): 3 (5.4%) epicardial, 2 (4.5%) endocardial	n/a	
Infection	3 (requiring explantation in 2)		
Haematoma or seroma	6		
Pleural effusion	3		
Pneumothorax	1		
Dislodgement or migration of leads	3		
Device dysfunction	5		
Overall complication	23% including an explantation rate of 2.1%		

TABLE 11 *Adverse events in included RCTs of primary prevention*

MADIT II[28]	**ICD**	**Medical**	***p*-Value**
Lead problems (%) leading to surgical intervention	13 (1.8)	n/a	
Non-fatal infections (%) leading to surgical intervention	5 (0.7)		
New or worsened heart failure requiring hospitalisation	148 (19.9)	73 (14.9)	Represents 11.3 and 9.4 patients so per hospitalised 1000 months of active follow-up (nominal $p = 0.009$)
CABG[39]	**Intervention**	**Comparison**	***p*-Value**
Adverse events (postoperative)			
MI	4.0	3.5	NS
Sustained VT	5.8	6.8	NS
VF	3.4	5.3	NS
Bradycardia	2.9	4.4	NS
Atrial fibrillation	22.9	20.7	NS
Shock	9.2	7.5	NS
New or more severe heart failure	15.7	12.6	NS
Conduction defect	14.1	14.5	NS
Residual central nervous system deficit	3.6	2.0	NS
Bleeding treated with surgery	4.9	3.1	NS
Postpericardiotomy syndrome	0.9	0.7	NS
Deep sternal-wound infection	2.7	0.4	$p < 0.05$
Infection at wound or catheter site	12.3	5.9	$p < 0.05$
Pneumonia	8.5	4.0	$p < 0.05$
Other infection	6.3	3.3	NS
Renal failure	6.7	4.8	NS
Adverse events during long-term follow-up			
Angina pectoris	27.0	27.5	NS
MI	0.5	4.2	$p < 0.05$
New or worsening heart failure	42.5	42.5	NS
Ventricular arrhythmias	19.4	14.3	NS
Atrial fibrillation	14.7	10.1	NS
Hospitalisation	61.4	55.2	NS
Repeat CABG surgery	0.0	0.7	NS
PTCA or artherectomy	2.9	2.1	NS
Permanent cardiac pacemaker	2.9	4.9	NS
MUSTT[41]			
Death due to ICD-related infection	1 at 18 months – infection complicated the revision of the lead system		
MADIT[37]	**ICD**	**Medical**	***p*-Value**
Adverse effects related to antiarrythmic therapy of ICD (some patients ≥ 1)			
Hypotension	0	1	Not reported
Syncope	1	5	Not reported
Hypothyroidism	0	1	Not reported
Sinus bradycardia	3	3	Not reported
Pulmonary fibrosis	0	3	Not reported
Pulmonary embolism	1	1	Not reported
Atrial fibrillation	4	0	Not reported
Pneumothorax	2	0	Not reported
Bleeding	1	0	Not reported
Venous thrombosis	1	0	Not reported
Surgical infection	2	0	Not reported
Problems with lead	7	0	Not reported
Malfunction ICD generator	3	2	Not reported
Total no. of patients with adverse effects	19	12	Not reported

continued

TABLE 11 *Adverse events in included RCTs of primary prevention (cont'd)*

CAT[29]	Intervention	Comparison	*p*-Value
Revisions due to device dislocation and bleeding	2	n/a	
Electrode dislocation and sensing/isolation defects	7	n/a	
Infection with total device replacement	2	n/a	
Perforation	1	n/a	
Adequate therapies for VTs >200 bpm	11		
Syncope	6		

- Two RCTs reported reduced rates of SCD in the ICD group compared with AAD therapy.
- Reduction in total mortality with ICDs is reported as 39, 27 and 31% at 1, 2 and 3 years, respectively, in one trial, with additional life associated with ICD of 2.7 months at 3 years. ICD is associated with a 23% non-significant reduction in all-cause mortality rates compared with AAD therapy in another trial. A non-significant RRR of 19% is reported in the third trial.

Primary prevention

- One good-quality systematic review and five RCTs met the inclusion criteria for the review. The RCTs were described as randomised, but none was double-blind.

Original indications

- Three trials reported results for ICD use in cardiac arrest patients with evidence of arrhythmia and LVEF <35%, with two showing benefits in the ICD group compared with the AAD group. A 54% reduction in total mortality in the ICD group compared with the AAD group was reported in one trial, and overall mortality rates at 5 years were 24% among patients who received a defibrillator and 55% among those who did not in the other trial. Actuarial mortality rates by 4 years of follow-up were 27% in the group assigned an ICD and 24% in the control group in the trial in which people were receiving ICD at the time of CABG.
- One study reported subgroup analyses which showed that the magnitude of survival benefit from ICD is directly related to the severity of cardiac dysfunction. Defibrillator use was associated with a significant reduction in mortality rate in high risk subsets with three risk factors (EF <26%, QRS duration ⩾0.12 second and a history of heart failure requiring treatment).

New indications

- One trial considered the prophylactic use of ICD in people with prior MI and LVEF <30% and reported improved survival associated with ICD implantation, with a 31% reduction in the risk of death at any interval among patients in the ICD group compared with patients in the AAD group. Mortality rates were 14.2% in the ICD group and 19.8% in the medical group during 20 months of follow-up.
- One trial considered the prophylactic use of ICD in patients with recent onset DCM and impaired LVEF (<30%). No differences in survival were found between the ICD group and the control group after 2 and 4 years.

Quality of life

- The two secondary prevention trials reporting QoL have inconsistent findings. One reports that ICD and AAD therapy are associated with similar self-perceived QoL, and the development of adverse symptoms and the occurrence of sporadic ICD shocks are each associated with significant impairment in QoL. The other reports better QoL with ICD therapy than with amiodarone therapy, although this is not evident in patients who receive numerous shocks from their device.
- The one primary prevention study reporting QoL found that patients in the ICD group had significantly lower levels of psychological well-being, perceptions of health and emotional role functioning compared with those in the control group.

Adverse effects

- Generally serious adverse events due to ICDs are infrequent.
- Complications that are reported include infection, haematomas and bleeding, lead dislodgement and migration, cardiac perforation, pleural effusion and pneumothorax and device dysfunction/malfunction of generator.

Chapter 5
Cost-effectiveness

Systematic review

A systematic search of the literature was undertaken to identify economic evaluations of ICDs. Details of the methodology and search strategy are presented in Appendices 2 and 3.

Quantity and quality of the literature on cost-effectiveness

Searches identified 175 possible papers. Of these, 12 papers relating to 11 separate economic evaluation studies,[42–53] met the inclusion criteria for the review. These economic evaluations are summarised in Appendix 10. Four of the included economic evaluations were based on individual RCTs,[42–45] each providing cost-effectiveness analyses in terms of life-years gained (LYG). Three of these related to the use of ICDs as secondary prevention and one[44] to primary prevention. The remaining seven economic evaluations were decision models based on data from a variety of sources.[46–52] Four of these provided cost-effectiveness analyses in terms of LYG and three provided cost–utility analyses. Six of these related to the use of ICD as secondary prevention, and one[47] as primary prevention.

None of the economic evaluations identified were shown to have both high external and internal validity. Assessment of the external validity of the economic evaluations (i.e generalisability of the economic study to the population of interest) was performed using a series of relevant questions.[25] Only one study, an early UK study,[50] was rated as demonstrating a high degree of external validity (see *Table 12* and Appendix 10). The healthcare systems and resource costs used in the remaining studies are not generalisable to a UK setting. The assessment of internal validity using a modified version of the Drummond and Jefferson criteria[24] (*Table 13* and Appendix 10) demonstrates that a number of studies show a high level of internal validity.[42,43,46–48] Four of these studies identify relevant costs[42,46–48] and all identify accurate and credible costs, apply discounting and undertake sensitivity analyses to the data. Additionally, four report cost-effectiveness/utility values in terms of incremental analyses.[42,43,46,47] The O'Brien study[50] that scored highly on external validity did not score highly on elements of internal validity. This was an early study; some costs were taken from actual data, but others were estimated.

The results of the included economic evaluations show a variation in the cost per LYG and cost per quality-adjusted life-year (QALY), with cost increasing over time (see *Table 14*). In the seven studies of secondary prevention the cost per LYG ranged from US$17,000 to Can$213,500 and the cost per QALY from US$37,000 to US$76,800. Of the two studies assessing primary prevention, one study found a cost per LYG of US$27,000 and another study found a cost per QALY of US$72,000–558,000.

Manufacturers' submissions

Two industry submissions, one joint one and one commissioned economic evaluation, used Markov models based on clinical effectiveness studies for survival data and resource use and cost data for the UK with a 12-year time horizon (more details are given in Appendix 11). There are discrepancies between the results of the two submissions. Incremental QALYs are reported as 0.32 for secondary prevention in one submission and 0.82 in the other, and 0.19 for primary prevention in one submission and 0.62 in the other. For secondary prevention incremental cost per QALY is reported as £25,887 in one submission and £47,191 on the other, and £39,385 for primary prevention in one submission and £82,703 in the other.

The manufacturers' submissions have relied on data from the literature and to a large extent assumptions for which there is no evidence, which explains the more favourable cost-effectiveness results compared with other reported results. However, the extensive multivariable sensitivity analyses made by the manufacturers are useful in showing that the parameters of importance are QoL utilities, device cost and relative risk of mortality, even if the estimates have had to use simulated distributions instead of real patient data.

TABLE 12 *External validity of economic evaluations*

	Kupperman, 1990[51]	Larsen, 1992[52]	O'Brien, 1992[50]	Kupersmith, 1995[49]	Wever, 1996[45]	Owens, 1997[48]	Mushlin, 1998[44]	O'Brien, 2001[43]	Sanders, 2001[47]	Owens, 2002[46]	Larsen, 2002[42]
Patients similar to UK	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Healthcare systems comparable to UK	No	No	Yes	No	No	No	No	No	No	No	No
Resource costs comparable to UK	No	No	Yes	No	No	No	No	No	No	No	No
Marginal costs used	No	?	No	No	No	Yes	No	No	No	No	No

?, Unclear.

TABLE 13 *Internal validity of economic evaluations*

	Kupperman, 1990[51]	Larsen, 1992[52]	O'Brien, 1992[50]	Kupersmith, 1995[49]	Wever, 1996[45]	Owens, 1997[48]	Mushlin, 1998[44]	O'Brien, 2001[43]	Sanders, 2001[47]	Owens, 2002[46]	Larsen, 2002[42]
Question defined	No	Yes	?	Yes	Yes	Yes	?	Yes	Yes	Yes	No
Alternatives described	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study type	?	No	No	No	?	No	Yes	Yes	?	No	Yes
Relevant costs	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes
Accurate costs	No	?	No	No	Yes	Yes	?	Yes	Yes	Yes	Yes
Credible costs	No	?	No	No	Yes	Yes	?	Yes	Yes	Yes	Yes
Discounting	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Incremental analysis	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes?
Sensitivity analysis	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Reasonable model	Yes	Yes	n/a	Yes	n/a	Yes	n/a	n/a	Yes	Yes	n/a

?, Unclear.
n/a, Not applicable.

TABLE 14 *Summary cost-effectiveness from included studies*

	LYG	Cost per QALY
Secondary prevention		
Year		
1990	US$17,100[51]	
1992	£15,400[50]–US$32,674[52]	
1995	US$31,100[49]	
1996	US$11,300[45] saved costs	
1997		US$36,300–76,800[48]
2001[a]	Can$213,543[43]	
2002[a]	US$66,677[42]	US$54,700[46]
Primary prevention		
Year		
1998	US$27,000[44]	
2001[a]		US$71,700–558,000[47]

[a] Incremental cost-effectiveness.

Summary of cost-effectiveness

- Eleven published economic studies were identified, none of which had both high external and internal validity. The literature shows that few studies used patient data, and in most studies considerable assumptions had to be made about outcomes and costs. Only one study from the beginning of the 1990s used UK data.
- Incremental cost/LYG ranges from US$27,000 to Can$213,543 and incremental cost/QALY from US$71,700 to US$558,000 in the published literature.
- One unpublished study of relevance to the UK was identified. Details of this study could not be included in the current review owing to the academic-in-confidence nature of the data, but it is expected to be in the public domain in due course when it is published in the HTA monograph series.

Chapter 6

Research in progress

A Cochrane protocol (Issue 3, 2003) for a systematic review assessing implantable defibrillators versus AADs for LV dysfunction is currently ongoing. The review has two aims: to compare the effectiveness of ICDs in patients with LV dysfunction (primary prevention in heart failure patients) and to compare effectiveness of ICDs in patients who have had an episode of resuscitated sudden cardiac death or a symptomatic arrhythmic event (secondary prevention). Outcomes include all-cause mortality, presumed arrhythmic death, cardiac death and adverse events.

A number of research projects relating to the use of ICDs are currently under way or were due to complete in 2003. Some of these studies are not evaluating the clinical or cost-effectiveness of ICDs but are described here if they are relevant to the use of ICDs in the UK.

'An investigation of the potential need for ICDs in England' is expected to end in September 2004. The study aims to review the epidemiology of ventricular arrhythmias and sudden cardiac death and the accuracy of tests used to diagnose ventricular arrhythmias. It also aims to investigate the incidents and characteristics of patients who fall into the three high-risk groups recommended by the original NICE guidance.

'OPTIC: optimal pharmacological therapy in ICD patients', a multicentre study, was expected to end in March 2004. This study aims to investigate what the effects of antiarrhythmic therapy are in preventing shocks in patients with ICDs.

'DINAMIT: Defibrillation in acute myocardial infarction trial', a multicentre RCT, is under way (completion date not specified). Patients with MI in the preceding 6 months and an EF of <35% will be given an ICD (comparison not specified).

'BEST-ICD: beta-blocker strategy plus ICD trial', a multicentre RCT, is under way (completion date not specified). This study aims to determine whether the addition of an ICD in patients post-high-risk MI (including sustained ventricular arrhythmias) will improve survival.

'MAVERIC: Midland trial of empiric amiodarone versus electrophysiology guided intervention and cardioverter implant in ventricular arrhythmias', a multicentre RCT, is under way (completion date not specified). Patients are those with a recent acute MI, shortened life expectancy or pregnancy.

'SADET: South European defibrillator trial', a multicentre RCT, is under way (completion date not specified). This study aims to compare ICD with standard treatment in patients who are post-acute MI that was ineligible for thrombolysis, and with depressed LV function at discharge.

'SCD-HeFT: sudden cardiac death in heart failure trial', a multicentre RCT, has recently completed recruitment of patients. This study aims to compare amiodarone or ICD with placebo in patients with chronic heart failure (NYHA class II or III).

'A prospective investigation of neuropsychological function and quality of life after ICD implantation', a multicentre study, is expected to end in October 2003. The study aims to compare ICD patients with patients on antiarrhythmic medication on neuropsychological assessments.

'A pilot study of the adjustment and coping of patients and their main carers following insertion of an ICD at Bristol Royal Infirmary' was expected to end in August 2003. This study aims to gather pilot data regarding the adjustment of ICD patients and their main carers.

'Short- and long-term measures of cardiac autonomic control in the prediction of further ventricular arrhythmia in patients with newly implanted internal cardiodefibrillators' was expected to end in March 2003. The study aims to find whether non-invasive indices of cardiac autonomic function can usefully predict the occurrence of further ventricular arrhythmia.

'Randomised trial of empiric versus electrophysiological study guided therapy for sustained ventricular arrhythmias' was expected to end in January 2003. The study randomised patients to EP therapy versus amiodarone. EP therapy patients would be considered for ICD if suppression failed.

'Mood and ventricular arrhythmias: a study in patients with automatic ICDs' was expected to end in January 2003. The aim of the study was to assess the relationship between mood and the frequency of therapies delivered by the ICD device in patients prone to lethal arrhythmias.

'Prevalence and predictors of post-traumatic stress disorder in automatic cardioverter defibrillator patients' was expected to end in January 2003. The study aims to determine the prevalence of post-traumatic stress disorder (PTSD) symptomatology in ICD patients, and to identify possible predictors of PTSD or impaired QoL.

Chapter 7

Implications for other parties

There are social costs to relatives of victims of SCD and economic losses resulting from the sudden death of productive wage earners. These factors are important but are difficult to quantify.

Chapter 8

Factors relevant to the NHS

Use of ICDs in the UK is increasing and more implanting centres are being established. However, there is an under-utilisation of ICDs for patients with accepted indications for implantation compared with other developed countries and the targets implied by NICE. The further likely increases in ICD use will impact on the provision of service within the UK in terms of cost and service capacity. There are associated issues of location of service provision, access and increased awareness of coronary heart disease by implementation of the National Service Frameworks for Coronary Artery Disease.[54]

Of particular importance is the possible extension of indications for ICDs to include patients with MI and cardiac dysfunction. At present only one trial has shown benefit to this group of patients and this may not be generalisable to all patients, but should these eligibility criteria be recommended the impact would be sizeable.

Another relevant factor is the potential use of ICDs in conjunction with cardiac resynchronisation therapy, which is undergoing clinical trials. Also, technological developments in ICDs will have an impact on service provision, either by increasing sophistication of devices with resulting increased costs, or minimal feature devices with lower costs but potentially wider application.

Chapter 9
Discussion

Statement of principal findings

Two systematic reviews, one meta-analysis and eight RCTs are included in the review. The RCTs were of variable quality and considered the use of ICDs in either secondary (three RCTs) or primary prevention (five RCTs) of sudden cardiac events.

For secondary prevention, the systematic reviews suggest that there is a 28% reduction in the RR of death with ICD that is due almost entirely to a 50% reduction in arrhythmic death. The RCTs report a reduction in total mortality with ICDs of 39, 27 and 31% at 1, 2 and 3 years, respectively, with an additional life associated with ICD of 2.7 months at 3 years, a 23% non-significant reduction in all-cause mortality rates associated with ICD compared with AAD therapy and a non-significant RRR of 19%.

For primary prevention, three trials reported results for ICD use in cardiac arrest patients with evidence of arrhythmia and LVEF <35%, with two showing benefits in the ICD group compared with the AAD group. A 54% reduction in total mortality in the ICD group compared with the AAD group was reported, and overall mortality rates at 5 years were 24% among patients who received a defibrillator and 55% among those who did not. Actuarial mortality rates by 4 years of follow-up were 27% in the group assigned an ICD and 24% in the control group in the trial in which people were receiving ICD at the time of coronary artery bypass graft (CABG). Subgroup analyses showed that the magnitude of survival benefit from ICD is directly related to the severity of cardiac dysfunction. Defibrillator use was associated with a significant reduction in mortality rate in high risk subsets with three risk factors (EF <26%, QRS duration ≥0.12 second and a history of heart failure requiring treatment).

One primary prevention trial considered the prophylactic use of ICD in people with prior MI and LVEF <30%. This reported improved survival associated with ICD implantation, with a 31% reduction in the risk of death at any interval among patients in the ICD group compared with patients in the AAD group. Mortality rates were 14.2% in the ICD group and 19.8% in the medical group during 20 months of follow-up.

One primary prevention trial considered the prophylactic use of ICD in patients with recent onset DCM and impaired LVEF (<30%). No differences in survival were found between the ICD group and the control group after 2 and 4 years.

QoL results in the use of ICDs for secondary prevention are inconclusive but suggest that patients who receive numerous shocks from their device experience significant impairment of QoL. The use of ICDs in primary prevention is associated with significantly lower levels of psychological well-being, perceptions of health and emotional role functioning compared with those in the control group.

Generally serious adverse events due to ICDs are infrequent, although complications that may occur include infection, haematomas and bleeding, lead dislodgement and migration, cardiac perforation, pleural effusion and pneumothorax and device dysfunction/malfunction of generator.

Eleven published economic studies were identified but none were shown to have both internal and external validity. Incremental cost/LYG ranges from US$27,000 to Can$213,543 and incremental cost/QALY from US$71,700 to US$558,000 in the published literature. One unpublished study of relevance to the UK, commissioned by the NHS HTA Programme, was identified and used as a source of data and for checking completeness of searches. Details could not be reported due to the academic-in-confidence nature of the data at the time of writing.

Strengths and limitations of the review

The review has certain strengths, including:

- It is independent of any vested interest.
- The review brings together the evidence for the clinical and cost-effectiveness of ICDs for

arrhythmias, applying consistent methods of critical appraisal, presentation and transparency.
- The review was guided by the principles for undertaking a systematic review. Prior to undertaking the review, the methods of the review were set out in a research protocol (Appendix 2), and this was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.
- The review of clinical effectiveness relied upon evidence from RCTs that reported mortality and systematic reviews.

In contrast, there were certain limitations placed upon the review:

- Synthesis of the included studies was through narrative review. Owing to differences in patient characteristics and duration of the trials, meta-analysis was considered inappropriate. Although the systematic reviews that met the inclusion criteria performed meta-analysis on the same trials, significant heterogeneity was shown between the studies, suggesting that pooling data should be treated with caution.
- The quality of the RCTs was assessed using the Jadad scale. Although the Jadad scale includes key elements by which to assess the quality of RCTs, including randomisation, blinding and withdrawals/dropouts, it could be criticised for excluding other elements that may cause bias (e.g. not including the level of withdrawal/dropout). It has also been pointed out that the Jadad scale 'gives more weight to the quality of reporting than to actual methodological quality'.

Other issues can be summarised as follows:

- There are some general points of concern relating to the trials of ICD use, most of which relate to unavoidable limitations. Studies are described as randomised but implantation of the device is often at the discretion of the surgeon if implantation is thought to be too risky. Crossovers may have reduced the power of studies and compromised intention-to-treat analysis. Participants in the studies may be different in detail and there have been changes to the intervention and methods of implantation over time. Trials have not been conducted in the UK and may not be generalisable. Blinding is an issue in ICD studies. It is accepted in systematic review methodology that the blinding of people assessing outcomes could be attempted even if blinding of patients and treating clinicians is not, but there is no reporting of this in included studies.
- General concern has been raised about the problems of evaluating ICD effectiveness by comparison with drug therapy rather than placebo. This is because many studies have found that a large percentage of patients with ICD require AA medication to suppress SVTs, to treat underlying ischaemic heart disease and to reduce the false-positive firing of the ICD. These drugs may interfere with the functioning of the device, by raising defibrillator thresholds or interfering with the ability to detect VT or VF. As a placebo-controlled trial would be considered unethical, these limitations are probably unavoidable.
- Some studies comparing ICD therapy with medical therapy may have underused medical therapies proved to minimise progression of cardiac disease, SCD and overall mortality. If patients serving as controls have not received proper medical management then conclusions that ICD are clearly better than medical therapy may not be appropriate.[55] Additionally, there is 100% compliance with ICDs but some patients receiving AAD therapy may not comply with effective treatment and so the potential health gain of AADs could be higher than that observed.
- In the AVID study, some of the survival benefit from ICD may have been due to beta-blocker therapy which was used more in this group. Beta-blockers have been shown to be an effective treatment in patients after MI, reducing arrhythmic deaths and total mortality.
- The CASH study had a long recruitment time, which exposed the study to developments in ICD technology and conventional therapy. Also, relatively healthy people were recruited compared with the AVID trial (mean EF 46%). Both factors could influence the results and have led to a possible underestimate of benefit.
- In the CIDS trial, 21% of ICD patients were also receiving amiodarone and 18% of amiodarone patients had received an ICD at 3 years. This rate of crossover plus the rate of beta-blocker treatment (30% of ICD patients receiving beta-blockers at 5 years compared with 22% of patients receiving amiodarone) exposed this trial to similar potential biases as in AVID. The smaller benefit of ICD therapy observed in the

CIDS trial compared with the AVID trial may be due to the longer duration of follow-up in CIDS. The AVID and CIDS trials have similar design and patient inclusion and exclusion criteria, and the CIs of the two estimates overlap substantially, indicating consistency between results. AVID was stopped early and therefore may have overestimated benefit.

- MADIT I used very limiting inclusion criteria such that potentially preventable deaths would be small. Risk stratification identified a narrowly defined group with highest mortality risk in whom ICD is effective (EF <0.26, QRS duration ≥0.12 seconds and history of heart failure requiring treatment). No evidence was found that the imbalance of AAD medication between the groups had an influence on the HR.
- The MUSTT study was designed to test the hypothesis that EP-guided AA therapy reduces SCD. After randomisation patients were assigned to receive EP-guided therapy (either ICD or drug therapy) or no AA therapy. It was shown that EP-guided ICD therapy improved survival. Caution should be used when assessing the true size of benefits of ICD therapy as the study did not randomise participants to drug therapy or ICD, and has the potential for bias and confounding of results. This study does not meet our inclusion criteria if strictly applied (in that randomisation determined EP-guided therapy not ICD therapy), but it does reflect a clinical situation and is generally regarded to be an appropriate RCT. It is also useful in that it substantiates the results of MADIT I showing that patients with ischaemic cardiomyopathy, non-sustained VT and inducible sustained VT had improved survival with ICD therapy.
- The CABG-Patch study showed no survival improvement by prophylactic implantation of defibrillators at the time of CABG. This may be due to lower risk groups recruited to this trial compared with MADIT and the possible effect of CABG in reducing the risk of SCD. A signal-averaged electrogram was used to identify abnormality for recruitment, which may not be as good a marker as sustained ventricular arrhythmia.
- The MADIT II trial found that new or worsened heart failure requiring hospitalisation was slightly more frequent in the ICD group than the medical therapy group. Patients saved from malignant VTs by the implantation of an ICD live longer than conventionally treated patients and would therefore have more time for heart failure to develop. Defibrillator shocks may contribute to rehospitalisation and myocardial injury. Careful monitoring of patients with ICD is therefore indicated. MADIT II was stopped early, after analysis revealed that the difference in mortality between the two groups had reached a prespecified efficacy boundary. This may have led to an underestimation of benefit.
- The CAT study was stopped early for futility because the overall mortality rate was too low. Short- and long-term mortality rates are low in patients recruited to this study, with recent onset DCM and EF <30%, which may be due to the use of angiotensin-converting enzyme (ACE) inhibitors. Even if all initially planned patients had been included, the trial would have been underpowered. Results do not favour prophylactic ICD use in patients with DCM and impaired LVEF <30% without further risk stratification.
- The meta-analyses showed that secondary prevention trials were consistent and that ICDs were more effective than AAD, with a statistically significant benefit for moderate to severe LVEF dysfunction. Statistical significance was not shown for individual trials.
- One systematic review performed a meta-analysis of the primary prevention trials by pooling data from the five trials. This may not have been appropriate owing to heterogeneity of studies, different patient groups and different lengths of follow-up. Also, it is not clear whether the review authors contacted the authors of the original studies to supply additional data to be used in the meta-analysis. Hence caution must be exercised when interpreting results. The authors of the current review attempted to reproduce the meta-analysis using the published trial data but without success.
- QoL data from the literature were limited to the initial year of follow-up. Longer term differences in QoL may exist owing to complications of ICD over time and toxicity associated with long-term drug therapy. Any differences in QoL that may evolve over time will impact on incremental cost-effectiveness.
- The COMPANION study was not included in the review because it did not meet the inclusion criteria for two reasons. It was designed to investigate the effects of cardiac resynchronisation therapy, with or without an ICD, and so did not include an arm with ICD only. Also, it included patients with LVEF <35% in chronic heart failure. It should be noted that the direction of evidence from the study is similar to other evidence with a greater advantage conferred through use of ICD.
- Where and how patients enter a trial can influence trial results, for example the site at

which patients are recruited into primary prevention trials (as inpatient or outpatient), can affect risk. If patients were recruited as inpatients, the mortality rate for a similar untreated outpatient group may be different and the benefit conferred by ICD may be different also.

- The cost-effectiveness studies identified in the literature use different methodologies and different types of economic models, which are often complex and difficult to interpret. It is noted that over time, as more data become available, the incremental cost/QALY of ICDs has increased. This is due to a smaller benefit with ICDs than originally anticipated in terms of LYG, higher follow-up costs and limited difference between treatment groups in QoL.
- Does reducing ICD shock frequency lead to improvement in QoL? There needs to be a prospective evaluation of QoL in AAD patients compared with ICD patients to assess the impact of ICD shock frequency on QoL, and to assess the impact of side-effects of AADs on QoL.
- For which subsets of patients is ICD therapy most likely to be clinically and cost-effective? Further risk stratification needs to be done as people with coronary heart disease and EF <30% are a high risk group but constitute a minority group of patients at risk for sudden death. Research should take into account any developments in ICD technology.
- Fundamental research on the mechanisms responsible for ventricular tachyarrhythmia is needed.

Implications for research

In undertaking the review of ICDs for arrhythmias, certain implications for research have become evident:

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Appendix 1

Device development

An ICD consists of three main parts: the defibrillator, the leads with electrodes and a programmer. The defibrillator is a small metal case that contains a microprocessor, circuitry and a battery. It detects and treats abnormal arrhythmia via electrical energy stored in the battery which may last up to 7 years depending on the type and number of shocks delivered. Leads are specialised thin insulated wires connected to the defibrillator that carry electrical energy from the defibrillator to the heart and relay information about the heart's electrical activity back to the defibrillator. The external programmer is a specialised computer used for monitoring and adjusting instructions to the ICD.

Initially, ICD implantation was a major operation requiring a thoracotomy and general anaesthesia. The defibrillator electrodes were patches sewn on to the myocardium, and leads were tunnelled subcutaneously to the device, which was implanted in a subcutaneous abdominal pocket. First-generation devices were associated with high morbidity and mortality. Modern ICDs are transvenous systems. The device is implanted either subcutaneously, as for a pacemaker, or subpectorally, in thin patients to prevent eroding the skin. The ventricular lead is positioned in the right ventricular apex, and a second lead can be positioned in the right atrial appendage to allow dual chamber pacing if required and discrimination between atrial and ventricular tachycardias. The ventricular lead has either one or two shocking coils. During implantation the unit is tested under conscious sedation. Adequate sensing during sinus rhythm, VT and VF is established, and also pacing and defibrillatory thresholds. Defibrillatory thresholds should be at least 10 J less than the maximum output of the defibrillator (~30 J).[56]

Over the last 10 years, there have been several important changes in ICD technology, particularly relating to the reduction in size and the implant technique. Reduction in size and evolution of a more physiological shape reduce the incision size and increase patient comfort. Also important is the development of the ability to record intracardiac electrograms. This allows the monitoring of each episode of anti-tachycardia pacing or defibrillation. If programming has been inappropriate, then programming changes can be made with a programming unit placed over the defibrillator site. Another important development has been the steady reduction in the energy required to terminate VF. This reduction in defibrillatory threshold has been achieved by improvements in electrode design, use of the generator as an active electrode and use of biphasic configuration of the shocking wave. This is turn has led to the shift from sternotomy approach with four leads and abdominal implantation to the present two-lead transvenous endocardial approach.

Current devices use anti-tachycardia pacing, and low- and high-energy shocks, known as tiered therapy. Devices recognise tachyarrhythmias by tachycardia cycle length, and can initiate the appropriate therapy. Anti-tachycardia pacing takes the form of adaptive burst pacing, with cycle length usually 80–90% of that of the VT. Should this fail, low-energy shocks are given to terminate ventricular arrhythmia with the minimum of pain. These are then followed if necessary by high-energy shocks. With rapid tachycardias, the device can be programmed to give high-energy shock as first-line therapy.

Further technological advances are likely and may include further reductions in defibrillator threshold, which will in turn increase the likelihood that a given shock will terminate ventricular arrhythmia, may shorten charge time by reducing the energy that has to be delivered, increase the life of the device and reduce the size of the device. Convergence of technology for defibrillation and for biventricular pacing may produce devices that can be used for both defibrillation and cardiac resynchronisation in patients with heart failure.

Another technological development is the production of minimal feature devices suitable for prophylactic implantation only. These are likely to have cheaper initial costs owing to the reduced parameter set and shorter, less technical follow-ups with reduced follow-up costs. After therapy has been delivered, the device would need to be replaced with a more advanced, fully featured device for secondary prevention.

Appendix 2

Review methods from the research protocol

Methods for reviewing effectiveness

The *a priori* methods used for the review are outlined below. The sources of information used are outlined in Appendix 3.

Inclusion and exclusion criteria

1. The intervention should be implantable cardioverter defibrillator compared with antiarrhythmic drug therapy or, if no direct comparison, placebo/control.
2. Participants should be adults at high risk of SCD due to arrhythmia, usually due to ventricular tachyarrhythmia. Specifically, patients in two categories:
   (a) 'Secondary prevention'
      (i) Cardiac arrest due to either VT or VF.
      (ii) Spontaneous sustained VT causing syncope or significant haemodynamic compromise.
      (iii) Sustained VT without syncope/cardiac arrest, and who have an associated reduction in EF (<35%) but are no worse than III in New York Heart Association functional classification of heart failure.
   (b) 'Primary prevention'
      (i) A history of previous MI and
         – non-sustained VT on Holter (24-hour ECG) monitoring:
         – inducible VT on electrophysiological testing:
         – LV dysfunction with an EF <35% and no worse than III on the New York Heart Association functional classification of heart failure.
      (ii) A history of previous MI and depressed heart function (EF ≤0.30).
      (iii) Non-ischaemic (dilated) cardiomyopathy with arrhythmia at high risk of SCD and depressed heart function (EF ≤0.30).
3. Study design: systematic reviews and meta-analyses of RCTs, in addition to individual RCTs, will be included in the review of effectiveness. Reports published only as abstracts and non-English language studies will be excluded from the review.
4. The primary outcome for the review is mortality. Secondary outcome of QoL will be data extracted from the studies included in the systematic review on the primary outcome measure.

Studies identified by the search strategy will be assessed for inclusion through three stages (see *Figure 1*). Titles and abstracts will be screened independently for inclusion by two reviewers. The full text of those studies included at this stage will be examined for inclusion by two reviewers, with any disagreements resolved through discussion.

Additional inclusion criteria for economic evaluations will be that studies must:

- include a comparator
- include both costs and consequences
- demonstrate high external and internal validity.

Data extraction strategy

Data extraction and quality assessment of the studies included in the review will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Quality assessment strategy

- Quality assessment of RCTs will be judged using Jadad criteria (see Appendix 4).
- The quality of included systematic reviews will be assessed using criteria recommended by NHS CRD (University of York) (Appendix 5).
- Quality of economic evaluations will be assessed for their internal validity (i.e. the methods used) using modified Drummond and Jefferson criteria,[24] and external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions.[25]

Methods of analysis/synthesis

- Clinical effectiveness of ICDs for arrhythmia will be synthesised through a narrative review with full tabulation of results of all included studies.
- Data will be combined statistically by meta-analysis, using Cochrane Review Manager software, if deemed inappropriate in terms of heterogeneity and number of studies.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

- Published cost-effectiveness studies will be reviewed in detail, comprising a narrative review with a tabulation of results where appropriate. Cost-effectiveness studies will be identified as part of the search strategy documented in Appendix 3.
- An economic model will be devised by adapting an existing cost-effectiveness model using the best available evidence to determine cost-effectiveness in a UK setting.
- In order to determine applicability and resource implications to the NHS, resources and costs will be sought from the published literature, NHS sources and industry submissions where appropriate and available. The perspective of the economic analysis will be that of the NHS and Personal Social Services.
- Effectiveness data, in terms of the outcomes described in the above section, will be extracted from published trials and used in association with cost data to populate the model to obtain measures of cost-effectiveness. QoL information obtained from the literature and other sources will be used to calculate cost-effectiveness/utility estimates in terms of cost per QALY.
- The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

Appendix 3

Sources of information, including databases searched and search terms

Clinical effectiveness and cost-effectiveness

The following databases were searched for published studies and ongoing research.

Searches were restricted to the English language. Bibliographies of related papers were assessed for relevant studies.

Industry submissions to NICE were searched for studies that met the inclusion criteria. (Submissions were requested from Biotronik UK Ltd, ELA Medical UK, Guidant, Medtronic UK Ltd and St Jude Medical UK Ltd.)

Search terms used for ICD were as follows: implant*, defib*, defibrillator, defibrillation, cardioversion, cardioverter, (internal near defibrillator*), (internal near defibrillation), (internal near cardioverter), (implant* near cardioverter), cardioversion, (implant* or internal), (cardiac near defibrillation), (implant and defib), (internal and defib), (cardiac and defib).

Primary search terms for economic searches were as follows: cost/, cost benefit analysis/, cost effectiveness analysis/, cost minimization analysis/, cost of illness/, cost utility analysis/, drug cost/, health care cost/, exp economics/, health economics/, economic evaluation/, pharmacoeconomics/, budget$, cost$, (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)), (economic$ or pharmacoeconomic$ or pharmaco economic$),(price$ or pricing$), (financial or finance or finances or financed), (fee or fees).

Databases searched	Clinical effectiveness: issues or dates searched	Cost-effectiveness: issues or dates searched
Cochrane Library (Database of Systematic Reviews and Controlled Trials Register)	Cochrane Library Issue 4, 2003 (28 November 2003)	
MEDLINE (OVID)	1996 to week 3, October 2003 (28 October 2003)	1996–week 3, October 2003 (28 October 2003)
PreMEDLINE (OVID)	July 2003 (28 October 2003)	
EMBASE	1996–2003, week 43 (3 November 2003)	1996–2003 week 43 (3 November 2003)
NHS Economic Evaluations Database (NHS Centre for Reviews and Dissemination, University of York)	DARE (Cochrane Library, Issue 4, 2003) (3 November 2003)	DARE Issue 4, 2003 (3 November 2003) NHS EED (Cochrane Library, Issue 4, 2003) (3 November 2003)
National Research Register	Issue 2, 2003 (10 November 2003)	
Current Controlled Trials	http://controlled-trials.com/ (10 November 03)	
NHS HTA database	HTA database (CRD databases) (3 November 2003)	
EconLit (ARC2)		1991–June 2003 (3 November 2003)

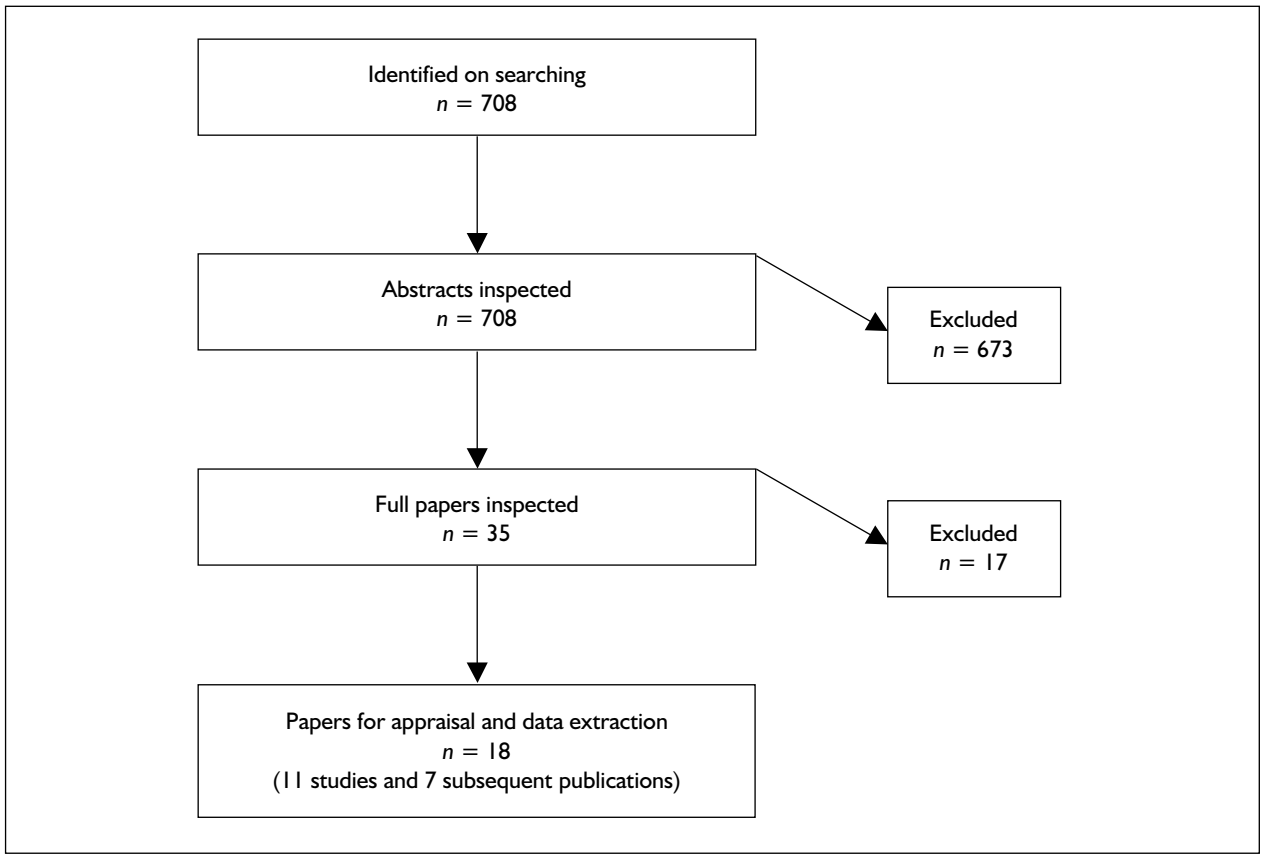

FIGURE 1 *Flowchart of identification of studies (RCTs, systematic reviews, and meta-analyses) for clinical effectiveness systematic review*

Full search strategies for economics searches are available upon request.

The process of identifying and including studies for assessment of effectiveness is illustrated in *Figure 1*. The primary reason for excluding studies was that they did not meet the inclusion criteria (e.g. they were not RCTs, did not compare ICD with alternative or did not include outcomes of interest). A list of studies excluded at various stages of the process can be found in Appendix 9.

Appendix 4

Quality assessment for RCTs (Jadad quality score)

Questions to assess the likelihood of bias

1. Was the study described as randomised (this includes the use of the words such as randomly, random and randomisation)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items

Either give a score of 1 point for each 'yes' or 0 points for each 'no'. There are no in-between marks.

Give one additional point if:

- For question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated, etc.) and/or
- If for question 2 the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.).

Deduct one point if:

- For question 1, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.) and/or
- For question 2, the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs injection with no double dummy).

Guidelines for assessment

Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

Double blinding

A study must be regarded as double blind if the word 'double blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Appendix 5

Quality assessment for systematic reviews

Criteria for assessing good-quality systematic reviews

Systematic reviews will be examined to determine how many of the following criteria for methodological quality they met.

Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?

A good review should focus on a well-defined question, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies.

The criteria should relate to the four components of study design, participants, healthcare intervention or organisation and outcomes of interest.

In addition, details should be reported relating to the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently and how disagreements between reviewers were resolved.

Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material and any contact with authors, industry and research institutes should be provided.

The appropriateness of the database(s) searched by the authors should also be considered, for example if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

Is the validity of included studies adequately assessed?

Authors should have taken account of study design and quality, either by restricting inclusion criteria or by systematic assessment of study quality. For example, if inclusion criteria have been restricted to 'double-blind randomised controlled trials, with at least 200 participants' then the need for quality assessment is not as crucial as when authors have less stringent inclusion criteria and/or include less rigorous study designs.

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g. method of randomisation, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), efficacious results and side-effects (adverse events).

Are the primary studies summarised appropriately?

The authors should attempt to synthesise the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews which incorporate a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g. according to sample size, or inverse of the

variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

For some reviews, it may be inappropriate to include a meta-analysis, and therefore a narrative synthesis of studies should be presented. It is not usual to include a formal assessment of heterogeneity or to introduce weighting in such syntheses, so a discussion relating to the main differences between studies, and the better sources of evidence, should be highlighted.

Appendix 6

Data extraction: secondary research

Reference	Methods
Authors: Lee *et al.*[32] Year: 2003 Country: Canada Study design: meta-analysis Funding: not reported	*Aim/objective:* to compare the effectiveness of ICD and medical strategies (with or without AAD) for prevention of arrhythmic events and death *Search strategy:* developed in collaboration with Cochrane heart group. Searched MEDLINE, EMBASE, Cochrane. Also searched reference lists **Inclusion criteria** *Interventions:* ICD vs medical therapy for the prevention of SCD. Studies whose primary objectives were the evaluation of defibrillation thresholds or mechanism of drug or device action and/or where the primary end-point of interest was not mortality were excluded *Participants:* Patients ≥ 18 years old who had an episode of resuscitated sudden death or symptomatic ventricular tachyarrhythmia or patients with low left ventricular EF (≤ 40%) and thought to be at risk for development of lethal cardiac arrhythmia *Outcome measures:* at least one of: all-cause mortality, cardiac death, arrhythmic mortality or cardiac arrest *Study design:* high-quality RCTs of primary or secondary prevention. Updated publications of additional outcomes not reported in primary articles were also retrieved *Quality criteria*: quality assessment by independent reviewers including (1) blinding of randomisation (allocation concealment), (2) complete follow-up, (3) blinding/objectivity of outcome assessment *Application of methods*: outcomes of all-cause mortality, arrhythmic death and non-arrhythmic death (when available) were abstracted independently from each included study. Any disagreements arbitrated by two of the authors. No details of who performed inclusion/exclusion criteria *Methods for analysis:* meta-analysis, Mantel–Haenszel method. RR and risk difference with 95% CIs using a fixed-effects model for all primary/secondary prevention trials separately and all trials in the overall analysis. If a statistically significant reduction noted then numbers needed to treat were calculated. Statistical heterogeneity identified using the χ^2 statistic, and $p \leq 0.10$ was deemed statistically significant. If heterogeneity identified then a random effects model performed. Adverse events were reported as weighted percentages
Results *Quantity and quality of included studies:* 1077 potential articles and 1003 were excluded on the basis of titles and abstracts. Of the 74 articles retrieved, 51 were excluded. Of the remaining 23 articles, a number were publications that evaluated the mode of death in the same patient sample as the primary study publication. There were 16 discrete randomised trials that were subsequently assessed for quality. Five trials were primary prevention trials and four were secondary prevention trials (assume the remaining seven were additional publications of these but not stated). No reporting of quality assessment findings *Treatment effect:* Over 5000 patients randomised **All-cause mortality** Summary RR for all-cause mortality in primary prevention trials: 0.66 (95% CI 0.46 to 0.96), $p = 0.03$, test for heterogeneity $p = 0.0001$ Summary RR for all-cause mortality in secondary prevention trials: 0.75 (95% CI 0.64 to 0.87), $p = 0.0002$, absolute reduction was 7% (95% CI 4 to 100%); number needed to treat 15, test for heterogeneity $p = 0.26$ Summary RRR for all-cause mortality in all trials: 0.30, random effects $p < 0.001$, absolute risk of any-cause death reduced by 10% (95% CI 4 to 16%).	

continued

Arrhythmic death
Summary RR for arrhythmic mortality in primary prevention trials: 0.34 (95% CI 0.23 to 0.50), $p < 0.00001$, no significant heterogeneity ($p = 0.21$)

Summary RR for arrhythmic mortality in secondary prevention trials: 0.50 (95% CI 0.34 to 0.62), absolute reduction of 7% (95% CI 5 to 10%), no significant heterogeneity ($p = 0.3$)

When all trials reporting arrhythmic deaths were pooled there was consistency between the individual trial results and no statistical heterogeneity ($p = 0.18$). Summary RR: 0.43 (95% CI 0.35 to 0.54), $p < 0.00001$. An 8% absolute reduction (95% CI 6 to 10%)

Non-arrhythmic death
Summary RR for non-arrhythmic mortality in primary prevention trials: 0.95 (95% CI 0.74 to 1.21)

Summary RR for non-arrhythmic in secondary prevention trials: 0.95 (95% CI 0.71 to 1.27)

Overall summary RR for non-arrhythmic mortality in all trials: 0.95 (95% CI 0.79 to 1.15) with no heterogeneity between studies ($p = 0.3$).

Sensitivity analyses
Primary prevention patients with ischaemic heart disease (four studies) favoured ICD RR 0.64 (95% CI 0.41 to 0.98) with a significant reduction in all-cause mortality, $p = 0.04$. Only CABG had protocol-driven revascularisation, the remaining three studies (MUSTT, MADIT I and II) may have differed in the potential for silent or residual ischaemia. When these three were combined, there was a reduction in RR of all-cause death of 0.53 (95% CI 0.37 to 0.76, $p < 0.001$).

Effect of industry versus non-industry sponsorship: seven trials were supported by manufacturers and pooling of these results showed a 33% RRR ($p < 0.01$). Of the two without industry support the results remained in favour of the ICD with a 25% RRR ($p = 0.001$)

Excluding MADIT I and II still demonstrated a significant benefit for ICD on all-cause mortality (RR 0.73, 95% CI 0.57 to 0.94, $p = 0.01$) and arrhythmic death (RR 0.44, 95% CI 0.35 to 0.56, $p < 0.001$)

Excluding MUSTT from pooled analysis of primary prevention the RR of arrhythmic death remained significant at 0.45 (95% CI 0.26 to 0.78, $p < 0.01$), but the reduction in all-cause mortality (RR 0.74, 95% CI 0.51 to 1.08) was no longer significant ($p = 0.12$)

Secondary prevention patients (all-cause mortality)
Excluding AVID: RR 0.81, 95% CI 0.67 to 0.98, heterogeneity $p = 0.34$, ICD benefit $p = 0.03$

Excluding CASH: RR 0.73, 95% CI 0.61 to 0.87, heterogeneity $p = 0.16$, ICD benefit $p = 0.0004$

Excluding CIDS: RR 0.69, 95% CI 0.57 to 0.84, heterogeneity $p = 0.28$, ICD benefit $p = 0.0002$

Excluding Wever: RR 0.76, 95% CI 0.65 to 0.89, heterogeneity $p = 0.32$, ICD benefit $p = 0.0005$

Treatment-related complications
Commonly reported adverse events (and weighted percentages): ICD group: infection (2.4%), haematoma or seroma (3.7%), pericardial effusion or tamponade (0.6%), pneumothorax (1.6%), lead dislodgement or fracture (2.3%), device malfunction (2.0%). AAD group: amiodarone pulmonary toxicity 3.0–5.7% (weighted mean 4.8%)

Conclusions
The ICD is highly effective in reducing the risk of arrhythmic death when used in either primary or secondary prevention context. Pooled analysis of all-cause mortality showed a reduction in risk of death with ICD implantation, but dependent on the patient population examined

Implications of the review
The impact of ICD strategies on health policy, cost-effectiveness, and access should be further evaluated

Methodological comments

- Search strategy: adequate
- Participants: adequate
- Inclusion/exclusion criteria: adequate – included one study that had large proportion of crossovers
- Quality assessment of studies: reported to have been undertaken, but no results presented
- Method of synthesis: appropriate, caution with meta-analysis of both primary and secondary prevention studies

General comments
- Funding: not reported

continued

Quality assessment for systematic reviews[23]	
Question	**Score**
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Cannot tell
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

Reference	**Methods**
Authors: Ezekowitz *et al*.[30] Year: 2003 Country: Canada Study design: systematic review and meta-analysis Funding: grant support from CIHR strategic training fellowship in TORCH (Tomorrow's research cardiovascular health professionals) and by the Alberta Herigate Foundation for Medical research NHS CRD score 4/5	*Aim/objective:* to assess the efficacy of implantable cardioverter defibrillators in persons at increased risk for SCD *Search strategy:* searched multiple databases, including MEDLINE, Cochrane, EMBASE, Web of Science, Clinical Trials Registry, NNR, Glaxo-Wellcome Clinical Trials Register, Latin American and Caribbean Health Science Literature, Computer Retrieval of Information on Scientific Projects, Online Computer Library Centre, NHS EED. Last accessed on 24 September 2002. Bibliographies or relevant papers hand-searched, experts, manufacturers, primary authors contacted. Conference proceedings searched. Search strategy appears to be appropriate, including text words and MESH headings **Inclusion criteria** *Interventions:* ICD versus placebo, or ICD versus antiarrhythmic therapy *Participants:* patients at risk of SCD or ventricular arrhythmia (sustained VT or VF) who had evidence of heart failure or CAD (primary prevention), or survivors of SCD or unstable ventricular rhythm (secondary prevention) *Outcome measures:* had to include SCD or all-cause mortality. Data also extracted on total cardiac mortality and total non-cardiac mortality *Study design:* RCTs Excluded those that did not report any of the outcomes of interest or had cross-over rates of >50% between study groups Because it was anticipated that the primary prevention trials would encompass a broad spectrum of patients, they were subdivided into those enrolling high-risk patients and those enrolling moderate-risk patients. High risk = those with expected rate of SCD of ≥ 5% per year (those with ischaemic cardiomyopathy, with or without ventricular arrhythmia) *Quality criteria:* no quality assessment presented in publication. States that intention-to-treat analyses were performed, and the outcome definitions used by the original researchers were accepted *Application of methods:* two reviewers independently reviewed titles and abstracts. Standardised data forms were used to review the full text of potentially relevant articles. A funnel plot was used to evaluate publication bias. All discrepancies in trial eligibility or data collection were resolved by consensus *Methods for analysis:* summary relative risks calculated using Metaview 4.1. Cochran Q-test to assess heterogeneity in each outcome. Meta-analysis using Der-Simonian and Laird random effects model, and also Mantel–Haenszel–Peto fixed-effects model (fixed effects only reported when results are the same and there was no significant heterogeneity). Sensitivity analyses to examine the effect of year of publication, study quality and allocation concealment

continued

Results

Quantity and quality of included studies: 9 parallel-group randomised trials identified (out of 385); 1 excluded as both groups received ICD therapy.

3 studies were secondary prevention studies, 5 primary prevention (3 involving high-risk, 2 moderate risk-patients). All trials were randomised and controlled. None were blinded owing to the nature of the intervention. Randomisation and allocation concealment were adequate in all trials. All-cause mortality and SCD were reported in all trials, but other outcomes were not consistently reported. For several trials, secondary publications were consulted, or authors were contacted to determine causes of death

Treatment effect: 4909 patients randomised.

SCD

Summary RR for SCD in all trials: 0.43 (95% CI 0.35 to 0.53)

Summary RR for SCD in primary prevention trials: 0.37 (95% CI 0.27 to 0.50)

Summary RR for SCD in secondary prevention trials: 0.50 (95% CI 0.38 to 0.66)

No significant heterogeneity was noted among the trials although no SCDs occurred in either study group in 1 trial because low-risk patients were recruited

There was no appreciable difference between types of ICD (transthoracic vs transvenous) in the summary effect estimates for prevention of SCD (data not given)

All-cause mortality

Summary RR for all-cause mortality in all trials: 0.74 (95% CI 0.67 to 0.82)

Summary RR for all-cause mortality in primary prevention trials: 0.72 (95% CI 0.63 to 0.84)

Summary RR for all-cause mortality in secondary prevention trials: 0.76 (95% CI 0.65 to 0.89)

Random effects models yielded similar summary RRs for overall mortality [0.72 (95% CI 0.58 to 0.90)], all-cause mortality in primary prevention [0.69 (95% CI 0.46 to 1.03)] and all-cause mortality in secondary prevention [0.77 (95% CI 0.65 to 0.91)]

Substantial heterogeneity in total mortality was observed between primary prevention trials enrolling high-risk patients and those enrolling moderate-risk patients ($p < 0.001$). The latter trials failed to demonstrate any survival benefit with ICD therapy

In the 3 trials demonstrating a substantial survival benefit, virtually all patients had known CAD and LV dysfunction; and in 2 of these trials, the patients also had inducible ventricular arrhythmias on electrophysiological testing (these were the trials defined as high risk by the reviewers). In the 'moderate-risk' trials all patients had LV systolic dysfunction; 1 only included patients with non-ischaemic DCM but no inducible ventricular arrhythmia, and the other patients after successful CABG, in which myocardial ischaemia was probably resolved

The risk difference for total mortality was 0.08 (95% CI 0.02 to 0.13) for all included trials, yielding a number needed to treat for benefit of 13 (95% CI 8 to 50). This summary score is, however, inadequate as calculation varies depending on baseline risk

Total cardiac mortality (reported in five trials)

Summary RR: 0.81 (95% CI 0.69 to 0.96)

Non-cardiac mortality (reported in 3 trials)

Summary RR: 0.91 (95% CI 0.60 to 1.38)

Adverse events (no summary scores given)

Perioperative infection rates ranged from 0.7 to 12.3% in the included trials

Lead fracture or device malfunction ranged from 1.8% to 14%

Serious bleeding rates ranged from 1% to 6%

Pneumothorax occurred in <1% of patients

The complication rates were higher for transthoracic ICD

Economic evaluation

Not reported

Conclusions

ICDs are highly efficacious in prevention SCD, both as primary and secondary prevention

ICDs reduce the RR for SCD by ~50% regardless of baseline risk

The effect of ICD on all-cause mortality varies according to baseline risk

continued

Implications of the review
Further research is needed to develop accurate risk stratification tools, to determine the economic impact of ICD therapy and to evaluate QOL issues

Methodological comments
- Search strategy: adequate – made an exhaustive search, also contacted authors, manufacturers, experts, searched relevant conference abstracts
- Participants: adequate
- Inclusion/exclusion criteria: adequate – included primary and secondary prevention studies. Excluded one study that had greater than 50% crossovers
- Quality assessment of studies: not reported
- Method of synthesis: some heterogeneity noted on all-cause mortality – caution with meta-analysis

General comments
- Funding: research grants, not from manufacturers

Quality assessment for systematic reviews[23]

Question	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	No
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

Reference	Methods
Authors: Connolly *et al*.[31] Year: 2000 Country: Canada Study design: meta-analysis (individual patient data) Funding: not reported	*Aim/objective*: (1) to assess the degree of consistency of the benefit of the ICD vs amiodarone amongst the three study estimates, (2) to provide the most precise estimate of the efficacy of the ICD and (3) to investigate the extent to which specific patient subgroups benefit differently from ICD therapy *Search strategy:* no databases searched, states that only three RCTs have been published and that planning for the meta-analysis was started before completion of these trials *Inclusion criteria:* secondary prevention trials *Interventions:* not stated *Participants:* not stated. Population divided based on date of implantation so provide a relatively unbiased and efficient way to investigate the effect of implant method on ICD efficacy, recognising there is confounding with whatever other changes in patient management occurred pre- and post-1991 *Outcome measures:* not stated *Study design:* not stated Only data pertaining to the amiodarone and ICD treatment arms of the CASH study were included in the analysis. 13/509 patients in the AAD group of the AVID study received sotolol at hospital discharge. To exclude them would disrupt the original randomisation procedure of the trial, and these were therefore included Data were curtailed at 6 years of follow-up, as relatively few patients were followed up beyond this time *Quality criteria:* not reported, assumed not used as only pooled data from the trials, did not review the studies *Application of methods:* each study extracted individual patient data corresponding to the required set of data fields. These were transferred by electronic means to the AVID study coordinating centre where they were merged into a master database

continued

Reference	Methods
	Methods for analysis: the effect of treatment on various fatal outcomes was investigated by means of proportional hazards modelling and log-rank testing. This method was also used to investigate the influence of various baseline clinical and demographic characteristics on the size of the ICD treatment effect and also to adjust for any study effect not accounted for by measured baseline covariants. All analyses by intention-to-treat principle. Also performed meta-analysis using fixed-effects and random-effects methods (similar results). The prolongation of life attributable to therapy was calculated by computing the difference in the areas under the two survival curves *Differences between individual studies inclusion criteria:* patient eligibility differed slightly between the studies. CASH only included patients with previously documented VF, whereas CIDS and the AVID study included patients with either VF or symptomatic sustained VT. Additionally, CIDS included patients with unmonitored syncope who were shown to have VT. The mean follow-up was longest in CASH, with some patients being followed for almost 10 years. The AVID study had the shortest follow-up (mean 1.51 years). The AVID was the largest with 1016 patients, the CASH randomised only 191 to the ICD/amiodarone comparison. However, due to the longer follow-up, the total patient years of follow-up was greatest in the CIDS. The mean duration of follow-up from the pooled database was 2.33±1.89 years.
Baseline characteristics of pooled database Baseline clinical characteristics within each trial reported in tables (not data extracted as data extracted from individual trials). Reported differences extracted: the patients in the AVID and CIDS studies were generally similar. Patients enrolled in CASH were younger and had a higher LVEF than in the other studies. In CIDS and AVID just under half of the patients were enrolled with a presenting diagnosis of VF; 14% of CIDs presented with unmonitored syncope. There were differences in ICD therapy among the three studies largely because CASH was initiated several years before the era when non-thoracotomy ICDs were available. In CASH 44% of patients had a thoracotomy ICD compared with 10% of CIDS and 5% of AVID patients. There was a post-randomisation imbalance in beta-blocker use in both AVID and CIDS, with higher rates of use in the ICD treatment arm. None of the amiodarone or ICD group patients in CASH received a beta-blocker at hospital discharge. Rates of crossover during follow-up were similar in CIDS and AVID *Baseline characteristics of the pooled database ICD* (n = *934) and amiodarone* (n = *932):* Age (years): ICD 63 ± 11, amiodarone 64 ± 10 Male gender (%): ICD 81, amiodarone 82 LVEF: ICD 34 ± 15, amiodarone 33 ± 14 NYHA class (CHF symptoms) ≥ 3: ICD 9%, amiodarone 12% Prior MI: ICD 69%, amiodarone 69% Non-ischaemic cardiomyopathy: ICD 12%, amiodarone 13% No heart disease (%): ICD 4, amiodarone 3 Presenting arrhythmia: VF: ICD 51%, amiodarone 52% VT: ICD 44%, amiodarone 43% Syncope: ICD 5%, amiodarone 4% Randomised in the 'epicardial era' (before July 1991): ICD 9%, amiodarone 8% Discharged beta-blocker: ICD 42%, amiodarone 19% [significantly different (*p* value not reported)] Discharged ACE inhibitor: ICD 63%, amiodarone 64% Discharged ASA (aminosalicylic acid): ICD 51%, amiodarone 51%	
Results *Quantity and quality of included studies* Not applicable *Treatment effect* Individual trials results are reported (not data extracted) **Pooled data:** • There were significant reductions in both all-cause mortality and in arrhythmic death with the ICD • For total mortality, the HR (ICD:amiodarone) was 0.73 (95% CI 0.60 to 0.87, $p < 0.001$) • For arrhythmic death, the HR was 0.49 (95% CI 0.36 to 0.67, $p < 0.001$) • For all non-arrhythmic deaths, the HR was 0.93 (95% CI 0.73 to 1.17, $p = 0.517$)	

continued

Cumulative risk of fatal events for the outcomes of all-cause mortality and of arrhythmic death (cumulative risks are estimated from figure), (assume percentages as no label on *y*-axis):

	ICD		Amiodarone	
	Number at risk	**Cumulative risk**	**Number at risk**	**Cumulative risk**
Death				
1 year	715	9	664	15
2 years	467	16	427	22
3 years	273	22	248	30
4 years	159	29	128	37
5 years	104	35	82	40
Arrhythmic death				
1 year	715	4	664	8
2 years	467	5	427	11
3 years	273	7	248	15
4 years	159	9	128	20
5 years	104	11	82	21

From text: for the outcome of death the two treatment arms separate incrementally for the first 3–4 years and then appear to come closer together. For arrhythmic death there appears to be steady incremental separation throughout the 6 years between the two treatment arms

- The prolongation of life by the ICD over amiodarone was 2.1 months at 3 years of follow-up and 4.4 months at 6 years of follow-up

Subgroup interactions

Subgroup	***n***	**Hazard ratio (95% CI)**	***p*-Value (interaction)**
LVEF >35%	643	1.2 (0.81 to 1.76)	
LVEF ≤ 35%	1189	0.66 (0.53 to 0.83)	0.011
Presenting arrhythmia:			
VT	809	0.73 (0.54 to 0.99)	
VF	934	0.78 (0.61 to 1.10)	0.766
Prior MI:			
Yes	1268	0.74 (0.60 to 1.02)	
No	564	0.79 (0.55 to 1.49)	0.591
Epicardial era:			
Yes	151	1.52 (0.92 to 2.50)	
No	1081	0.69 (0.56 to 0.85)	0.029
Discharge beta-blocker:			
Yes	566	0.58 (0.38 to 0.89)	
No	1266	0.88 (0.71 to 1.09)	0.095
Non-ischaemic cardiomyopathy:			
Yes	225	0.78 (0.45 to 1.37)	
No	1607	0.77 (0.63 to 0.94)	0.885
Coronary artery disease:			
Yes	1493	0.78 (0.63 to 0.95)	
No	339	0.80 (0.48 to 1.33)	0.973
NYHA class (CHF symptoms):			
≥3	1637	0.74 (0.59 to 0.91)	
<3	195	0.75 (0.48 to 1.17)	0.516
CABG at baseline:			
Yes	131	1.40 (0.26 to 3.17)	
No	1701	0.73 (0.60 to 0.89)	0.106

continued

Cumulative risk of death for patients with LVEF >35% and ≤ 35% (cumulative risks are estimated from figure):

	ICD		Amiodarone	
	Number at risk	**Cumulative risk**	**Number at risk**	**Cumulative risk**
LVEF >35%				
1 year	272	7	233	7
2 years	191	12	162	13
3 years	121	18	97	20
4 years	71	23	57	22
5 years	53	26	40	22
LVEF ≤35%				
1 year	432	10	417	19
2 years	265	18	255	28
3 years	145	27	145	37
4 years	86	31	68	47
5 years	49	40	40	49

Meta-analysis
Fixed-effects model
Total mortality:

Name	**Number**	**Events**	**HR (95% CI)**
AVID	1016	80	0.62 (0.47 to 0.81)
CIDS	659	83	0.82 (0.61 to 1.10)
CASH	191	37	0.83 (0.52 to 1.33)

Fixed effects HR = 0.72 (95% CI 0.60 to 0.87)
Test for association (U = 11.77 on 1 df), p = 0.00060
Test for heterogeneity (Q = 2.37 on 2 df), p = 0.30550

Arrhythmic mortality:

Name	**Number**	**Events**	**HR (95% CI)**
AVID	1016	24	0.48 (0.27 to 0.66)
CIDS	659	30	0.68 (0.43 to 1.08)
CASH	191	7	0.32 (0.15 to 1.698)

Fixed effects HR = 0.50 (95% CI 0.37 to 0.67)
Test for association (U = 21.73 on 1 df), p = 0.00000
Test for heterogeneity (Q = 3.57 on 2 df), p = 0.16807

Conclusions

- The results of the three trials of secondary prevention are consistent with one another
- The lack of any evidence of heterogeneity indicates that the differences in treatment benefit shown in the individual trials are not major and are likely due to play of chance
- In patients surviving sustained VT or VF, the trials of ICD therapy vs amiodarone demonstrate a 28% reduction in death with ICD
- The ICD prolonged life by an average of 4 months during 6 years of follow-up
- Assessment of LVEF appears to stratify those who respond best to the ICD

Implications of the review
Two different analytic methods were used: an analysis of the pooled databases (stratified by study) and a fixed-effects meta-analysis. The meta-analytical method makes fewer assumptions about the similarity of the studies in design and execution, whereas the pooled analysis offers more scope for graphic presentation. Both yielded similar results

continued

Methodological comments
- Search strategy: no searches undertaken. Study authors worked with the trialists of the included studies
- Participants: pooled baseline characteristics similar between groups except the proportion of patients discharged with beta-blockers
- Inclusion/exclusion criteria: not stated explicitly
- Quality assessment of studies: not undertaken
- Method of synthesis: fixed-effects meta-analysis and pooled data analysis (states also random effects meta-analysis but data not reported)

General comments
- Funding: not reported

Appendix 7

Data extraction: secondary prevention trials

Reference and design	Intervention	Participants	Outcome measures
Author: AVID investigators (Antiarrhythmics versus implantable defibrillators),[33] (and Schron *et al*.[34]) Year: 1997 (and 2002) Country: USA and Canada Study design: RCT Number of centres: not reported (59 centres noted in appendix as contributing) Funding: National Heart, Lung, and Blood Institute	Comparisons of different interventions: 1. AADs 2. ICD. Any advanced, state-of-the-art ICD meeting prespecified criteria (published) could be used. Almost all were transvenous systems that could be implanted without thoracotomy and provided tiered therapy, including antitachycardia pacing functions, bradycardia pacing, diagnostic memory and, in many, a capability for pectoral implantation. All either approved by FDA or implanted under an investigational device exemption. Manufacturers used were Guidant, Sulzer, Medtronic, and Ventritex Other interventions used: consideration of the use of sotalol was left to the judgement of the physician (common reasons for exclusion were history of asthma, low LVEF or history of congestive heart failure). If patients randomly assigned to AADs were also eligible for sotolol, a second randomisation assigned them to amiodarone at doses determined empirically or sotalol guided by electrophysiological testing, Holter monitoring or both The daily maintenance dose of amiodarone was	Number of participants: 6035 patients were screened, 4621 entered the registry, 1885 were eligible for randomisation. Of these, 1016 were randomised: 507 ICD (non-thoracotomy lead system in 93%, epicardial device in 5%, and no device in 2%) 509 antiarrhythmic therapy (356 immediately began empirical therapy with amiodarone as thought not able to tolerate sotolol; 153 were further randomised with 79 amiodarone and 74 sotolol, but only 13 (2.6% of total group) given sotolol had adequate suppression of arrhythmia and were receiving sotalol at discharge). The remainder received amiodarone (58 patients), another AAD (1) or an ICD (2) Sample attrition/dropout: not reported Sample crossovers: length of time to crossover – ~20% crossed over to or added the other therapy by 24 months. The crossover rate was higher among those initially assigned to therapy with an ICD ($p < 0.001$). Cumulative probability of crossover: **Rate** / **ICD (%)** / **Antiarrhythmia (%)** 1 year (no. at risk: 553) / 17.7 / 12.6 2 years (no. at risk: 270) / 25.7 / 18.9 3 years (no. at risk: 83) / 33.7 / 24.3 Inclusion/exclusion criteria for study entry: patients who had been resuscitated from near-fatal VF, sustained VT with syncope or sustained VT with an ejection fraction of ≤ 0.40 and symptoms suggesting severe haemodynamic compromise due to the arrhythmia (near-syncope, congestive heart failure and angina). If patients underwent revascularisation, the EF had to be ≤ 0.40 for them to be eligible. Eligible for treatment with amiodarone Excluded if NHYA class IV A registry of all patients who were eligible but not randomised, and another followed patients with VT or VF who were not eligible for randomisation	Primary outcomes: overall mortality Secondary outcomes: costs, QoL, complications, adverse symptoms, adverse symptoms and relationship with QoL scores, ICD shocks Method of assessing outcomes: patients were assessed every 3 months and at the time of events QoL (first year instruments tested for reliability, then used a reduced set of 3 questionnaires): Instruments were generic and disease specific: 1. SF-36 evaluates limitations in physical, emotional or social functioning, bodily pain, general health perceptions, vitality and general mental health. Four subscales measure physical health, four evaluate the impact of disease or treatment on mental health. A summary measure calculated for each subscale, physical component summary score (PCS) and a mental component summary (MCS) 2. Patient concerns checklist (PCC), disease specific to VF or symptomatic VT. Adapted from a 63-item assessment

continued

Reference and design	Intervention	Participants	Outcome measures
	progressively decreased throughout the course of follow-up (mean 389 ± 112 mg at 3 months, 331 ± 99 mg at 1 year, 294 ± 94 mg at 2 years and 256 ± 95 mg at 3 years). Most people receiving amiodarone at discharge continued to take the drug (87% at 1 year and 85% at 2 years). The mean daily maintenance dose of sotalol during follow-up was stable (258 ± 81 mg at 3 months, 248 ± 88 mg at 1 year, 280 ± 121 mg at 2 years, 240 ± 113 mg at 3 years) During hospitalisation for the index arrhythmia, 10% of ICD and 12% of AAD groups underwent coronary revascularisation Concurrent therapies at hospital discharge and during follow-up (see below)	Characteristics of participants: overall sample mean age 65 years, 79% male, 86% white, 455 had VF, 561 had VT (216 with syncope and 345 with other symptoms of serious haemodynamic compromise and with an EF ≤0.40) Mean ±SD: Age (years): ICD 65 ± 11, AAD 65 ± 10 Male gender (%): ICD 78, AAD 81 White race (%): ICD 87, AAD 86 Index arrhythmia (no.): VF: ICD 226, AAD 229 Sustained VT: ICD 281, AAD 280 Clinical history before index AAD (%): Atrial fibrillation/flutter: ICD 21, AAD 26 VF: ICD 5, AAD 5 VT: ICD 14, AAD 15 Unexplained syncope: ICD 11, AAD 15 Coronary artery disease: ICD 81, AAD 81 MI: ICD 67, AAD 67 Congestive heart failure (CHF): ICD 46, AAD 47 Hypertension: ICD 55, AAD 56 Diabetes: ICD 25, AAD 24 Angina: ICD 48, AAD 50 Peripheral vascular disease: ICD 16, AAD 15 AAD therapy: ICD 16, AAD 15 LVEF: ICD 0.32 ± 0.13, AAD 0.31 ± 0.13 Median time from index event to measurement (days): ICD 3, AAD 3 Angina at enrolment (%): None: ICD 64, AAD 65 Canadian cardiovascular society (CCS) class I or II: ICD 34, AAD 33 CCS class III: ICD 2, AAD 2 Congestive heart failure at enrolment (%): None: ICD 45, AAD 40 NYHA class I or II: ICD 48, AAD 48 NYHA class III: ICD 7, AAD 12 Findings on baseline ECG (when taking no AADs and without cardiac pacing): Heart rate (bpm): ICD 77 ± 18, AAD 78 ± 17 PR interval (ms): ICD 178 ± 37, AAD 183 ± 37 QRS complex (ms): ICD 116 ± 26, AAD 117 ± 26 Corrected QT interval (ms): ICD 441 ± 40, AAD 445 ± 39 Paced (% of patients): ICD 3, AAD 4 Bundle-branch block (%): ICD 23, AAD 25 QoL baseline: see results below Baseline characteristics for those included in the QoL substudy not data extracted – 1 significant difference which is noted below	3. Cardiac version of the QoL index: issues relevant to heart disease including satisfaction and health perception, functioning, socioeconomic factors, psychological and spiritual wellbeing and family life For scoring of 1, 2 and 3, see below Measurements at 3, 6 and 12 months post-randomisation for SF-36 and PCC, cardiac QoL at 12 months Adverse symptoms: cardiovascular, such as pulmonary, neurological, ocular, dermatological, gastrointestinal, genitourinary, musculoskeletal, endocrine or infectious. Symptoms that resulted in minor change of study therapy categorised as mild or moderate. Severe symptoms = requiring temporary or permanent discontinuation of therapy. Assessed at follow-up ICD shocks: 3, 6 and 12 months follow-up or if symptoms. Categorised by experienced cardiac electrophysiologists Length of follow-up: mean 18.2 ± 12.2 months Recruitment began on 1 June 1992 and concluded on 7 April 1997

continued

Therapy at discharge (%)	**ICD (*n* = 497)**	**AAD (*n* = 496)**
ICD	98.6	1.4
Amiodarone	1.8	95.8
Sotalol	0.2	2.8
Beta-blocker (BB)	42.3	16.5
Calcium channel blocker (CB)	18.4	12.1
Both BB and CB	5.3	2.4
Digitalis	46.8	40.6
Diuretic	48.2	50.7
Other AAD	4.2	1.2
ACE inhibitor	68.8	68.2
Nitrate	36.4	37.0
Other antihypertensive agent	7.6	8.8
Lipid-lowering agent	13.2	11.5
Aspirin	60.7	59.2
Warfarin	21.9	34.8
Therapy at follow-up (12 months)[a]	**ICD (*n* = 338)**	**AAD (*n* = 306)**
ICD	97.9	9.5
Amiodarone	8.3	84.7
Sotalol	1.8	5.8
BB	38.1	11.0
CB	22.9	16.6
Both BB and CB	6.8	2.1
Digitalis	45.8	37.9
Diuretic	56.0	59.3
Other AAD	7.1	3.8
ACE inhibitor	68.4	65.5
Nitrate	29.1	27.9
Other antihypertensive agent	9.0	9.4
Lipid-lowering agent	19.5	17.2
Aspirin	55.4	55.4
Warfarin	24.8	35.4
Therapy at follow-up (24 months)[a]	**ICD (*n* = 171)**	**AAD (*n* = 162)**
ICD	95.7	9.8
Amiodarone	9.3	82.4
Sotalol	3.1	8.5
BB	39.4	10.1
CB	19.4	14.1
Both BB and CB	5.6	0.7
Digitalis	44.4	32.3
Diuretic	56.9	56.4
Other AAD	10.0	4.0
ACE inhibitor	68.1	63.1
Nitrate	28.1	29.5
Other antihypertensive agent	10.0	6.1
Lipid-lowering agent	23.1	19.5
Aspirin	62.5	56.4
Warfarin	22.5	30.2

Comments: more patients were taking beta-blockers ($p < 0.001$) and slightly more patients were taking digitalis ($p = 0.04$) in the ICD group than the ADD group at discharge and during follow-up.

[a] Patients who died while in the hospital after the index event ($n = 19$) are excluded, as are patients still in the hospital at the termination of the study ($n = 4$).

continued

Results			
Outcomes	**ICD (n = 507)**	**AAD (n = 509)**	***p*-Value**
Death	80	122	
Crude death rates over mean follow-up (%)	15.8±3.2	24.0±3.7	
Overall survival (%):			
1 year (overall n = 644)	89.3	82.3	<0.02 (adjusted
2 years (overall n = 333)	81.6	74.7	for repeated analysis,
3 years (overall n = 104)	75.4	64.1	n = 6)
Comments: these survival figures represent a decrease in death rates (states with 95% CI but assume an SD) of 39 ± 20, 27 ± 21 and 31 ± 21% at 1, 2 and 3 years, respectively, although the accuracy of long-term data is limited because few patients had been followed up beyond 2 years at the time the study ended. The average unadjusted length of additional life associated with ICD therapy was 2.7 months at 3 years.			
HRs for death from any cause (95% CI) (estimated from figure)	Age: <60 years: 0.58 (0.3 to 1.2) 60–69 years: 0.63 (0.39 to 1.2) ≥ 70 years: 0.64 (0.43 to 1.0) LVEF: >0.35: 0.85 (0.46 to 1.62) ≤0.35: 0.57 (0.41 to 0.79) Cause of arrhythmia: Coronary artery disease: 0.63 (0.47 to 0.78) Other: 0.62 (0.29 to 1.37) Rhythm: VF: 0.57 (0.38 to 0.85) VT: 0.68 (0.46 to 0.82) Overall: 0.62 (0.45 to 0.85)		
Comments: HRs for death from any cause in subgroups: age, LVEF, cardiac diagnosis, qualifying arrhythmia (not significantly different but the early termination of the study diminishes its power). Multivariate analysis showed that the beneficial effect of the implantation of the ICD persisted after adjustment for other factors, such as age, beta-blocker use, presence or absence of congestive heart failure and EF at baseline. Furthermore, revascularisation after the index arrhythmia did not alter survival. Estimates in which the Cox model was used to adjust for baseline differences in the presence or absence of heart failure, the EF and history with respect to atrial fibrillation indicated that the reductions in mortality (with apparent 95% CI) attributable to ICD were 37 ± 22% at 1 year, 24 ± 22% at 2 years and 29 ± 23% at 3 years. Estimates adjusted for the use of beta-blockers were unchanged from the unadjusted values.			
QoL	**ICD**	**AAD**	***p*-Value**
SF-36			
Mean PCS	37.4 ± 10.9	36.5 ± 11.2	
PCS change over time (estimated from figure)	Baseline: 38 3 months: 39 6 months: 39 12 months: 40	Baseline: 36 3 months: 37 6 months: 37 12 months: 37	Baseline scores p = 0.3, increased over time (p = 0.01) but similarly p = 0.03[a]
Mean MCS	45.9 ± 11.8	47.5 ± 11.5	
MCS change over time (estimated from figure)	Baseline: 45 3 months: 46 6 months: 47 12 months: 47	Baseline: 49 3 months: 47 6 months: 48 12 months: 47	Baseline scores lower in ICD group (p = 0.006). Time trend NS (p = 0.27)[b]
PCC			
Mean PCC	15.9 ± 8.6	16.2 ± 8.9	
PCC change over time	No data	No data	Baseline scores p = 0.6 (during follow-up p = 0.1) but scores declined as a group (p = 0.001)[c]

continued

QoL	ICD	AAD	*p*-Value
QoL index (cardiac)			
Mean QoL index	22.1 ± 4.9	21.9 ± 5.0	
QoL index change over time	No data	No data	Baseline and follow-up scores similar, and scores did not change over time

Comments: overall SF-36 scores, PCS scores and MCS scores each range from 0 to 100, with higher scores indicating superior QoL. The PCC scores range from 0 to 46, with higher scores indicating increased concern and poorer QoL. The cardiac version of the QoL index scores range from 0 to 30 with higher scores indicating better QoL.

QoL participants were younger (65 vs 68 years), more likely to be male (81 vs 70%), white (88 vs 70%), be living with a spouse/partner (71 vs 51%) and graduated from high school (73 vs 42%) than non-participants. QoL substudy participants (those alive at 1 year) were more likely to be living with a spouse/partner (72 vs 62%) and graduated from high school (74 vs 65%) than those who died. They also had higher LVEF (0.32 vs 0.27), were less likely to have a history of heart failure (43 vs 70%), more likely to receive an ICD (52 vs 37%) and more often discharged with a beta-blocker (30 vs 17%) than those who died.

Complete QoL data were available for most patients at each specified time point. A larger amount of information was missing at later compared with earlier assessments. Most (49%) incomplete data were considered missing because of their collection outside of specified time periods. Other reasons include too ill, refusal, forgotten, cannot read English and missing.

[a] When patients who died in the first year were included, similar results in baseline scores ($p = 0.1$), alteration in scores over time ($p = 0.01$) and change in two treatment groups over time ($p = 0.3$) were observed.

[b] When patients who died in the first year were included, similar results in baseline scores ($p = 0.04$) and temporal changes were observed ($p = 0.9$).

[c] When patients who died in the first year were included, similar results in baseline ($p = 0.6$) and follow-up ($p = 0.2$) were observed.

Patients who received an ICD and were discharged with beta-blockers had similar MCS ($p = 0.9$) and PCS ($p = 0.9$) scores compared with patients with ICD not receiving beta-blockers.

		p-Value
Automatic pacing or shocks in ICD group (cumulative percentage of patients with any activation)	For those with VT: 36% at 3 months 68% at 1 year 81% at 2 years 85% at 3 years For those with VF: 15% at 3 months 39% at 1 year 53% at 2 years 69% at 3 years	*p*-Value <0.001 for those with VT vs those with VF
Impact of shocks on QoL (any vs none)		
SF-36 PCS (95% CI)	–1.45 (–2.74 to –0.18), $p = 0.03$	Not tested
SF-36 MCS (95% CI)	–1.82 (–3.56 to –0.08), $p = 0.04$	Not tested
PCC (95% CI)	2.15 (1.07 to 3.23), $p < 0.001$	Not tested

Comments: QoL paper reports shocks as 144 (39%) experiencing ≥ 1 shock during the initial year of follow-up. Similar numbers of those with shocks had 1 or 2 shocks (71, 49%) versus ≥ 3 shocks ($n = 73$, 51%). In the initial 3 months of follow-up, 85 patients experienced ≥ 1 shocks, whereas 52 suffered shocks between 3 and 6 months and 55 experienced shocks in the last 6 months. The occurrence of ≥ 1 versus no shocks was independently associated with significant reductions in mental well-being and physical functioning and an increase in patient concerns. The development of more frequent shocks (≥ 3 vs <3) was associated with similar alterations in self-perceived QoL.

continued

Adverse effects

Complications of therapy	ICD	AAD	*p*-Value
Non-fatal torsade-de-pointes VT		1	
Suspected pulmonary toxicity at 1 year		3% at 1 year 5% at 2 years	
Thyroid replacement medication	1% at 1 year 1% at 2 years	10% at 1 year 16% at 2 years	
30-day mortality (or by hospital discharge, if later than 30 days)	12 (2.4%)	18 (3.5%)	0.27
Bleeding requiring operation or transfusion	6		
Serious haematomas	13		
Infection	10		
Pneumothorax	8		
Cardiac perforation	1		
Early dislodgement or migration of leads	3		
Unsuccessful first attempt at implantation without thoracotomy	5[a]		

Comments: one patient died from pulmonary toxicity.
[a] 4 because of excessively high defibrillation threshold and 1 due to perforation; 3 of these subsequently underwent successful implantation.

Reports of adverse symptoms	All patients: Within 3 months: 49% At 6 months: 36% At 1 year: 54%	The proportions were similar in the 2 treatment groups ($p = 0.8$)

Comments: most adverse symptoms (62%) were cardiovascular (34%) or relating to worsening heart failure (28%). Severe adverse symptoms were reported in 17% at 3 months, 7% at 6 months and 14% at 1 year. Most of these (69%) were ICD complication (35%), cardiovascular (18%) or related to worsening heart failure (16%).

The occurrence of adverse symptoms was associated with significant reductions in PCS and MCS scores in patients randomised to ICD and reduced PCS scores in patients in the AAD group. A similar relationship between severe adverse symptoms and alterations in QoL scores was observed. Significant increases in patient concerns were observed, independent of the randomised therapy.

Impact of adverse symptoms on QoL (any vs none)

	ICD	AAD	*p*-Value
SF-36 PCS (95% CI)	–2.25 (–3.32 to –1.18), $p < 0.001$	–1.64 (–2.89 to –0.41), $p = 0.009$	Not tested
SF-36 MCS (95% CI)	–2.32 (–3.76 to –0.88), $p = 0.002$	–0.51 (–1.97 to 0.94), $p = 0.5$	Not tested
PCC	1.84 (0.91 to 2.76), $p < 0.001$	0.91 (0.07 to 1.75), $p = 0.03$	Not tested

Percentage rehospitalised	ICD	AAD	*p*-Value
1 year (no. at risk: 290)	59.5	55.6	
2 years (no. at risk: 118)	74.8	64.7	
3 years (no. at risk: 28)	83.3	75.5	

Comments: by one year 60% of ICD patients vs 56% AAD group ($p = 0.04$).

continued

Methodological comments

- Allocation to treatment groups: not reported
- Blinding: no report of blinding of outcome assessors
- Comparability of treatment groups: baseline characteristics similar except for a history of atrial fibrillation or flutter and NYHA class III heart failure. Minor differences in LVEF but these were confined to the patients with VF (0.36 ± 0.15) in the ICD group vs 0.33 ± 0.15 in the AAD group. The LVEF was virtually identical (0.29 ± 0.10 vs 0.29 ± 0.11) among the patients with VT in both groups. The QoL subgroups baselines of ICD and AAD groups similar except ICD patients more likely to be discharged from hospital with beta-blocker therapy
- Method of data analysis: analysis according to intention-to-treat (ITT) principle. Significance based on a two-sided alpha level of 0.05 for comparisons of survival distributions. QoL paper: χ^2 test or *t*-test for pairwise comparisons. Analysis limited to patients who survived 1 year. Sensitivity analysis of all QoL participants. Generalised estimating equations used to model change in QoL scores over time to account for correlation of individual values and to deal with missing follow-up data. Separate models to assess PCS, MCS and PCC scores. Models adjusted for baseline characteristics to assess the independent relationship of variables with QoL. All conducted on an ITT principle
- Sample size/power calculation: a sample size of 1200 patients was estimated to be sufficient, assuming an average follow-up of 2.6 years and an event rate of 40% in the AAD group at 4 years to detect a 30% decrease in mortality. Sequential data monitoring was performed every 6 months. Criteria for termination of the study were based on an O'Brien–Fleming spending function, which requires a substantial difference between treatment groups to stop the study early. At its meeting on 3 October 1996, the Data and Safety Monitoring Board recommended that enrolment be extended to allow this goal to be reached. The board subsequently recommended stopping the trial on 7 April 1997, when analysis revealed that the difference in the primary outcome variable had crossed to the statistical boundary for early termination of the study. 1016 patients had been randomised
- Attrition/drop-out: not reported. For QoL variables 905 of the 1016 patients were included, and of these 800 were alive at 1 year. Data on QoL are for these 800 participants (ICD 416, AAD 384).

General comments

- Generalisability: strict eligibility criteria meant that many patients were not eligible
- Outcome measures: appropriate
- Inter-centre variability: not reported
- Conflict of interests: none reported

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	n/a
Was there a description of withdrawals and dropouts?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	n/a

Reference and design	Intervention	Participants	Outcome measures
Author: Siebels *et al*.[27] and Kuck *et al*.[26] The Cardiac Arrest Study Hamburg (CASH) Year: 1993 and 2000 Country: Germany Study design: RCT Number of centres: several (number not reported) Funding: grant from CPI/Guidant Corporation and ASTRA GmbH	Comparisons of different interventions: 1. ICD therapy with no concurrent AAD therapy [Cardiac Pacemakers (St Paul, MN, USA) were used]. Cut-off rates set between 170 and 200 bpm. All given an epicardial device until June 1991 and endocardial device after July 1991 2. AADs [either amiodarone loading dose 1000 mg/day for 7 days and (200) 600 mg/day maintenance; mean dose was 225 ± 75 mg; metoprolol (starting at low initial dose of 12.5–25 mg/day and if tolerated dosage advanced during 7–14 days up to the maximally tolerated dose or 200 mg/day; mean dose was 85 ± 73 mg); or propafenone (discontinued) (starting at a low initial dose of 450 mg/day, and if tolerated the dosage was advanced during 8–14 days up to the maximally tolerated dose or 900 mg/day)] Other interventions used: clinical and electrophysiological testing (noted below). If surgical revascularisation was required, implantation of epicardial and endocardial devices was performed at the time of or 7 to 15 (mean 10 ± 3) days after CABG, respectively	Number of participants: after elimination of patients assigned to propafenone, 288 patients were assigned to ICD (99), amiodarone (92) or metoprolol (97) Sample attrition/drop-out: all patients in the ICD group received the assigned therapy; 2 patients assigned amiodarone refused to start therapy Sample crossovers: 6 (6.1%) ICD patients and 11 (5.8%) AAD patients crossed over or added the other therapy by 24 months; 3 (3%) ICD patients received beta-blockers Inclusion/exclusion criteria for study entry: patient resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias Excluded if cardiac arrest occurred within 72 hours of an acute MI, cardiac surgery, electrolyte abnormalities or proarrhythmic drug effect Characteristics of participants: the index arrhythmia was VF in 293 (84%) and VT in 56 (16%) of patients. (Overall group 80% males, mean age 58 ± 11 years, 73% underlying coronary artery disease, 10% no organic heart disease) Male: ICD 79, amiodarone 82, metoprolol 79 Age (years): ICD 58 ± 11, amiodarone 59 ± 10, metoprolol 56 ± 11 LVEF (%): ICD 0.46 ± 0.19, amiodarone 0.44 ± 0.17, metoprolol 0.47±0.17. Heart disease: Coronary artery disease: ICD 73, amiodarone 77, metoprolol 70 Dilated cardiomyopathy: ICD 12, amiodarone 10, metoprolol 14 Others: ICD 6, amiodarone 2, metoprolol 5 No heart disease: ICD 9, amiodarone 11, metoprolol 11 Congestive heart failure at enrolment (%): NYHA I: ICD 23, amiodarone 25, metoprolol 32 NYHA II: ICD 59, amiodarone 57, metoprolol 55. NYHA III: ICD 18, amiodarone 18, metoprolol 13 Findings on baseline ECG: Heart rate (bpm): ICD 81 ± 17, amiodarone 80 ± 17, metoprolol 76 ± 16 Corrected QT interval (ms): ICD 437 ± 42, amiodarone 430 ± 51, metoprolol 430 ± 48 Bundle-branch block (%): ICD 17, amiodarone 23, metoprolol 19 Exposure time to primary events (months): ICD 4767.36, amiodarone 4169.41, metoprolol 5078.40	Primary outcomes: total (all-cause) mortality Secondary outcomes: recurrence of cardiac arrest, sudden death Method of assessing outcomes: in ICD patients, those discharges occurring during syncope are counted as VF recurrences, whereas those occurring during presyncope are/or documented VT are counted as VT recurrences; discharges were not classified if their nature remained unknown Sudden death was defined as death within 1 hour of the onset of symptoms or an unwitnessed death; cardiac arrest was defined as sudden circulatory collapse requiring resuscitation Length of follow-up: planned follow-up was at 2, 4, 6, 12, 18 and 24 months and every 12 months thereafter until termination of the study. Mean duration of follow-up was 57 ± 34 months After an average of 11 months, the propafenone arm was prematurely stopped by the safety board because total mortality and recurrences of cardiac arrest differed significantly from those of ICD-treated patients

continued

Results			
Outcomes	**ICD (*n* = 99)**	**AAD (*n* = 189)**	***p*-Value**
Crude death rate (%)	36.4 (95% CI 26.9 to 46.6)	44.4 (95% CI 37.2 to 51.8)	$p = 0.081$ (see below)
Survival (Kaplan–Meier), *N* (%)	**ICD**	**AAD**	**% reduction in all-cause mortality of ICD patients**
1 year	91 (92)	161 (85)	41.9
2 years	82 (83)	142 (75)	39.3
3 years	68 (69)	115 (61)	28.4
4 years	61 (62)	99 (52)	27.7
5 years	50 (51)	79 (42)	22.8
6 years	36 (36)	64 (34)	11.4
7 years	29 (30)	51 (27)	9.1
8 years	15 (15)	34 (18)	10.6
9 years	9 (9)	22 (12)	24.7
Overall survival was higher, but not significantly, in patients assigned to ICD than drug therapy, $p = 0.081$, HR 0.766 (97.5% CI upper bound 1.112). No difference in crude death rates between amiodarone and metoprolol			
Crude sudden death rate	13.0% (95% CI 7.9 to 19.6%)	33.0% (95% CI 27.2 to 41.8%)	$p = 0.005$ (see below)
Survival (Kaplan–Meier) (%, estimated from figure)	**ICD**	**AAD**	**% reduction in sudden death rates of ICD patients**
1 year	98	91	81.8
2 years	98	83	86.7
3 years	96	81	76.2
4 years	95	80	78.3
5 years	95	76	80.8
6 years	94	75	73.1
7 years	93	74	64.3
8 years	88	73	56.7
9 years	88	70	60.6
Survival free of sudden death was significantly higher in patients assigned to ICD than drug therapy, $p = 0.005$, HR 0.423 (97.5% CI upper bound 0.721).			
Crude rates of non-fatal cardiac arrest	11.1% (95% CI 6.9 to 16.5%)	19.5% (95% CI 12.2 to 25.6)	$p = 0.072$ (see below)
Survival free of cardiac arrest was higher, but not significantly, in patients assigned to ICD than drug therapy, $p = 0.072$, HR 0.481 (97.5% CI: upper bound 1.338). The decrease in cardiac arrest rates of patients assigned to ICD therapy was 61.8, 65.5, 59.2, 53.8, 50.4, 58.6. 49.2. 52.8, and 42.1% at years 1–9 of follow-up, respectively.			
Among patients with inducible sustained ventricular arrhythmia at baseline PES, death rates were 49.4 (95% CI 42.9 to 57.2%) in 46 ICD patients and 52.6% (95% CI 47.9 to 59.4%) in 88 AAD patients ($p = 0.290$).			
Of patients non-inducible, death rates were 35.7% (95% CI 26.4 to 45.7%) in 51 ICD patients and 49.3% (95% CI 42.9 to 56.2%) in 100 AAD patients ($p = 0.170$). Over a mean follow-up of 37 ± 26 months, a similar outcome was observed in 55 patients receiving an epicardial device and 44 patients receiving an endocardial device ($p = 0.189$).			
There were no significant differences concerning the HR for death from any cause in subgroups defined according to LVEF, NYHA and presence of organic disease. Data provided but not extracted.			

continued

Adverse effects	ICD	AAD	*p*-Value
Drug-related pulmonary toxicity	n/a	0	
Hyperthyroidism	n/a	3 (3.3%)	
Perioperative death[a]	5 (5.1%): 3(5.4%) epicardial, 2 (4.5%) endocardial	n/a	
Infection	3 (requiring explantation in 2)		
Haematoma or seroma	6		
Pleural effusion	3		
Pneumothorax	1		
Dislodgement or migration of leads	3		
Device dysfunction	5		
Overall complication	23% including an explantation rate of 2.1%		

Comments: drug discontinuation was required in 9 (9.8%) patients assigned to amiodarone and 10 (10.3%) to metoprolol.
[a] Within the same time frame, 2 (1.1%) of patients in the antiarrhythmic arm died (both amiodarone), *p* versus ICD arm = 0.029).

Methodological comments

- Allocation to treatment groups: after electrophysical testing, all patients were randomised, independent of clinical findings or testing results. The ratio of randomisation assignment between the ICD and the drug arm was 1:3 (i.e. ICD: amiodarone: metoprolol: propafenone = 1:1:1:1). No method of randomisation reported
- Blinding: no reported blinding of outcome assessors
- Comparability of treatment groups: no differences between groups on baseline characteristics
- Method of data analysis: time to occurrence of clinical events was analysed by the Kaplan–Meier method. The cumulative survival functions were compared by means of a log-rank (Mantel–Cox) test. For calculation of HRs, the Cox proportional regression model was used. The alpha level for comparison of survival distributions between the ICD and the AAD arms was based on a one-sided test, and the significance test was set at a 0.025 level. Analysis was by ITT. After interim analysis the overall significance level was adjusted according to Bonferroni inequality
- Sample size/power calculation: the design had a power of 80% to detect a difference of 19% points in 2-year mortality rates between the two arms (50% expected mortality rate in patients assigned to the drug arm, 31% in the ICD arm). A sample size of 390 patients, with a 1:3 ratio of randomisation between ICD and drug arms, was estimated to be sufficient
- Attrition/drop-out: not reported

General comments

- Generalisability: minimal inclusion criteria reported
- Outcome measures: appropriate
- Inter-centre variability: not reported how many centres involved, no report of inter-centre variability
- Conflict of interests: reported

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	n/a
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	n/a

Reference and design	Intervention	Participants	Outcome measures
Author: Connolly *et al*., Canadian Implantable Defibrillator Study (CIDS)[35,57] (and Irvine *et al*.[36]) Year: 2000 (and 2002) Country: Canada, Australia, USA Study design: RCT Number of centres: 24 Funding: Medical Research Council of Canada. Amiodarone supplied by Wyeth-Ayerst Pharmaceuticals Ltd	Comparisons of different interventions: 1. ICD. Scheduled at earliest possible date. Implant criteria were met with 3 consecutive successful defibrillations at ≥ 10 J below maximum device output. Lead systems were thoracotomy in 33, non-thoracotomy in remainder. Median time to implant 7 days, with 91.3% within 21 days 2. Amiodarone. ≥ 1200 mg/day for ≥ 1 week in hospital, ≥ 400 mg/day for ≥ 10 weeks, then ≥ 300 mg/day. In patients with intolerable side-effects, the dose could be lowered to a minimum of 200 mg/day. Mean doses at 2 months and 1, 3 and 5 years were 390, 306, 262 and 255 mg/day, respectively Other interventions used: AADs could be used for patients in either treatment group to control supraventricular or non-sustained VTs that were symptomatic or that might cause discharge of the ICD Concomitant medications at discharge and 1, 3 and 5 years are noted below	Number of participants: 659; 328 randomised to ICD, 310 (94.5%) received one; 331 amiodarone Eligible patients who did not give consent were asked to take part in a follow-up study. QoL was only planned for the first 400, and of these 317 participated Sample attrition/drop-out: of the 18 patients not receiving ICD, 7 died while waiting, 10 patient or physician decided against, 1 technical problem. 16 had ICD permanently or temporarily explanted (infection, heart transplant or patient preference). Amiodarone patients receiving it at 2 months and 1, 3 and 5 years were 96.2, 88.7, 80.3 and 85.4%, respectively. No details of withdrawals Sample crossovers: ICD patients receiving amiodarone at 1, 3 and 5 years were 17.4, 21.7 and 28.1%, respectively. 52 amiodarone patients received an ICD. At 1, 3 and 5 years proportions were 9.0, 18.6 and 21.4%, respectively Inclusion/exclusion criteria for study entry: eligible if, in the absence of either recent acute MI (≤ 72 h) or electrolyte imbalance, manifested any of (1) documented VF, (2) out-of-hospital cardiac arrest requiring defibrillation or cardioversion, (3) documented sustained VT causing syncope, (4) other documented, sustained VT at a rate of ≥ 150 bpm, causing presyncope or angina in a patient with an LVEF ≤ 35%, or (5) unmonitored syncope with subsequent documentation of either spontaneous VT ≥ 10 s or sustained (≥ 30 s) monomorphic VT induced by programme ventricular stimulation. Patients could meet criteria 3 or 4 on the basis of a ventricular tachyarrhythmia induced in the electrophysiology laboratory if both of the following conditions were met: (1) they had prior, spontaneous, documented sustained VT and (2) the induced arrhythmia in the electrophysiology laboratory was monomorphic sustained VT Excluded for any of the following: (1) ICD or amiodarone not considered appropriate as a treatment for the tachyarrhythmia, (2) excessive perioperative risk for ICD implantation, (3) previous amiodarone therapy for ≥ 6 weeks, (4) non-arrhythmic medical condition making 1-year survival unlikely, (5) long-QT syndrome Participants were excluded from the QoL assessment when they could not read English or did not give consent	Primary outcomes: any-cause mortality Secondary outcomes: arrhythmic death (based on Hinkle and Thaler), QoL. Protocol publication states costs as outcomes but not described in trial publication Method of assessing outcomes: all deaths were adjudicated by an external validation committee whose members had no other affiliation to the study. Not always possible to blind the committee to treatment allocation. Results of ICD interrogation after death were not used to determine cause-specific mortality because this information was only available in ICD patients To classify deaths, used hospital notes, autopsy reports, interviews with family/witnesses. *Definition of arrhythmic death*: circumstances are such that it is reasonable to presume death was brought about by rapid VT or VF, and had this not occurred, survival for at least 4 months likely. Loss of cardiac output and pulse appeared to precede collapse of circulation. Patient not already in shock or severe pulmonary oedema Other cardiac death: developed collapse prior to loss of cardiac output and fatal arrhythmia *Special category*: monitored patient observed, immediately prior to abrupt circulatory collapse, to

continued

Reference and design	Intervention	Participants	Outcome measures
		Characteristics of participants: Mean age ±SD (years): amiodarone 63.8 ± 9.9, ICD 63.3 ± 9.2 Male gender (%): amiodarone 83.7, ICD 85.4 Index arrhythmia (%): VF or cardiac arrest: amiodarone 50.1, ICD 45.1 VT with syncope: amiodarone 10.6, ICD 15.9 Other VT: amiodarone 26.9, ICD 23.8 Unmonitored syncope: amiodarone 12.4, ICD 15.2 Cardiac history (%): Angina pectoris: amiodarone 57.1, ICD 51.2 MI: amiodarone 75.8, ICD 77.1 CABG surgery: amiodarone 28.1, ICD 31.4 Congestive heart failure (%): None: amiodarone 49.5, ICD 51.2 NYHA class I or II: amiodarone 39.9, ICD 37.8 NYHA class III or IV: amiodarone 10.6, ICD 11.0 Left ventricular function: LVEF, mean ± SD: amiodarone 33.3 ± 14.1, ICD 34.3 ± 14.5 LVEF<20%: amiodarone 13.3, ICD 11.3 Primary cardiac diagnosis (%): Ischaemic heart disease (IHD) with MI: amiodarone 73.1, ICD 75.6 IHD without MI: amiodarone 9.1, ICD 7.3 Dilated cardiomyopathy: amiodarone 10.6, ICD 8.5 Valvular heart disease: amiodarone 3.0, ICD 1.2 Other heart disease: amiodarone 2.4, ICD 3.7 No heart disease: amiodarone 1.8, ICD 3.7 Medical conditions (%): Liver disorder: amiodarone 2.7, ICD 1.5 Respiratory disorder: amiodarone 17.8, ICD 17.5 Thyroid disease: amiodarone 3.9, ICD 5.8 Chest X-ray (%): Interstitial abnormality: amiodarone 17.6, ICD 15.5 Other abnormality: amiodarone 34.6, ICD 31.4 Baseline electrophysiological study (%): Ever done: amiodarone 62.8, ICD 62.2 Inducible VT or VF: amiodarone 147/208 (70.7%), ICD 154/204 (75.7%) Coronary angiography (%): Ever done: amiodarone 78.2, ICD 75.6 3-vessel disease: amiodarone 18.9, ICD 19.0 These baseline characteristics also given in the 317 QoL patients but not data extracted. For baseline QoL scores, see below	have profound bradycardia or asystole or a rhythm usually compatible with normal cardiac output Non-cardiac vascular death: e.g. aortic dissection, ruptured aneurysm, other haemorrhage, stroke, pulmonary embolus. Non-vascular death: e.g. traumatic, infectious, malignancy QoL measures: Rand Corporation's 38-item Mental Health Inventory (reliable and valid) scored for mental health and psychological distress and psychological well-being, and the Nottingham Health Profile (reliable and valid) measuring physical mobility, emotional reactions, social isolation, energy level, pain, sleep disturbance, lifestyle impairment QoL assessment before or just after randomisation, and then at 2, 6 and 12 months Length of follow-up: all seen for follow-up at 2 and 6 months after randomisation and every 6 months thereafter. Mean duration of follow-up was 2.9 and 3.0 years for amiodarone and ICD patients, respectively

continued

Concomitant antiarrhythmic medications (%):

	ICD	Amiodarone
Hospital discharge:		
Beta-blocker	33.5	21.4
Sotalol	19.8	1.5
Digoxin	29.6	22.7
Class I[a]	5.5	2.4
1 year		
Beta-blocker	37.0	21.2
Sotalol	21.5	2.5
Digoxin	34.5	21.9
Class I[a]	8.4	2.8
3 years		
Beta-blocker	33.3	19.0
Sotalol	23.3	4.9
Digoxin	34.7	22.5
Class I[a]	10.0	2.1
5 years		
Beta-blocker	29.6	22.4
Sotalol	24.1	4.1
Digoxin	33.3	24.5
Class I[a]	9.3	2.0

An imbalance existed between the use of each of the 4 types: significantly more drugs were used in the ICD patients (no *p*-Values reported).
[a] Any Vaughan Williams class I drug.

Results

Outcomes	**ICD (*n* = 328)**		**Amiodarone (*n* = 331)**		**Adjusted[a] treatment effect (95% CI)**
	No events	**Rate/year (%)**	**No events**	**Rate/year (%)**	
Survival					
All-cause mortality	83	8.3	98	10.2	RRR 19.7% (–7.7 to 40.0), $p = 0.142$
Arrhythmic death	30	3.0	43	4.5	RRR 32.8% (–7.2 to 57.8), $p = 0.094$
Other cardiac death	37	3.7	40	4.2	RRR 13.5% (–35.4 to 44.7), $p = 0.526$
Non-cardiac vascular death	3	0.3	2	0.2	RRR –36.6% (–71.9 to 77.2), $p = 0.732$
Non-vascular death	13	1.3	13	1.4	RRR 4.5% (–106.1 to 55.7), $p = 0.908$
Total cardiac death		6.7		8.6	RRR 23.4% (–5.7 to 44.5), $p = 0.104$

RRR, relative risk reduction.
Comments: The total patient-years of follow-up for patients allocated to amiodarone and ICD were 957 and 995, respectively.
[a] Adjusted for LVEF stratification.

Cumulative risk of any cause death (Kaplan–Meier) (%)			
1 year	(At risk: 288): 9.46	(At risk: 285): 11.18	ARR 1.72, RRR 15.4
2 years	(At risk: 215): 14.75	(At risk: 204): 20.97	ARR 6.22, RRR 29.7
3 years	(At risk: 153): 23.32	(At risk: 152): 27.03	ARR 3.71, RRR 13.7

continued

Cumulative risk of arrhythmic death (Kaplan–Meier) (%)			
1 year	4.37	6.23	ARR 1.86, RRR 29.9
2 years	6.68	9.74	ARR 3.06, RRR 31.4
3 years	9.77	11.88	ARR 2.11, RRR 17.8

ARR, absolute risk reduction.

Subgroup analysis (HR) for death from any cause (point estimate and 95% CI estimated from figure)

Index arrhythmia:	
VF or cardiac arrest	0.72 (0.47 to 1.12)
VT	0.81 (0.48 to 1.3)
Syncope	0.92 (0.47 to 1.92)
Age (years):	
≤65	0.92 (0.60 to 1.48)
>65	0.70 (0.47 to 1.02)
Gender:	
Male	0.79 (0.58 to 1.1)
Female	0.92 (0.46 to 1.95)
LVEF (%):	
≤35	0.78 (0.53 to 1.03)
>35	1.08 (0.54 to –)
NYHA class:	
I or II	0.81 (0.56 to 1.11)
III or IV	0.64 (0.32 to 1.3)
Cause of arrhythmia:	
CAD	0.78 (0.54 to 1.02)
Cardiomyopathy	0.81 (0.32 to 2.0)
Other	1.72 (0.48 to –)
Overall	0.8 (0.60 to1.8)

Comments: ICD not significantly greater benefit for any subgroup (*p*-value for heterogeneity not significant).

QoL MHI	**ICD (*n* = 86)**	**Amiodarone (*n* = 92)**	**Time by group *p*-value**
Total index[a]			
Baseline	173.2 ± 25.5	180.4 ± 27.8	
6 months	183.1 ± 30.2[c]	180.2 ± 31.1	
12 months	184.3 ± 27.9[d]	178.3 ± 28.7	0.001
Psychological distress[b]			
Baseline	51.3 ± 14.1	47.8 ± 16.5	
6 months	45.1 ± 17.6[c]	47.6 ± 18.3	
12 months	43.4 ± 15.9[d]	48.8 ± 16.8	0.001
Psychological well-being[a]			
Baseline	58.5 ± 12.7	62.2 ± 12.3	
6 months	62.2 ± 13.4[c]	61.8 ± 14.1	
12 months	61.7 ± 13.2[d]	61.1 ± 13.1	0.03

Comments: of the 317 participants recruited, 287 were alive at the 12-month follow-up. Of these, 22 were missing a baseline QoL assessment (11 from each treatment group) and 127 had missing data at one of the follow-up assessments (63 amiodarone, 64 ICD).

[a] Higher value represents better functioning.

[b] Higher value represents poorer functioning.

[c] Comparisons significant $p < 0.05$ with *post hoc* test from baseline to 6 months.

[d] Comparisons significant $p < 0.05$ with *post hoc* test from baseline to 12 months.

continued

QoL NHP[a]	ICD	Amiodarone	Time × group *p*-value
Energy level (*n*):	83	88	
Baseline	27.5 ± 32.2	24.4 ± 32.4	
6 months	18.6 ± 30.1[b]	27.8 ± 32.1	
12 months	17.7 ± 26.1[c]	36.8 ± 37.3[c]	0.0001
Physical mobility (*n*):	84	90	
Baseline	10.9 ± 12.0	13.2 ± 20.5	
6 months	10.5 ± 13.7	15.1 ± 19.2	
12 months	9.1 ± 13.6	17.7 ± 19.2[c]	0.002
Social interaction (*n*):	81	88	
Baseline	8.5 ± 15.4	9.9 ± 17.7	
6 months	9.8 ± 18.6	12.2 ± 22.4	
12 months	8.5 ± 18.4	11.1 ± 22.6	0.9
Emotional reactions (*n*):	76	86	
Baseline	17.3 ± 18.1	14.3 ± 20.1	
6 months	11.1 ± 18.2[b]	15.3 ± 22.4	
12 months	8.3 ± 16.6[c]	14.5 ± 19.6	0.002
Pain (*n*):	83	90	
Baseline	4.4 ± 7.9	7.5 ± 15.1	
6 months	7.5 ± 17.1	6.3 ± 13.6	
12 months	4.5 ± 9.9	8.2 ± 15.4	0.52
Sleep disturbance (*n*):	78	88	
Baseline	31.4 ± 27.4	29.6 ± 31.5	
6 months	25.0 ± 29.7[b]	30.8 ± 31.0	
12 months	23.9 ± 29.4[c]	30.2 ± 32.4	0.02
Lifestyle impairment (*n*):	78	83	
Baseline	2.0 ± 1.9	1.6 ± 1.7	
6 months	1.6 ± 1.8	1.9 ± 1.9	
12 months	1.6 ± 1.3[c]	1.8 ± 1.9	0.005

[a] Higher values represent poorer functioning.
[b] Comparisons significant with *post hoc* test from baseline to 6 months.
[c] Comparisons significant with *post hoc* test from baseline to 12 months.

QoL subgroup analyses

ICD shocks and QoL MHI (mean ± SD)	ICD, no shocks (*n* = 66)	ICD, 1–4 shocks (*n* = 27)	ICD, ≥ 5 shocks (*n* = 15)	Amiodarone (*n* = 95)	*p*-Value between groups
Total index:					
Baseline	175.3 ± 26.5	171.7 ± 22.7	171.2 ± 32.0	177.9 ± 27.1	
12 months	186.2 ± 26.9[a,b]	186.6 ± 21.7[a,b]	168.8 ± 41.2	175.6 ± 29.2	
Within-group *p*-value	0.001	0.001	0.725		0.001
Psychological distress:					
Baseline	50.2 ± 15.2	50.8 ± 12.3	51.9 ± 18.1	49.8 ± 16.3	
12 months	42.5 ± 15.3[a,b]	41.4 ± 11.7[a,b]	52.7 ± 25.2	50.9 ± 17.5	
Within-group *p*-value	0.001	0.001	0.833		0.001
Psychological well-being:					
Baseline	60.1 ± 12.5	56.6 ± 11.6	57.1 ± 15.0	61.7 ± 12.0	
12 months	62.8 ± 13.1	62.1 ± 10.9[b]	55.6 ± 16.8	60.6 ± 13.3	
Within-group *p*-value	0.074	0.004	0.642		0.02

Comments: amiodarone patients without ICD (no crossovers) only. Within group effects were not retested in the amiodarone group.
[a] Groups that differed significantly from amiodarone without ICD group ($p < 0.05$).
[b] Groups that differed significantly from the ICD ≥ 5 shocks group ($p < 0.05$).

continued

ICD shocks and QoL NHP (mean ± SD)	ICD, no shocks	ICD, 1–4 shocks	ICD ≥ 5 shocks	Amiodarone	*p*-Value between groups
Energy level (*n*):	64	27	15	90	
Baseline	28.6 ± 32.5	28.5 ± 30.5	22.6 ± 34.2	24.3 ± 30.8	
12 months	19.5 ± 27.1[a]	24.8 ± 33.4[a]	23.5 ± 29.5	37.0 ± 37.6	
Within-group *p*-value	0.02	0.115	0.859		0.003
Physical mobility (*n*):	65	27	15	93	
Baseline	13.1 ± 15.0	12.4 ± 10.2	7.1 ± 9.8	13.18 ± 20.1	
12 months	9.3 ± 12.4[a]	15.5 ± 17.3	8.0 ± 13.3	17.2 ± 19.1	
Within-group *p*-value	0.05	0.638	0.747		0.02
Social isolation (*n*):	66	27	15	92	
Baseline	10.6 ± 16.7	4.3 ± 9.2	8.9 ± 16.1	11.8 ± 18.5	
12 months	8.8 ± 19.5	6.4 ± 15.5	12.8 ± 23.9	12.5 ± 23.0	
Within-group *p*-value	0.03	0.991	0.817		0.57
Emotional reactions (*n*):	61	27	14	90	
Baseline	16.2 ± 17.4	16.3 ± 17.1	21.6 ± 21.1	16.3 ± 19.8	
12 months	7.1 ± 14.6[a,b]	6.8 ± 10.2[a]	22.0 ± 31.0	15.9 ± 20.3	
Within-group *p*-value	0.001	0.02	0.886		0.001
Pain (*n*):	66	27	15	92	
Baseline	6.8 ± 11.8	4.0 ± 8.5	5.3 ± 8.3	8.5 ± 15.6	
12 months	6.4 ± 14.7	5.4 ± 11.7	5.5 ± 7.1	7.7 ± 14.5	
Within-group *p*-value	0.086	0.710	0.721		0.71
Sleep disturbance (*n*):	62	27	14	89	
Baseline	30.0 ± 26.9	36.3 ± 31.4	27.3 ± 27.1	30.4 ± 30.5	
12 months	22.1 ± 28.1	29.1 ± 33.9	34.6 ± 35.4	30.1 ± 33.6	
Within-group *p*-value	0.002	0.042	0.680		0.3
Lifestyle impairment (*n*):	65	26	14	82	
Baseline	2.0 ± 2.0	2.4 ± 1.9	2.2 ± 1.9	1.7 ± 1.6	
12 months	1.3 ± 1.5[a]	1.4 ± 1.5[a]	1.4 ± 1.6	1.9 ± 1.9	
Within-group *p*-value	0.061	0.033	0.334		0.03

[a] Groups that differed significantly from amiodarone without ICD group ($p < 0.05$).
[b] Groups that differed significantly from the ICD ≥ 5 shocks group ($p < 0.05$).

Adverse effects ever reported, *n* (%)	ICD	Amiodarone	
Pulmonary infiltrate		18 (5.7)	Risk 1.9% per year
Visual symptoms (blurred, halo or decreased)		48 (14.5)	
Bradycardia		10 (3.0)	
Skin discoloration		21 (6.3)	
Photosensitivity		34 (10.3)	
Ataxia		97 (17.2)	
Tremor		91 (15.4)	
Insomnia		64 (19.3)	
Peripheral neuropathy		1 (0.3)	
ICD project discomfort	25 (7.6)		
ICD malfunction	2 (0.6)		Rate 1.4% per year
ICD pocket infection	15 (4.6)		
ICD lead dislodgement/fracture	8 (2.4)		

Comments: the cumulative risk of receiving an ICD shock was 65.4% at 4 years.

continued

Methodological comments

- Allocation to treatment groups: randomisation was stratified by clinical centre and by left ejection fraction (≤ 35% and >35%). Randomisation centrally by telephone
- Blinding: states not always possible to blind the patient intervention group from the outcome assessors
- Comparability of treatment groups: the baseline and clinical characteristics are reported to be well balanced. QoL: only differences observed were that a higher proportion of patients in the amiodarone group had no more than a high school education ($p < 0.02$) and a higher proportion of men had been randomised to receive an ICD ($p < 0.02$). Tests of the prognostic significance of these variables revealed that QoL did not differ with sex or education
- Method of data analysis: cumulative mortality by survival curve (Kaplan–Meier) and compared using a Mantel–Haenszel test incorporating stratification for LVEF. Cox's proportional hazards method used to adjust for imbalances in baseline prognostic risk and to investigate possible subgroup effects. Two-sided statistics are presented. Analysis based on ITT principle. An external safety and efficacy monitoring committee reviewed the unblinded study data every 6 months for safety and did 3 interim analyses of efficacy on the basis of an intention to stop the study early in favour of ICD if one-sided $p \leq 0.001$. QoL: to minimise the loss of subjects because of missing data, missing baseline data were replaced by the mean for the variable and the 2-month data were excluded. Analysis of variance with repeated measures used, and significant results were tested *post hoc* with Tukey Honestly Significantly Difference test, adjusting for unequal cell sizes. Scores on the NHP had to be normalised by use of a log-plus-1 transformation. ITT analysis. Subgroup analysis of QoL on ICD patients with no shocks, those with 1–4 shocks and those with ≥ 5 shocks in the first 12 months of follow-up. Analysis of covariance with control for disease severity effects, LVEF, NYHA and age
- Sample size/power calculation: original study designed with arrhythmic death as primary end-point, in 1993 the primary outcome was changed to measure all-cause mortality because of concerns that the ICD might prevent some arrhythmic deaths, but have little effect on overall mortality. This change led to an increase in the patient enrolment target from 400 to 650 patients, which provided 90% power to detect a relative reduction in all-cause mortality of 33% by the ICD from an anticipated 3-year mortality rate of 30% on amiodarone. Crossover rates of 5% per year were anticipated for both groups
- Attrition/drop-out: crossovers and those not receiving intervention noted, no details of withdrawals

General comments

- Generalisability: strict eligibility criteria, reports in protocol publication that those not consenting taking part in follow-up study but no details reported
- Outcome measures: outcomes clearly defined
- Inter-centre variability: not reported
- Conflict of interests: none reported, pharmaceutical company provided the amiodarone

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	n/a
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Between 5 and 15% did not receive the intervention, no details of drop-outs

Appendix 8

Data extraction: primary prevention trials

Reference and design	Intervention	Participants	Outcome measures
Author: Moss *et al.*,[37,38] the Multicentre Automatic Defibrillator Implantation Trial (MADIT) Year: 1996 (and 2001) Country: USA, Germany and Italy Study design: RCT Number of centres: 32 Funding: grant from CPI/Guidant Corporation (also provided the pulse generators and leads)	Comparisons of different interventions: 1. ICD therapy; only ICDs and lead systems approved and released by the FDA were used; monophasic (n = 79) and biphasic (n = 11) pulse generators were used 2. Conventional medical therapy, the choice of which was left to the patients' physician. Other interventions used: antiarrhythmic medications approved by the FDA could be administered to patients in either group. At 1 month after enrolment percentage cardiac medications in the medical groups/ICD group were: Antiarrhythmics: Amiodarone: 74/2 Beta-blockers: 8/26 Class I antiarrhythmic agents: 10/12 Sotalol: 7/1 Beta-blockers or sotalol: 15/27 None: 8/56 Other cardiac: ACE inhibitors: 55/60 Digitalis: 38/58 Diuretics: 52/53 At the last recorded contact at the end of the trial, on the last clinic visit before death or lost to follow-up, the percentage cardiac medications in the medical groups/ICD group were:	Number of participants: 253 patients qualified in terms of clinical eligibility and electrophysiological testing (no numbers kept of those not eligible based on electrophysiological testing) and 196 consented. ICD group 95, conventional therapy group 101 Sample attrition/drop-out: 3 patients were lost to follow-up, 2 conventional group, 1 ICD. 2 ICD patients had their ICDs deactivated during the trial Sample crossovers: 16 crossovers occurred. 11 patients in the conventional group received an ICD because of an adverse drug reaction (n = 2), unexplained syncope (n = 2), episodes of VT that were of concern to the investigator (n = 6) and aborted cardiac arrest (VF) (n = 1). 5 patients from ICD group never had an ICD implanted (1 = high defibrillation threshold, 4 = patient's preference) Inclusion/exclusion criteria for study entry: patients of either sex; age 25–80 years; Q-wave or enzyme-positive MI $\geq$ 3 weeks before entry; an episode of asymptomatic, unsustained VT (a run of 3–30 ventricular ectopic beats at a rate $>$ 120 bpm) unrelated to an acute MI that was documented by a 12-lead ambulatory, or exercise electrocardiography; an EF $\leq$ 0.35, as assessed by angiography, radionuclide scanning or echocardiography; NYHA functional class I, II, or III; no indications for cardioartery bypass grafting or coronary angioplasty on the basis of a cardiac evaluation within the last 3 months. Excluded if one or more of the following were present: previous cardiac arrest or VT causing syncope that was not associated with an acute MI; symptomatic hypotension while in a stable rhythm; MI within the past 3 weeks. Also excluded if undergone CABG within the past 2 months or coronary angioplasty within the past 3 months; women of childbearing age who were not using medically prescribed contraceptives, patients with advanced cerebrovascular disease, patient with any condition other than cardiovascular disease that was associated with a reduced likelihood of survival for the duration of the trial and patients who were participating in other clinical trials Eligible patients were referred for electrophysiological study at the discretion of	Primary outcomes: death from all causes Secondary outcomes: therapy-related adverse events, time to first shock in ICD patients, subgroup analysis risk factors and mortality Method of assessing outcomes: patients were seen in the follow-up clinic 1 month after randomisation and every 3 months thereafter until the trial was completed. At each visit, an appropriate clinical evaluation was carried out, medication use was recorded and the ICD was tested. The patients underwent a final evaluation 1 month after completion of the trial. There were 1838 scheduled follow-up visits: the ICD group attended 92% and the conventional group 86% A 2-member end-point committee reviewed information on the causes and circumstances of deaths occurring on or before March 1996. Each death was categorised as due to either a cardiac or a non-cardiac cause, and the classification of Hinkle and Thaler was used to evaluate the suspected mechanism of death from cardiac causes (arrhythmic or non-arrhythmic) A data and safety monitoring committee independently reviewed

continued

Reference and design	Intervention	Participants	Outcome measures
	Antiarrhythmics: Amiodarone: 45/7 Beta-blockers: 5/27 Class I antiarrhythmic agents: 11/11 Sotalol: 9/4 Beta-blockers or sotalol: 14/31 None: 23/44 Other cardiac: ACE inhibitors: 51/57 Digitalis: 30/57 Diuretics: 47/52 When the trial began in December 1990, only transthoracic implants were approved for use. Non-thoracotomy transvenous leads were incorporated into the trial in August 1993 Every effort was made to achieve defibrillation with a 10-J safety margin	their physician. They qualified for enrolment if sustained VT or fibrillation was reproducibly induced and not suppressed after the intravenous administration of procainamide (or an equivalent i.v. antiarrhythmic agent if the patient had a previous reaction to procainamide) according to a prespecified protocol Three physiologically meaningful risk factors (EF, QRS duration, history of CHF requiring treatment) were selected for subgroup analysis. EF and QRS were dichotomised at their median value, CHF was dichotomised in terms of a history that required specific decongestive therapy (diuretics, digitalis and/or ACE inhibitors) versus either the absence of a history or mild heart failure in which therapy was not initiated Characteristics of participants (± SD): Age (years): medical 64 ± 9, ICD 62 ± 9 Gender (M/F): medical 92/8, ICD 92/8 Cardiac history (%): ≥ 2 prior MI: medical 29, ICD 34 Treatment (Tx) ventricular arrhythmias: medical 35, ICD 42 NYHA class II or III: medical 67, ICD 63 Tx CHD: medical 51, ICD 52 Tx hypertension: medical 35, ICD 48 Insulin-dependent diabetes: medical 5, ICD 7 Cigarette (any time): medical 73, ICD 79 CABG: medical 44, ICD 46 Angioplasty: medical 27, ICD 17 Pacemaker: medical 7, ICD 2 Interval of ≥ 6 months between most recent MI and enrolment (%): medical 76, ICD 75 Cardiac findings at enrolment (%): Pulmonary congestion (defined radiographically as mild, moderate, severe) : medical 21, ICD 18 Blood urea nitrogen >25 mg/dl: medical 21, ICD 22 Cholesterol >200 mg/dl: medical 49, ICD 41 Left-bundle branch block: medical 8, ICD 7 EF: medical 0.25 ± 0.07, ICD 0.027 ± 0.07 Qualifying unsustained VT (no consecutive beats): medical 9 ± 10, ICD 10 ± 9 Electrophysiological study (%): Initial induction: Monomorphic VT: medical 91, ICD 87 Polymorphic VT: medical 7, ICD 7 VF: medical 2, ICD 6 Induction after antiarrhythmic challenge (procanimide): Monomorphic VT: medical 94, ICD 92 Polymorphic VT: medical 5, ICD 7 VF: medical 1, ICD 1 Baseline characteristics of patients in the low- and high-risk subsets of EF, QRS duration and heart failure ($^{a}p < 0.05$ between low- and high-risk subsets):	the results at regular intervals Length of follow-up: the first patient was followed up for 61 months, the last for <1 month. The average duration of follow-up was 27 months, with an average of 37 months for the earlier transthoracic stratum ($n = 98$: 45 ICD, 53 conventional therapy) and 16 months for the later transvenous stratum ($n = 98$: 50 ICD and 48 conventional therapy)

continued

Reference and design	Intervention	Participants			Outcome measures
			EF 0.26–0.35 (*n* = 94)	**EF <0.26 (*n* = 102)**	
		Age (years, mean ± SD)	64 ± 9	62 ± 9	
		Male	87	96	
		Cardiac findings:			
		NYHA II or III	55	74[a]	
		Treatment for hypertension	44	39	
		Insulin diabetes	6	6	
		CABG	38	51	
		Qualifying VT (no. of beats)	8 ± 6	10 ± 12	
		Therapy at 1 month:			
		Amiodarone	38	43	
		Beta-blockers	18	19	
		Mortality rate	22	32	
			QRS duration <0.12 s (*n* =96)	**QRS duration ≥0.12 s (*n* = 99)**	
		Age (years, mean ± SD)	63 ± 9	63 ± 9	
		Male	92	92	
		Cardiac findings:			
		NYHA II or III	64	66	
		Treatment for hypertension	42	40	
		Insulin diabetes	7	5	
		CABG	42	47	
		Qualifying VT (no. of beats)	9 ± 8	10 ± 11	
		Therapy at 1 month:			
		Amiodarone	46	35	
		Beta-blockers	18	18	
		Mortality rate	25	30	
			No heart failure[a] (*n* = 95)	**Heart failure (*n* = 101)**	
		Age (years, mean ± SD)	63 ± 8	63 ± 9	
		Male	94	90	
		Cardiac findings:			
		NYHA II or III	47	81	
		Treatment for hypertension	36	41	
		Insulin diabetes	4	8	
		CABG	37	52	
		Qualifying VT (no. of beats)	10 ± 8	9 ± 11	
		Therapy at 1 month:			
		Amiodarone	46	36	
		Beta-blockers	17	19	
		Mortality rate	20	35	

[a] Requiring treatment.

continued

Results

Outcomes	ICD (n = 95)	Comparator (n = 101)	p-Value
Five-year overall mortality (average follow-up 27 months)	15	39	HR 0.46 (95% CI 0.26 to 0.82), p = 0.0009
Cause of death			
Cardiac cause:	11	27	
Primary arrhythmia	3	13	
Non-arrhythmia	7	13	
Uncertain	1	1	
Non-cardiac cause	4	6	
Unknown cause	0	6	
Kaplan–Meier survival (estimated from figure):			0.0009
1 year	0.98	0.76	
2 years	0.88	0.68	
3 years	0.84	0.58	
4 years	0.72	0.52	
5 years	0.72	0.28	

Comments: there was no evidence that the effects of the defibrillator differed between patients implanted with transthoracic leads and transvenous leads (ratio of the HRs, 0.86, p = 0.78).

Cox regression analyses revealed no evidence that antiarrhythmic medications, including amiodarone and beta-blockers, or other cardiac medications being given 1 month after enrolment or any of the 11 prespecified baseline variables had a meaningful influence on the hazard ratio ($p > 0.2$ for all interactions). However, the power of the analysis is limited, especially for amiodarone as only 2 patients in the ICD group received it.

The beneficial effect of ICD therapy was assessed in each of the two centres with the highest enrolments (42 and 21 patients) and compared the results in the high-enrolment centres with the results in the other 30 centres. The reductions in mortality with the defibrillator were similar among these groups.

Subgroup analyses

Each higher risk subset (EF < 0.26, QRS width ≥ 0.12 s, history of CHF with treatment) had a higher mortality rate than the lower-risk subset (EF 0.26–0.35, QRS width <0.12 s, HF without treatment). Some overlap existed in the distribution of patients in the high- and low-risk partitions of the 3 risk variables: EF and heart failure (odds ratio 2.4, p = 0.003); QRS duration and heart failure (odds ratio 1.8, p = 0.04); EF and QRS duration (odds ratio 1.4, p = 0.22).

Survival benefit	ICD (%)	Comparator (%)	HR[a], p-value
EF:			
0.26–0.35	19	34	0.50, p = 0.12
<0.26	15	50	0.27, p = 0.002
QRS duration (s):			
<0.12	14	38	0.45, p = 0.08
≥ 0.12	19	47	0.27, p = 0.002
CHF requiring treatment:			
Yes	12	28	0.43, p = 0.09
No	16	54	0.30, p = 0.002

[a] Ratio of risk of death per unit of time among patients with defibrillator to those receiving conventional therapy; smaller values <1.0 indicate greater benefit from defibrillator therapy.

continued

Risk of death by risk factors and ICD in relation to number of risk factors	No. of patients	Risk factor HR[a]	ICD: non-ICD HR[b]
None	33	1.0	0.69
Any 1	61	1.63	0.46
Any 2	63	2.66	0.30
All 3	38	4.33	0.20

[a] Ratio of the risk of death per unit of time among patients with risk factors compared with those without. Subjects with no risk factors form the reference group, with HRs set to unity by convention ($p < 0.01$) for trend in increasing HRs from none to all 3 risk factors.

[b] Ratio of the risk of death per unit of time among patients receiving ICD therapy to those not ($p = 0.19$ for trend in decreasing HRs from none to all 3 risk factors for those with versus without ICD therapy).

Probability of discharge of first shock in ICD patients (Kaplan–Meier – estimated from figure)	ICD group	Comments
1 year	0.44	The overall appropriateness of the defibrillator discharges could not be assessed reliably, since only a small number had pulse generators with electrogram storage and these units were implanted late in the trial
2 years	0.58	
3 years	0.72	
4 years	0.72	
5 years	0.9	

Adverse effects related to antiarrythmic therapy of ICD (some patients had more than one)	ICD	Conventional	*p*-Value
Hypotension	0	1	Not reported
Syncope	1	5	Not reported
Hypothyroidism	0	1	Not reported
Sinus bradycardia	3	3	Not reported
Pulmonary fibrosis	0	3	Not reported
Pulmonary embolism	1	1	Not reported
Atrial fibrillation	4	0	Not reported
Pneumothorax	2	0	Not reported
Bleeding	1	0	Not reported
Venous thrombosis	1	0	Not reported
Surgical infection	2	0	Not reported
Problems with lead	7	0	Not reported
Malfunction of ICD generator	3	2	Not reported
Total no. of patients with adverse effects	19	12	Not reported

continued

Methodological comments

- Allocation to treatment groups: randomisation scheme reported to include stratification according to the interval between the most recent MI and enrolment (<6 or ≥6 months) and according to centre. No details of randomisation procedure or allocation concealment. No numbers of those not eligible based on electrophysiological testing, and 57 patients declined to consent (reports that no differences between these and those that did consent but no details)
- Blinding: not applicable to double blind, no details of blinding of outcome assessors
- Comparability of treatment groups: at baseline the two groups were clinically similar. The distribution of the qualifying Q-wave MI in terms of anterior, inferior and posterior locations was similar in the two groups. Medications used between the groups varied, but adjustment for these variables suggest no significant effects on outcomes
- Method of data analysis: the data were analysed weekly, beginning at the point at which 10 deaths had been reported. The trial was determined to be terminated when the path of the log-rank statistic, measuring imbalance between the survival curves for the 2 randomised groups, crossed one of the preset termination boundaries (efficacy, inefficacy or no difference in outcome) of sequential design. Analyses were stratified according to the type of device (transthoracic or transvenous) and followed the ITT principle. All analyses and potential covariates were specified in advance of the trial's completion. After termination of the trial, sequential analysis methods were used to calculate a *p*-value and hazard ratio (median unbiased), along with a 95% confidence interval based on the *p*-value function. Secondary analysis with the Cox proportional hazards regression model, with adjustment for covariates. Separate Cox regression analysis carried out on the transthoracic and transvenous strata to determine whether the efficacy of defibrillators was similar in the two groups. Preselected baseline covariates (age, gender, ≥ 2 prior MI, Tx for heart failure, NYHA class, Tx for hypotension, CABG, ≥ 6 months between most recent MI and enrolment, BUN, LBBB, EF) and prescribed cardiac medications recorded at the 1-month visit were evaluated in the Cox model to determine their effect on the risk of death per unit of time in the ICD groups as compared with that in the conventional therapy group (the HR). Survival curves for patients assigned to defibrillator treatment and conventional treatment were determined by the Kaplan–Meier method. Subgroup analysis of survival by risk factor undertaken by HR, Kaplan–Meier and additional Cox regression analysis
- Sample size/power calculation: the trial was designed to have an 85% power to detect a 46% reduction in the mortality rate among the ICD patients as compared with a postulated 2-year mortality rate of 30% among the patients assigned conventional therapy, with a two-sided significance level of 0.05. A triangular sequential design modified for two-sided alternatives was used, with preset boundaries to permit termination of the trial if the efficacy or inefficacy of ICDs was established or if there was evidence that there was no difference in outcomes between the two treatment groups. The executive committee were unaware of the results of the study throughout the trial. During the course of the trial, the sequential design was revised by the executive committee on 2 occasions. When transvenous leads were introduced, since this could alter the type of patient referred for entry, the power requirement was increased to 90%. Because of slow enrolment and before the first patient enrolled had reached the 5th year of the study, it was decided in November 1995 that data on patients would be censored for analytical purposes at 5 years, with subsequent follow-up information on such patients censored from the ongoing sequential analysis. The efficacy boundary was crossed when 51 deaths were reported and the study was stopped at this time
- Attrition/drop-out: 3 patients lost to follow-up, assume no withdrawals

General comments

- Generalisability: inclusion criteria strict which may limit generalisability
- Outcome measures: definitions for all variables were prespecified in a manual of operations
- Inter-centre variability: not reported
- Conflict of interests: supported totally by a research grant from CPI/Guidant Corporation. All investigators agreed in writing in advance of their participation not to hold stock in CPI/Guidant or any other defibrillator manufacturing company and to abide by the conflict of interest standards described by Healy *et al*.[58]

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	n/a
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	1.5%

Reference and design	Intervention	Participants	Outcome measures
Author: Bigger[39] (for the Coronary Artery Bypass Graft Patch trial investigators) and Namerow *et al*.[40] Year: 1997 (and 1999) Country: USA and Germany Study design: RCT Number of centres: 37; 35 in USA, 2 in Germany Funding: grant from National Heart, Lung and Blood Institute and Guidant (manufacturer)	Comparisons of different interventions: 1. ICD – most were committed devices (devices that deliver a shock even if the arrhythmia stops before the end of charging) that were not capable of storing electrograms 2. Control group (not defined) Other interventions used: the protocol prohibited the use of AADs for asymptomatic ventricular arrhythmia and specified that patients without contraindications should be treated with aspirin At hospital discharge drug therapy, percentage of patients (ICD/control): Oral antiarrhythmics: None: 63.3/35.2 Class I antiarrhythmic agents: 16.7/12.0 Amiodarone: 3.7/3.2 Sotolol: 0.5/0.2 Beta-blockers (not sotalol): 17.9/24.2 Other cardiac: ACE inhibitors: 54.7/53.8 Diuretics: 57.2/47.1 Digitalis: 68.6/64.5 Nitrates:8.1/8.1 Calcium channel blockers: 10.5/7.0 Antiplatelet: 82.8/85.1 Oral anticoagulants: 15.3/14.7 Lipid-lowering: 9.5/8.4 At 3-months post-discharge drug therapy, percentage of patients [ICD (n = 403)/control (n = 411)]: Oral antiarrhythmics: None: 70.7/70.1 Class I antiarrhythmic agents: 8.2/5.8 Amiodarone: 4.2/3.6 Sotolol: 1.0/0.5	Number of participants: during screening, 1422 eligible patients, of whom 1055 (74%) consented. Of these, 900 were randomised; ICD group 446, control 454. 155 were not randomised, 67 because had one or more exclusion criteria between enrolment and randomisation, 88 due to intraoperative events that made the implantation too risky In the QoL substudy, it was expected that 719 patients could complete the instrument, and 490 (68%) of these did Sample attrition/drop-out: not reported, except 12 ICD patients noted below Sample crossovers: 70 crossovers: 18 control group patients had ICD; 12 ICD patients never had ICD implanted due to death or haemodynamic instability in the operating room; 40 in the ICD group had them removed, primarily owing to infection (19), the ICD had reached the end of its service period and was not replaced (5), the patient requested removal (5). At 42 months the cumulative rate of crossover to the control group was 10%; the cumulative rate of crossover to the ICD group was <5% Inclusion/exclusion criteria for study entry: patient of either gender, scheduled for CABG, <80 years, left ventricular EF <0.36, had abnormalities on a signal-averaged ECG (duration of the filtered QRS complex, ≥ 114 ms; root mean square voltage in the terminal 40 ms of the QRS complex, <20 μV; or duration of the terminal filtered QRS complex at <40 μV, >38 s). The signal-averaged ECG was the most feasible marker of arrythmia for use in identifying patients for enrolment, given the short time between hospital admission and surgery Excluded if history of sustained VT or fibrillation, diabetes mellitus with poor blood glucose control or recurrent infections, previous or concomitant aortic or mitral valve surgery, concomitant cerebrovascular surgery, a serum creatinine concentration >3 mg/dl, emergency coronary bypass surgery, a non-cardiovascular condition with expected survival of <2 years or an inability to attend follow-up visits Characteristics of participants: Age (± SD) (years): ICD 64 ± 9, control 63 ± 9 Gender (M/F): ICD 386/60, control 373/81	Primary outcomes: mortality, Kaplan–Meier survival, QoL Secondary outcomes: subgroup analyses of mortality with prespecified variables, Kaplan–Meier probability of first discharge in ICD group, adverse events Method of assessing outcomes: All qualifying signal-averaged ECGs were interpreted a second time at the core study laboratory. Quality control procedures for the measurement of the LVEF are described in ref. 13 Data were reviewed by an independent data and safety monitoring board. In April 1997, 76% of anticipated information on mortality was available and the interim analysis showed no difference between study groups. The board recommended that data on the primary end point be reported as of 30 April 1997 QoL assessed at 6 months after CABG surgery (no baselines), all responses confidential 1. Seven scales of the SF-36: general health/perception of health status; physical functioning/limits to physical activities; physical role functioning/interference work or daily activities; bodily pain/intensity of pain and effect on work; social functioning/interference with normal social activities; emotional role functioning/interference with work; mental health (anxiety, behavioural–emotional control, depression, positive affect). For each a raw score is computed, and then transformed

continued

Reference and design	Intervention	Participants	Outcome measures
	Beta-blockers (not sotalol): 16.4/21.7 Other cardiac: ACE inhibitors: 60.3/63.7 Diuretics: 61.3/57.2 Digitalis: 70.7/62.5 Nitrates:10.9/12.2 Calcium channel blockers: 9.2/7.1 Antiplatelet:78.2/83.7 Oral anticoagulants: 20.6/16.8 Lipid-lowering: 12.9/13.4 At 1 year post-discharge drug therapy, percentage patients [ICD (n = 374)/control (373)]: Oral antiarrhythmics: None: 70.2/72.9 Class I antiarrhythmic agents: 7.5/4.8 Amiodarone: 6.1/2.9 Sotolol: 0.8/0.5 Beta-blockers (not sotalol): 16.0/19.8 Other cardiac: ACE inhibitors: 64.2/67.8 Diuretics: 64.7/55.2 Digitalis: 70.6/60.1 Nitrates:15.8/16.9 Calcium channel blockers: 12.0/9.7 Antiplatelet: 79.1/82.6 Oral anticoagulants: 20.1/16.6 Lipid-lowering: 23.0/23.3	Cardiovascular history (%): Cigarettes at any time: ICD 79, control 76 Angina pectoris: ICD 76, control 76 MI: ICD 83, control 82 ≥ 2 prior MI: ICD 30, control 33 Heart failure: ICD 51, control 49 NYHA class II or III: ICD 71, control 74 Treatment for hypertension: ICD 54, control 52 Diabetes mellitus: ICD 36, control 40 Diabetes with insulin: ICD 17, control 20 Treatment for ventricular arrhythmias: ICD 7, control 7 PTCA or atherectomy: ICD 11, control 11 CABG: ICD 12, control 10 Electronic cardiac pacemaker: ICD 2, control 2 Heart rate (bpm): ICD 79 ± 15, control 79 ± 14 Systolic BP (mmHg): 126 ± 19, control 123 ± 19 Pulmonary rates (%): ICD 20, control 25 S3 gallop (%): ICD 14, control 11 Finding of 12-lead ECG (%): Duration QRS >100 ms: ICD 71, control 74 Left bundle branch block: ICD 10, control 12 Q-wave MI: ICD 52, control 53 LVEF: ICD 0.27 ± 0.06, control 0.27 ± 0.06 Left ventricular end-diastolic pressure (mmHg): ICD 21 ± 10, control 22 ± 10 Findings of coronary angiography (%): One-vessel disease: ICD 8, control 9 Two-vessel disease: ICD 36, control 36 Three-vessel disease: ICD 55, control 55 Baselines for those in the QoL substudy are presented but not data extracted here. No baseline scores of QoL outcome	into a scale from 0 to 100, from lowest to highest scores, respectively. 2. Reported health transition (current health relative to 1 year ago) with five responses: much better now, somewhat better now, about the same, somewhat worse now, much worse now. 3. Additional indicators examining work status and perceptions of body image. Body image is measured with two 2-item scales. The first measures satisfaction with appearance and the second perceptions regarding change of appearance as a result of CABG surgery. Higher scores represent greater satisfaction with appearance and less of a sense that the scars were disfiguring or bothersome. Conceptually the indicators of QoL were grouped into 3 categories: (1) perception of health status, (2) ability to function and (3) psychological well-being Length of follow-up: average follow-up of 32 (SD 16) months Patients were scheduled for follow-up visits every 3 months Nearly all (93%) of 8854 scheduled follow-up visits occurred on schedule

continued

Results			
Outcomes	**ICD (*n* = 446)**	**Comparator (*n* = 454)**	***p*-Value**
30-day mortality	24	20	$p = 0.60$
Mortality during average follow-up	101 (71 cardiac cause)	95 (72 cardiac cause)	HR comparing risk of death per unit of time was 1.07 (95% CI 0.81 to 1.42)[a]
[a] Cox regression model stratified according to clinical centre and LVEF yielded almost identical results [HR 1.02 (95% CI 0.76 to 1.35)]. The HR derived from a Cox model after adjustment for the 10 prespecified covariates was similar to the value obtained without adjustments, as was that for the period beginning 30 days after randomisation [HR 1.03 (95% CI 0.75 to 1,41)]. Separate Cox regression analyses were performed for each of the 10 prespecified covariates, and no significant interaction with ICD therapy was found – the HR was similar in ICD compared with controls patients. Additional analyses were performed to examine the proportional hazards assumption of the Cox model according to clinical centre and LVEF. The assumptions in the model remained valid in this stratified analysis.			
Kaplan–Meier cumulative mortality (% estimated from figure)	**ICD**	**Comparator**	***p*-Value**
12 months	14 $n = 384$	12 $n = 399$	At 48 months $p = 0.64$
24 months	16 $n = 313$	16 $n = 308$	
36 months	21 $n = 213$	20 $n = 199$	
48 months	27 $n = 61$	24 $n = 57$	
Kaplan–Meier cumulative probability of first discharge of ICD (% estimated from figure)	**ICD**	**Comparator**	***p*-Value**
12 months	50	N/A	N/A
24 months	57		
36 months	60		
48 months	66		
QoL (post-intervention only)	**ICD (*n* = 262)**	**Control group (*n* = 228)**	***p*-Value[b]**
Perception of health			
General health status	54.8 ± 22.9	58.3 ± 23.6	NS
Perception of health transition[a]	2.4 ± 1.2	2.1 ± 1.2	0.030
Physical limitations	41.7 ± 42.3	49.2 ± 42.8	0.055
Bodily pain	57.4 ± 24.6	58.8 ± 24.8	NS
Ability to function			
Employment status	0.25 ± 0.4	0.29 ± 0.5	NS
Physical role functioning	58.3 ± 27.5	61.8 ± 28.3	NS
Emotional role functioning	55.4 ± 43.4	67.3 ± 39.9	0.003
Social functioning	70.5 ± 27.2	70.8 ± 26.4	NS
Psychological well-being			
Mental health	72.5 ± 18.3	77.2 ± 17.0	0.004
Satisfaction with appearance	6.0 ± 1.3	6.3 ± 1.1	0.008
Satisfaction with scar	7.0 ± 1.2	7.2 ± 1.1	0.040
[a] Lower scores reflect a tendency to rate one's health as better now, relative to 1 year ago. For all other measures, higher scores represent more favourable scores. [b] *p*-Values represent significance of *t*-tests comparing mean scores of control versus ICD patients.			

continued

Adverse events (postoperative)	ICD	Control	*p*-Value
MI	4.0	3.5	NS
Sustained VT	5.8	6.8	NS
VF	3.4	5.3	NS
Bradycardia	2.9	4.4	NS
Atrial fibrillation	22.9	20.7	NS
Shock	9.2	7.5	NS
New or more severe heart failure	15.7	12.6	NS
Conduction defect	14.1	14.5	NS
Residual central nervous system deficit	3.6	2.0	NS
Bleeding treated with surgery	4.9	3.1	NS
Postpericardiotomy syndrome	0.9	0.7	NS
Deep sternal-wound infection	2.7	0.4	<0.05
Infection at wound or catheter site	12.3	5.9	<0.05
Pneumonia	8.5	4.0	<0.05
Other infection	6.3	3.3	NS
Renal failure	6.7	4.8	NS
Adverse events during long-term follow-up			
Angina pectoris	27.0	27.5	NS
MI	0.5	4.2	<0.05
New or worsening heart failure	42.5	42.5	NS
Ventricular arrhythmias	19.4	14.3	NS
Atrial fibrillation	14.7	10.1	NS
Hospitalisation	61.4	55.2	NS
Repeat CABG surgery	0.0	0.7	NS
Percutaneous transluminal coronary angioplasty (PTCA) or artherectomy	2.9	2.1	NS
Permanent cardiac pacemaker	2.9	4.9	NS

Comments: no adjustments made for multiple comparisons to significance level.

QoL	ICD with shocks (*n* = 101)	ICD with no shocks (*n* = 161)	Control group (*n* = 228)	95% CI, control group vs ICD fired
Perception of health				
General health status	52.1 ± 22.1	56.6 ± 23.3	58.3 ± 23.6	NS
Perception of health transition[a]	2.5 ± 1.3	2.3 ± 1.2	2.1 ± 1.2	(95% CI –0.73 to –0.01)[b,c]
Physical limitations	36.8 ± 41.1	44.8 ± 42.9	49.2 ± 42.8	(95% CI 0.31 to 24.6)[d]
Bodily pain	56.8 ± 25.3	57.8 ± 24.1	58.8 ± 24.8	NS
Ability to function				
Employment status	0.18 ± 0.4	0.30 ± 0.5	0.29 ± 0.5	NS
Physical role functioning	53.2 ± 27.0	61.5 ± 27.5	61.8 ± 28.3	(95% CI 0.7 to 16.6)
Emotional role functioning	49.1 ± 42.8	59.5 ± 43.4	67.3 ± 39.9	(95% CI 6.2 to 30.1)
Social functioning	68.8 ± 27.7	71.6 ± 26.9	70.8 ± 26.4	NS
Psychological well-being				
Mental health	70.6 ± 18.5	73.6 ± 43.4	77.2 ± 17.0	(95% CI 1.5 to 11.6)
Satisfaction with appearance	6.0 ± 1.4	6.0 ± 1.3	6.3 ± 1.1	(95% CI –0.01 to 0.71)
Satisfaction with scar	7.1 ± 1.2	7.0 ± 1.2	7.2 ± 1.1	NS

[a] Lower scores reflect a tendency to rate one's health as better now, relative to 1 year ago. For all other measures, higher scores represent more favourable scores.
[b] 95% confidence intervals control the experiment-wise Type 1 error rate to be 0.05 using Tukey's method.
[c] *F*-test for ANOVA has *p*-value of 0.0507.
[d] *F*-test for ANOVA has *p*-value of 0.0549.

continued

Methodological comments

- Allocation to treatment groups: two independent randomisation schedules were set up for each hospital, one for patients with LVEF of ≤ 0.20 and another for patients with LVEF from 0.21 to 0.35. Patients were randomised within randomly permuted blocks. Randomisation took place in the operating room after bypass grafting had been completed and patients were back on partial cardiopulmonary bypass. The trial had a two-group design with patients randomly assigned with equal probability to prophylaxis with an ICD or to no ICD (controls). The surgeons had the option not to randomise if they thought that implanting and testing a defibrillator system was too risky
- Blinding: not applicable to double blind. No report of blinding of outcome assessors
- Comparability of treatment groups: no significant differences between groups at baseline. The use of cardiac drugs was similar in the 2 groups at the time of discharge after CABG surgery and at 3 months and 1 year after discharge. The rates of class I or III antiarrhythmic drugs and beta-blockers were similar in the two groups throughout the trial
- Method of data analysis: four interim analyses were performed; these were based on sequential monitoring procedures for the groups, with prospective stopping rules defined by a Lan–DeMets boundary with an O'Brien–Fleming spending function. Cumulative survival curves for each group were estimated by the Kaplan–Meier method. Cox proportional hazards regression models were used to estimate HRs (instantaneous relative risks). Log-rank tests, stratified according to EF and clinical centre, were used to test hypotheses about differences between groups. The secondary analyses reported were also based on Cox models and examined survival after surgery and treatment interactions for prespecified subgroups. 10 covariates were prospectively selected and evaluated for their interactions with the effect of ICD on the risk of death: age, gender, presence or absence of heart failure, NYHA functional class, LVEF, presence or absence of diabetes mellitus, duration of the QRS complex (>100 or ≤ 100 ms), use of ACE inhibitors, use of class I or III antiarrhythmic drugs and use of beta-blockers. All analyses adhered to the ITT principle. Comparisons of QoL scales between the intervention and control groups assessed by *t*-tests. Analysis of variance used to test for differences in QoL scales between three groups: controls; ICD group whose device did not fire; ICD group whose device did fire. For scales found to differ significantly between these 3 groups based on an *f*-test, subsequent pairwise comparisons were made, by Tukey's method, to maintain an overall 0.05 Type I error probability. No correction for testing the several scales from the QoL instrument
- Sample size/power calculation: pilot study conducted showed that patients with an abnormal signal-averaged ECG had a mortality rate in the 2 years after CABG that was twice as high as that among patients with a normal signal-averaged ECG. The design ensured that the study had a power of >80% to detect a difference of 26% in mortality between the groups, a difference that corresponded to a 40% reduction in the HR for death from all causes in the ICD group compared with the control group, allowing for anticipated crossovers
- Attrition/drop-out: crossovers reported, but no report of withdrawals or losses to follow-up

General comments

- Generalisability: inclusion criteria strict, which may limit generalisability
- Outcome measures: all variables were defined in a manual of operations
- Inter-centre variability: not reported
- Conflict of interests: Guidant supported with a grant and supplied leads and pulse generators

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	n/a
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	n/a

Reference and design	Intervention	Participants	Outcome measures
Author: Buxton *et al.*,[41] the Multicentre Unsustained Tachycardia Trial (MUSTT) Year: 1999 Country: USA and Canada Study design: RCT Number of centres: 85 Funding: grants from National Heart, Lung and Blood Institute, C.R. Bard, Berlex laboratories, Boehringer-Ingelheim Pharmaceuticals, Guidant Cardiac Pacemakers, Knoll Pharmaceuticals, Medtronic, Searle, Ventritex–St. Jude Medical and Wyeth-Ayerst Laboratories	Comparisons of different interventions: 1. Antiarrhythmic therapy guided by the results of electrophysiological testing. Patients underwent serial drug testing with AADs approved by FDA. Drugs were assigned randomly, with the exception of amiodarone. Amiodarone could be tested at the discretion of the investigator in patients in whom at least 2 tests had failed. (Protocol document states: if side-effects were noted the next agent in the randomisation scheme will be given.) After 4–5 half-lives (~2–3 days; amiodarone was tested after at least 1 week of loading), programmed stimulation was repeated. If <15 complexes were induced, long-term therapy with that regimen was permissible. If no drug regimen could be found that rendered the tachyarrhythmia non-inducible, the investigator could discharge the patient with a drug regimen that was associated with haemodynamic stability during induced tachycardia. No empirical AAD therapy was used. Implantation of a defibrillator could be recommended after at least one unsuccessful drug test. This aspect of	Number of participants: 2202 patients were enrolled; 767 had inducible sustained tachyarrythmia, of whom 704 agreed to participate. EGT $n = 351$, no antiarrythmic therapy (no therapy) $n = 353$ Complications of the baseline electrophysiological study occurred in 5 (0.7%) of those with inducible sustained tachyarrythmias; none were fatal Sample attrition/drop-out: 7% of patients in the EGT group refused antiarrythmic therapies at various points during the study. Most of the patients adhered to the therapy to which they had been assigned. At the last follow-up, 305 patients (87%) assigned to EGT were receiving treatment. 103 patients (29%) were receiving AADs, and 202 (58%) received ICDs. All but 4 patients were followed up for 2 years or more, and all but 2 events could be classified on the basis of information that was available Sample crossovers: of those randomised to no therapy, 96% received no therapy. After discharge, 17% of the EGT group had a change in the type of drug therapy and 12% switched from drug therapy to an ICD. In the no therapy group, at follow-up, 3% received an ICD and 10% had been given AADs without having had cardiac arrest, sustained VT or syncope. Atrial fibrillation was the indication for AADs in 57% of these cases Inclusion/exclusion criteria for study entry: coronary artery disease, LVEF of ≤ 40% and asymptomatic unsustained VT (lasting ≥ 3 beats). The qualifying unsustained tachycardia had to occur ≤ 6 months before enrolment, and ≥ 4 days after the most recent MI or revascularisation procedure Cardiac catheterisation or exercise testing within 6 months before enrolment was required. If exercise-induced ischaemia was detected, appropriate treatment was required before enrolment Excluded patients with history of syncope or sustained VT or VF more than 48 h after the onset of MI and those whose unsustained VT occurred in the setting of acute ischaemia, metabolic disorders, or drug toxicity Electrophysiological study was performed which included the delivery of 1–3 extra stimuli and burst pacing at two right ventricular sites during two paced cycle lengths in the absence of AADs. Stimulation	Primary outcomes: Cardiac arrest (defined as sudden loss of consciousness requiring direct-current countershock to restore consciousness or a stable blood pressure and rhythm), death from arrhythmia (included unwitnessed deaths, witnessed instantaneous deaths, non-sudden deaths due to incessant tachycardia, deaths considered to be sequelae of cardiac arrest, deaths caused by the toxic effects of antiarrhythmic drugs and deaths resulting from the complications of ICDs. Did not include deaths from patients with end-stage heart failure or cardiogenic shock) Secondary outcomes: death from all causes, death from cardiac causes, spontaneous, sustained VT, subgroup analyses of ICD subgroup Method of assessing outcomes: a modified Hinkle–Thaler system was used to classify deaths. Narrative descriptions of events and hospital records were edited by the data-coordinating centre to ensure that the outcomes were classified without knowledge of treatment assignment or whether tachycardia could be induced in any of the patients An independent data coordinating centre responsible for collecting data and statistical analysis Length of follow-up: at least 2 years (median duration 39 months) Patients were evaluated 1 month after discharge and every 3 months thereafter. Protocol document states that patients living too far to return for routine outpatient visits will be followed by telephone contact at the same intervals

continued

Reference and design	Intervention	Participants	Outcome measures
	the protocol was changed during the course (after 358 patients) of the trial in order to reflect changes in practice (initially required ≥ 3 drug test failures). Patients refusing ICD were discharged receiving no antiarrhythmic drugs. Among this group, 45% (351) had antiarrhythmic drugs (class I agents, 26%; amiodarone, 10%; sotolol, 9%) and 45% (161) were given ICDs 2. No antiarrhythmic therapy Other interventions used: treatment with beta-adrenergic blockers and ACE inhibitors was strongly recommended. The rate of cardiac medications was similar between groups, except the use of beta-blockers, which was higher in the no therapy group. The use of AADs with beta-blocking properties accounted for much of the disparity in the use of beta-blockers. In addition to the 29% of patients who were taking pure beta-blockers in the EGT group, 23% were taking AADs with beta-blocking properties. During follow-up an additional 11% of EGT patients and 2% of the no therapy patients were being treated with beta-blockers	was stopped after sustained VT had been reproducibly induced Characteristics of participants (25th–75th percentiles): Median age (years): EGT 67 (60–72), no therapy 66 (58–72). Male gender (%): EGT 90, no therapy 90 White race (%): EGT 90, no therapy 86 Median EF (%): EGT 30 (20–35), no therapy 29 (22–35) History of MI (%): EGT 96, no therapy 93 Time between most recent MI and enrolment (%): ≤ 1 month: EGT 16, no therapy 18 ≤ 1 years: EGT 40, no therapy 38 >3 years: EGT 49, no therapy 52 Prior CABG (%): EGT 56, no therapy 56 Uniform, sustained VT induced at baseline (%): EGT 88, no therapy 92 Median cycle length of uniform VT induced at baseline (ms): EGT 245 (227–265), no therapy 250 (230–272) NYHA class (%)[a]: I: EGT 37, no therapy 36 II: EGT 39, no therapy 38 III: EGT 24, no therapy 25 IV: EGT 0, no therapy 0 Medications at hospital discharge (%): Beta-blockers: EGT 29, no therapy 51 ACE inhibitors: EGT 72, no therapy 77 Aspirin: EGT 64, no therapy 63 Digitalis: EGT 52, no therapy 53 Diuretic agent: EGT 58, no therapy 58	

[a] Data available for 59% of patients in each group. Percentages do not equal 100 owing to rounding.

continued

Results			
Outcomes	**EGT (n = 351)**	**No therapy (n = 353)**	***p*-Value**
Deaths during hospitalisation	6 (2%)	0	
2-year rate of cardiac arrest or death from arrhythmia (Kaplan–Meier) (%)	12	18	
5-year rate of cardiac arrest or death from arrhythmia (Kaplan–Meier) (%)	25	32	$p = 0.04$; RR 0.73 (95% CI 0.53 to 0.99)
Kaplan–Meier 1-, 3-, and 4-year rates of cardiac arrest or death (estimated from figure) (%)	1 year: 9 3 years:16 4 years: 20	1 year: 12 3 years: 22 4 years: 26	
Overall 2-year mortality (Kaplan–Meier) (%)	22	28	
Overall 5-year mortality (Kaplan–Meier) (%)	42	48	$p = 0.06$; RR 0.80 (95% CI 0.64 to 1.10)
Kaplan–Meier 1-, 3-, and 4-year rates of mortality (estimated from figure) (%)	1 year: 13 3 years: 29 4 years: 36	1 year: 16 3 years: 36 4 years: 42	
Rate of death due to cardiac causes at 5 years (%)	34	40	$p = 0.05$
Incidence of spontaneous, sustained VT (%)	20	21	$p = 0.90$
Comments: the lower rates of arrhythmic events among the patients assigned EGT were largely attributable to the use of ICDs.			
Subgroup analyses	**ICD subgroup of EGT**	**No ICD subgroup of EGT**	***p*-Value**
Five-year rate of cardiac arrest or death from arrhythmia (Kaplan–Meier) (%)	9	37	$p < 0.001$
Kaplan–Meier 1-, 2-, 3- and 4-year rates of cardiac arrest or death from arrhythmia (estimated from figure) (%)	1 year: 2 2 years: 3 3 years: 6 4 years: 7	1 year: 17 2 years: 20 3 years: 27 4 years: 32	
Five-year rate of overall mortality (Kaplan–Meier) (%)	24	55	$p < 0.001$
Kaplan–Meier 1-, 2-, 3- and 4-year rates of overall mortality (estimated from figure) (%)	1 year: 4 2 years: 10 3 years: 16 4 years: 20	1 year: 19 2 years: 31 3 years: 40 4 years: 47	
Cardiac arrest or death from arrhythmia (number of events)	12	56	Unadjusted RR: 0.24 (95% CI 0.13 to 0.43); adjusted RR: 0.24 (95% CI 0.13 to 0.45), $p < 0.001$
	ICD subgroup of EGT	**No therapy group**	
Death from all causes (number of events)	35	97	Unadjusted RR: 0.42 (95% CI 0.29 to 0.61); adjusted RR: 0.40 (95% CI 0.27 to 0.59), $p < 0.001$
Cardiac arrest or death from arrhythmia (number of events)	12 (as before)	90	Unadjusted RR: 0.28 (95% CI 0.16 to 0.49); adjusted RR: 0.27 (95% CI 0.15, 0.47), $p < 0.001$
Death from all causes (number of events)	35 (as before)	158	Unadjusted RR: 0.49 (95% CI 0.35 to 0.69); adjusted RR: 0.45 (95% CI 0.32 to 0.63), $p < 0.001$

continued

Comments: adjustments made on the basis of all available prognostic factors.

Adverse effects

Death due to ICD-related infection: 1 at 18 months – infection complicated the revision of the lead system.

Methodological comments

- Allocation to treatment groups: patients with sustained, monomorphic VT induced by any method of stimulation and those with sustained polymorphic VT (including ventricular flutter and fibrillation) induced by one or two extra stimuli were randomly assigned in equal numbers to receive either antiarrhythmic therapy guided by the results of electrophysiological testing or no antiarrhythmic therapy. Protocol document states that randomisation would use a random number generator, no details of concealment of allocation
- Blinding: blinding of outcome assessors
- Comparability of treatment groups: baseline characteristics were similar except the use of beta-blockers at discharge, which was higher in the no therapy group, $p = 0.001$
- Method of data analysis: ITT analysis, all statistical tests were two-tailed. Cumulative event rates were calculated by the Kaplan–Meier method, with the first event as the outcome variable. The significance between treatment groups was assessed by the log-rank test. RR was expressed as an HR derived from the Cox proportional hazards model. Interim analyses were performed at regular intervals and reviewed by an independent data and safety monitoring board. Comparisons of major outcomes in the interim analyses were monitored with two-sided, symmetric O'Brien–Fleming boundaries generated with the Lan–DeMets spending function approach to sequential testing. Observational comparisons were used to compare those with ICDs and those without. The outcomes of the patients who received ICDs within 90 days after enrolment and before the occurrence of any arrhythmic event were compared with the outcomes of patients who were not given ICDs before that time. In addition, covariate-adjusted assessments of the effect of defibrillator therapy on major outcomes were performed with the Cox proportional hazards regression model, in which receipt of a defibrillator was treated as a time-dependent covariate. Covariates examined included age, gender, race, date of enrolment (relative to start of the trial), whether or not patient had prior MI, prior bypass surgery, prior angioplasty, palpitations or angina, EF and the use or non-use of digitalis, beta-blockers and ACE inhibitors at baseline
- Sample size/power calculation: on the basis of the authors' previous reports, a 2-year rate of arrhythmic events of 15–20% in the group assigned to no antiarrhythmic therapy and a reduction of at least 33% in the rate of events in the electrophysiologically guided therapy group was anticipated. Using these rates and an alpha level of 0.05, a total of 900 patients with inducible, sustained tachycardia would provide the study with >80% power to detect an event rate of 15% and >90% power to detect a rate of 20%. Considerable difficulty in meeting the target was encountered, and the enrolment stopped in October 1996, after 704 patients had undergone randomisation. The follow-up was to be at least 2 years
- Attrition/drop-out: not reported

General comments

- Generalisability: patients were required to have inducible ventricular arrhythmias; 1435 patients did not (they were followed up in a registry), so high-risk patients included only
- Outcome measures: all clearly defined. Only a subsection of patients applicable to ICD therapy question, and comparison between this subgroup and other patients not a randomised comparison
- Inter-centre variability: not reported
- Conflict of interests: a number of manufacturers and pharmaceutical companies sponsored the trial

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	n/a
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Not known

Reference and design	Intervention	Participants	Outcome measures
Author: Moss *et al.*,[28] Multicentre Automatic Defibrillator Implantation trial (MADIT II) Year: 2002 Country: USA, Germany, the Netherlands, Israel Study design: RCT Number of centres: 76 (71 in USA, 5 in Europe) Funding: Guidant (transvenous defibrillator systems)	Comparisons of different interventions: 1. ICD – transvenous defibrillator systems 2. Conventional medical therapy Duration of treatment: patients followed to common termination date Other interventions used: programming the defibrillator and prescribing medications was left to the discretion of the patients' physicians. The appropriate use of beta-blockers, ACE inhibitors and lipid-lowering drugs was strongly encouraged in both study groups	Number of participants: 1232 patients randomised; ICD group 742, medical therapy group 490 Sample attrition/drop-out: the status of 1 medical and 2 ICD patients was not known at termination of trial. All were known to be alive within 6 months before the trial ended Sample crossovers: 54 crossovers occurred – 22 from medical group (4.5%) received a defibrillator (21 for documented or suspected malignant ventricular arrhythmias and 1 at physician's discretion), 21 from ICD group (2.8%) did not have an ICD implanted and 11 had their ICD removed (1.5%), including 9 who underwent heart transplantation. 12 patients had their ICD deactivated during the trial, usually as a result of terminal illness Inclusion/exclusion criteria for study entry: age >21 years (no upper age limit), MI 1 month or more before entry (documented by abnormal Q-wave on ECG, elevated cardiac enzyme levels on laboratory testing during hospitalisation for suspected MI, fixed defect on thallium scanning or localised akinesis on ventriculography with evidence of obstructive coronary disease on angiography), an EF = 0.30 within 3 months before entry (assessed by angiography, radionuclide scanning or echocardiogram). Potentially eligible participants were referred by local cardiologists, internists and primary care physicians. Patients were not required to undergo electrophysiological screening for inducible ventricular arrhythmias. Excluded if had an indication approved by the FDA for an implantable defibrillator, were in NYHA functional class IV at enrolment, had undergone coronary revascularisation within the preceding 3 months, had an MI within the last month (as evidenced by measurement of cardiac enzymes), had cerebrovascular disease, were of childbearing age and were not using medically prescribed contraceptive measures, had any condition other than cardiac disease that was associated with a high likelihood of death during the trial or were unwilling to consent When the trial began in 1997, participants had to have frequent or repetitive ventricular ectopic beats during 24-h Holter monitoring. After recruitment of	Primary outcomes: death from any cause Secondary outcomes: adverse effects Method of assessing outcomes: not reported Length of follow-up: averaged 20 months (range 6 days to 53 months) There were 8749 scheduled follow-up visits during the trial, with a 94% rate of attendance in the medical group and 97% in the ICD group

continued

Reference and design	Intervention	Participants	Outcome measures
		23 patients, on 1 January 1998 this requirement was eliminated because almost all eligible participants had such arrythmias Characteristics of participants (± SD): Age (years): ICD 64 ± 10, medical 65 ± 10 Male (%): ICD 84, medical 85 NYHA class I (%): ICD 35, medical 39 NYHA class II (%): ICD 35, medical 34 NYHA class III (%): ICD 25, medical 23 NYHA class IV (%): ICD 5, medical 4 (values reflect NYHA class recorded in the 3-month period before enrolment. Eligibility was restricted to those in I, II or III at enrolment) Hypertension treatment (%): ICD 53, medical 53 Diabetes (%): ICD 33, medical 38 Current/former smoker (%): ICD 80, medical 82 Coronary bypass surgery (%): ICD 58, medical 56 Coronary angioplasty (%): ICD 45, medical 42 Interval of >6 months between most recent MI and enrolment (%): ICD 88, medical 87 *Cardiac findings at enrolment (%):* Blood urea nitrogen >35 mg/dl: ICD 29, medical 32 Atrial fibrillation: ICD 9, medical 8 QRS interval ≥ 0.12 s: ICD 50, medical 51 Non-specific conduction defect: ICD 22, medical 26 Right bundle-branch block: ICD 9, medical 7 Left bundle-branch block: ICD 19, medical 18 LVEF: ICD 23 ± 5, medical 23 ± 6 *Medications at last contact (%):* Amiodarone: ICD 13, medical 10 ACE inhibitors: ICD 68, medical 72 Beta-blockers: ICD 70, medical 70 Calcium channel blockers: ICD 9, medical 9 Class I antiarrhythmic agents: ICD 3, medical 2 Digitalis: ICD 57, medical 57 Diuretics: ICD 72, medical 81 Lipid-lowering statins: ICD 67, medical 64	

continued

Results			
Outcomes	**ICD (n = 742)**	**Medical (n = 490)**	**HR**
Number of deaths (%)	105 (14.2)	97 (19.8)	0.69 (95% CI 0.51 to 0.93), p = 0.016
Survival (Kaplan–Meier) at 12 months	503 (0.91)	329 (0.90)	Reduction of 12% (95% CI –27 to 40)
Survival (Kaplan–Meier) at 24 months	274 (0.84)	170 (0.78)	Reduction of 28% (95% CI 4 to 46)
Survival (Kaplan–Meier) at 36 months	110 (0.78)	65 (0.69)	Reduction of 28% (95% CI 5 to 46)
Comments: the difference in survival between the two groups was significant (nominal p = 0.007) on log-rank test.			
Subgroup analysis (from figure)	**HR (95% CI)**		
Survival/age	<60 years (n = 370), HR 0.5 (95% CI 0.22 to 0.95) 60–69 years (n = 426), HR 0.82 (95% CI 0.45 to 1.25) ≥70 years (n = 436), HR 0.62 (95% CI 0.44 to 0.98)		
Survival/gender	Male (n = 1040), HR 0.72 (95% CI 0.52 to 0.96) Female (n = 192), HR 0.58 (95% CI 0.3 to 1.18)		
Survival/EF	≤ 0.25 (n = 831), HR 0.64 (95% CI 0.50 to 0.92) >0.25 (n = 771), HR 0.72 (95% CI 0.4 to 1.22)		
Survival/NYHA	I (n = 461), HR 0.64 (95% CI 0.5 to 0.94) ≥ II (n = 771), HR 0.7 (95% CI 0.44 to 1.02)		
Survival/QRS interval	<0.12 s (n = 618), HR 0.76 (95% CI 0.48 to 1.16) 0.12–0.15 s (n = 352), HR 0.62 (95% CI 0.38 to 1.1) >0.15 s (n = 262), HR 0.52 (95% CI 0.3 to 0.88)		
Comments: HRs in the subgroups were similar, with no statistically significant interactions. There were also no significant differences in the effect of ICD therapy on survival in subgroup analyses classified according to the presence or absence of hypertension, diabetes, left bundle branch block or atrial fibrillation; the interval since the most recent MI (≤6 months vs >6 months); the type of defibrillator implanted (single chamber vs dual chamber); or the blood urea nitrogen level (≤25 mg/dl vs >25 mg/dl).			
Adverse effects	**ICD**	**Medical**	***p*-Value**
Lead problems (%) leading to surgical intervention	13 (1.8)	n/a	
Non-fatal infections (%) leading to surgical intervention	5 (0.7)	–	
New or worsened heart failure requiring hospitalisation (%)	148 (19.9)	73 (14.9)	Represents 11.3 and 9.4 patients so hospitalised per 1000 months of active follow-up (nominal p = 0.009)
Comments: serious complications related to defibrillator therapy were infrequent. No deaths occurred during inplantation.			
Methodological comments • Allocation to treatment groups: after written consent, a baseline clinical history and 12-lead ECGs were obtained and a physical examination was conducted. The patients were randomly assigned in a 3:2 ratio to receive ICD or medical therapy. No details of randomisation method or allocation concealment • Blinding: double blinding not applicable, no blinding of outcomes assessors reported • Comparability of treatment groups: baseline characteristics and prevalence of use of various cardiac medications at the time of last follow-up visit were reported to be similar between groups • Method of data analysis: used ITT principle. Used a triangular sequential design, which was modified for two-sided alternatives and corrected for the lag in obtaining data accrued but not reported before the termination of the trial, for weekly monitoring, with preset boundaries to permit termination of the trial if the defibrillator therapy was found to be superior to, inferior to or equal to conventional medical therapy. Secondary analyses were performed using			

continued

the Cox proportional hazards regression model. Survival curves were determined using the Kaplan–Meier method with comparisons of cumulative mortality based on logarithmic transformations. *p*-Values were termed nominal when they were not adjusted for sequential monitoring. All were two-tailed. At the recommendation of the data and safety monitoring board, the trial was stopped in November 2001, shortly after analysis revealed that the difference in mortality between the two groups had reached the prespecified efficacy boundary ($p = 0.027$)

- Sample size/power calculation: the trial was designed to have 95% power to detect a 38% reduction in the 2-year mortality rate among the patients in the defibrillator group, given a postulated 2-year mortality rate of 19% among patients assigned medical therapy, with a two-sided significance level of 0.05. For proportional hazards modelling, power was maintained for a true HR of 0.63, after allowance for crossovers. On 4 May 2001, the executive committee increased the enrolment goal from 1200 to 1500 so that enrolment would be ongoing while data on outcomes were still accruing
- Attrition/drop-out: 3 patients lost to follow-up. Attendances to follow-up visits were 94% in the medical group and 97% in the ICD group. Some crossovers noted

General comments

- Generalisability: patients with prior MI and LVEF <0.30. Large sample size
- Outcome measures: appropriate
- Inter-centre variability: not reported
- Conflict of interests: trial funded by Guidant (transvenous defibrillator systems). Two authors have given lectures sponsored by Guidant. The investigators had full access to the data and performed the data analysis with no limitations imposed by the sponsor

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double blind?	N/A
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	>1% lost to follow-up, <5% crossed over

Reference and design	Intervention	Participants	Outcome measures
Author: Bänsch *et al*.,[29] Cardiomyopathy Trial (CAT) Year: 2002 Country: Germany Study design: RCT Number of centres: 15 Funding: Guidant (manufacturer)	Comparisons of different interventions: 1. Transvenous defibrillator system (ICD), (defibrillator threshold <20 J was mandatory. ICD testing by current guidelines). A VT zone with a detection rate of 200 bpm was programmed in all patients. All shocks were programmed to a maximum output of 30 J. The pacemaker rate was programmed to 40 bpm 2. Control Other interventions used: no changes in the medication of ACE inhibitors, digitalis, and diuretics between	Number of participants: 104 patients (between July 1991 and March 1997). 50 patients in ICD group and 54 in control group Sample attrition/dropout: not reported Sample crossovers: not reported Inclusion/exclusion criteria for study entry: age 18–70 years, with symptomatic DCM for ≤9 months and impaired LV function (LVEF ≤30% obtained during LV angiography) and in NYHA class II or III. Excluded by angiography if coronary artery disease (coronary stenosis >70%). Also excluded if had a history of a prior MI, myocarditis or excessive alcohol consumption, symptomatic bradycardia, VT and VF, or if they were listed for heart transplantation at the time of presentation. Patients with significant valvular disease and hypertrophic or restricted cardiomyopathy were also excluded from the trial, as were patients in NYHA class I or IV and patients who were mentally unable to understand the protocol Characteristics of participants (all not significant unless *p*-value stated):	Primary outcomes: all-cause mortality at 1 year Secondary outcomes: heart transplantation, cardiac mortality (sudden and non-sudden cardiac death), sustained VT (adequate ICD therapy), symptomatic VTs requiring antiarrhythmic treatment. Complications caused by ICD therapy, such as revision procedures and infection, were documented Adequate ICD therapy was assumed if documented tachycardia electrograms had a morphology different from sinus rhythm and if tachycardias started suddenly with no cycle

continued

Reference and design	Intervention	Participants	Outcome measures
	baseline and 24-month follow-up were documented	Gender (M/F): ICD 43/7, control 40/14 Age (years): ICD 52 ± 12, control 52 ± 10 Duration of symptoms (median): ICD 3.0 months, control 2.5 months Baseline violators: ICD 8, control 11 NYHA II: ICD 66.7%, control 64.1% NYHA III: ICD 33.3%, control 35.8% Orthopnoe: ICD 4.1%, control 2.0% Oedema: ICD 8.3%, control 9.4% EF: ICD 24 ± 6%, control 25 ± 8% LVED pressure (mmHg): ICD 16 ± 9, control 18 ± 10 Echocardiography: LV diastolic (mm): ICD 69 ± 7, control 69 ± 8 LV systolic (mm): ICD 58 ± 9, control 59 ± 10 Baseline ECG: Rhythm: Sinus rhythm: ICD 79.6%, control 86.8% Atrial fibrillation/flutter (chronic or intermittent): ICD 20.4%, control 11.3% Paced: ICD 0%, control 1.9% QRS morphology: Normal: ICD 72.9%, control 55.1% Not normal: ICD 27.1%, control 44.9% LBBB: ICD 84.9%, control 81.8% RBBB: ICD 7.7%, control 18.2% Other or undefined BB: ICD 7.7%, control 18.2% QRS width (ms)[a]: ICD 102 ± 29, control 114 ± 29 QT duration (ms)[a]: ICD 347±69, control 369 ± 43 Holter ECG: Patients with nsVTs: ICD 53.1%, control 58% Median duration of nsVT (s, 25%/75%): ICD 5 (3.0/6.5), control 3.5 (2.3/6.0) Rate of nsVTs (bpm): ICD 175 ± 39, control 157 ± 23 Bradycardias (%): ICD 2.1%, control 18.8%, $p = 0.015$ SA block: ICD 0%, control 4.2% AV block: ICD 2.1%, control 14.6 Baseline electrophysiological studies: AH interval (ms): ICD 86 ± 22, control 97 ± 31 HV interval (ms): ICD 51 ± 15, control 55 ± 14 Inducible VT: ICD 6.1%, control 0% Inducible VF: ICD 16.0%, control 3.7% Medication: Beta-blocker: ICD 4.0%, control 3.7% Ca antagonist: ICD 16.0%, control 7.4% Digitalis: ICD 80.8%, control 75.9% Diuretics: ICD 88.0%, control 85.2% Nitrates: ICD: 32.0%, control 25.9% ACE inhibitor: ICD 94.0%, control 98.1% Warfarin: ICD 24.0%, control 35.2%	length variation, indicative of atrial fibrillation Method of assessing outcomes: follow-up visits every 3 months and encouraged to schedule additional visits if the first shock, cluster of shocks or syncope occurred. Central registry held. No details of how outcomes assessed Length of follow-up: per protocol, all patients 22.8 ± 4.3 months: ICD 22.7 ± 4.5, control 22.9 ± 4.2 months Years per August 2000, all patients 5.5 ± 2.2: ICD 5.7 ± 2.2, control 5.2 ± 2.1 years

[a] Patients with pacemakers not included.

continued

Results

Outcomes	ICD (n = 50)	Comparator (n = 54)	p-Value
Mortality during 1st year of follow-up[a]	4 deaths (all cardiac)	2 deaths (non-cardiac)	NS
Mortality during follow-up (mean 5.5 ± 2.2 years)	13	17	NS
Cumulative survival (%):			
2 years	92	93	Log-rank,
4 years	86	80	p = 0.554
6 years	73	68	

nsVT, non-sustained VT.
[a] No sudden deaths occurred in either group. No deaths occurred as a result of the implantation procedure (within 30 days).

Predictors of mortality	The only predictor of total mortality was impaired LVEF. Compared with patients with EF ≥ 28%, the odds ratio was 4.1 (95% CI 1.5 to 11.3, p = 0.0006) for patients with EF = 21% and 2.1 (95% CI 0.7 to 6.2, p = 0.19) for patients with EF 22–27%

Survival in patients with nsVTs during baseline Holter monitoring was 87, 72 and 63% compared with 98, 93 and 77% in patients without nsVTs, after 2, 4 and 6 years, respectively (NS).

Survival of patients with nsVTs during baseline Holter monitoring was not improved by ICD therapy, whereas 85, 77 and 72% of patients with nsVTs survived in the ICD group and 90, 67 and 55% survived in the control group after 2, 4 and 6 years, respectively (NS).

Comments: all baseline variables were tested accordingly but did not show any statistically significant impact on survival.

Adverse effects	ICD	Comparator
Revisions due to device dislocation and bleeding[a]	2	N/A
Electrode dislocation and sensing/isolation defects[a]	7	N/A
Infection with total device replacement[a]	2	N/A
Perforation[a]	1	N/A
Adequate therapies for VTs >200 bpm	11	
Syncope	6	

[a] During 24 months of follow-up.

Comments: survival free of VTs and adequate therapies in the ICD group was 90, 87 and 82% after 2, 4 and 6 years, respectively. All-cause mortality rates were different in patients with and without adequate therapies in the ICD group. Whereas 92, 90 and 83% of patients survived if no VT was stored in the ICD (n = 39), only 91, 73 and 44% survived 2, 4 and 6 years if VT were stored and adequately terminated by the ICD (n = 11, p = 0.024).

Methodological comments

- Allocation to treatment groups: random assignment was performed centrally. Closed envelopes with the assigned study group were sent to each centre. No details of how the random sequence was generated
- Blinding: double blinding not applicable, no blinding of outcomes assessors reported
- Comparability of treatment groups: baseline characteristics did not differ between groups except for bradycardias caused by sinus arrest and atrioventricular block I and II (Wenckebach), which were noted more frequently during Holter monitoring in the control group. Mean QRS duration was longer in the control group but was not significantly different. More ICD patients had inducible VT and VF than controls but neither were significant
- Method of data analysis: because all-cause mortality rates varied between different heart failure studies and included mostly patients with heart failure caused by coronary heart disease, it was decided to perform a blinded interim analysis after the inclusion of 100 patients at 1 year of follow-up (pilot). Survival rates presented as Kaplan–Meier curves and compared by log-rank statistics. Despite having an interim analysis, there was no need to perform an α-adjustment on significance for the primary end-point because no differences were detected between the two groups. Cox proportional regression models were calculated to estimate the prognostic relevance of patient characteristics. Data described as mean ± SD if normally distributed, or by median with 25% and 75% percentiles if not. Quantitative comparisons between groups were performed by two-sided analysis, with the Mann–Whitney exact test; qualitative characteristics were compared by means of the Fisher exact χ^2 test
- Sample size/power calculation: based on literature all-cause mortality rate of 30% in the first year, with 40% of deaths being sudden, was used as the assumption for study size. On this assumption, 1348 patients had to be included to show a

continued

1-year survival benefit of 6% for ICD treatment, with a power of 80% and a probability value of 0.05. Survival analysis of all patients with at least 1 year of follow-up was performed (June 1997). The interim analysis showed that the overall 1-year mortality rate for all patients was only 5.6%. The difference between study groups was only 2.6%. According to protocol, the randomisation was stopped, and all randomly assigned patients completed the scheduled follow-up period of 2 years
- Attrition/drop-out: not reported

General comments
- Generalisability: strict inclusion criteria may reduce generalisability. Small sample size
- Outcome measures: appropriate
- Inter-centre variability: not reported
- Conflict of interests: manufacturer was sponsor

Quality assessment for RCTs (Jadad score 1)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	n/a
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Not reported

Appendix 9
Excluded studies

Companion trial

The companion trial was an RCT comparing medical therapy, pacing and defibrillation in patients with chronic heart failure. Participants in the trial were all NYHA functional class III or IV with EF ≤35%. Outcomes assessed included a composite score of mortality and hospitalisation and morbidity. The trial was designed primarily to evaluate whether optimal drug therapy used resynchronisation therapy alone or resynchronisation therapy combined with an ICD. Preliminary results indicated a reduction in the combination of all-cause mortality and all-cause hospitalisation for people receiving cardiac resynchronisation therapy as compared with optimal pharmaceutical therapy alone. The trial did not meet the inclusion criteria for the current review because there was not a comparison of ICD versus control or AAD, and the participants were LVEF ≤35%, with chronic heart failure.

Bristow MR, Feldman AM, Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators. *Cardiac Failure* 2000;**6**:276–85.

Wever *et al.*

The Wever trial was an RCT of ICD versus conventional therapy in 60 patients with secondary prevention indications (previous SCD caused by documented ventricular arrhythmia). Outcomes included mortality, hospitalisations and adverse events. The trial was designed to compare the effectiveness of ICD implantation as a first-choice therapy with conventional therapy as a comparator. The conventional therapy in the trial was a three-tiered strategy of pharmacological treatments, then possible ablative surgery and/or ICD if necessary. The trial did not meet the inclusion criteria of the current review as the comparison group includes patients with ICD therapy (15/31 patients).

Wever EF, Hauer RN, van Capelle FJ. Randomised study of implantable cardiac defibrillator as first choice therapy versus conventional strategy in post infarct sudden death survivors. *Circulation* 1995; **91**:2195–203.

Definite trial

The Definite trial is a multicentre randomised trial of patients with non-ischaemic cardiomyopathy (LVEF ≤35%), a history of symptomatic heart failure and spontaneous arrhythmia. Patients were randomised to ICD versus no ICD. Outcomes included mortality and QoL. Preliminary results show that ICD recipients had a statistically significant reduction in rate of arrhythmic death and showed a strong trend toward reduction of overall mortality rates. The trial did not meet the inclusion criteria of the current review as the patients did not have LVEF ≤30%.

Kadish A, Quigg R, Schaechter A, Anderson KP, Estes M, Levine J. Defibrillators in nonischemic cardiomyopathy treatment evaluation. *Pacing Clin Electrophysiol* 2000;**23**:338–43.

Amiovert study

The purpose of this multicentre randomised trial was to compare total mortality during therapy with amiodarone or an implantable cardioverter–defibrillator (ICD) in patients with non-ischaemic dilated cardiomyopathy and non-sustained VT, and with LVEF ≤35%. The trial did not meet the patient inclusion criteria.

Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, *et al*. Amiodarone versus ICD: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. *J Am Coll Cardiol* 2003;**41**:1707–12.

Other excluded studies

Alings AM. Implantable defibrillator therapy. *Neth J Med* 2003;**61** (5:Suppl):Suppl-7 (not a systematic review, meta-analysis or RCT).

Bocker D, Breithardt G. Evaluating AVID, CASH, CIDS, CABG-Patch and MADIT: are they concordant? *J Intervent Cardiac Electrophysiol* 2000;**4**:Suppl-8 (not a systematic review, meta-analysis or RCT).

Burke JL, Hallas CN, Clark-Carter D, White D, Connelly D. The psychosocial impact of the implantable cardioverter defibrillator: a meta-analytic review. *Br J Health Psychol 2003;***8**(Pt 2):165–78 (no survival data).

Cannom DS. Implantable cardioverter defibrillator trials: what's new? *Curr Opin Cardiol* 2002;**17**:29–35 (not a trial).

Domanski MJ, Epstein A, Hallstrom A, Saksena S, Zipes DP. Survival of antiarrhythmic or implantable cardioverter defibrillator treated patients with varying degrees of left ventricular dysfunction who survived malignant ventricular arrhythmias. *J Cardiovasc Electrophysiol* 2002;**13**:580–3 (*post hoc* subgroup AVID study).

Exner DV, Sheldon RS, Pinski SL, Kron J, Hallstrom A. Do baseline characteristics accurately discriminate between patients likely versus unlikely to benefit from implantable defibrillator therapy? Evaluation of the Canadian implantable defibrillator study implantable cardioverter defibrillatory efficacy score in the antiarrhythmics versus implantable defibrillators trial. *Am Heart J* 2001;**141**:99–104 (*post hoc* comparison of CIDS and AVID).

Gold MR, Nisam S, Multicenter Automatic Defibrillator Implantation Trial. Multicenter Unsustained Tachycardia Trial. Primary prevention of sudden cardiac death with implantable cardioverter defibrillators: lessons learned from MADIT and MUSTT. *Pacing Clin Electrophysiol* 2000;**23**(11: Pt 2):t-5 (not a systematic review, meta-analysis or RCT).

Higgins SL. Impact of the Multicenter Automatic Defibrillator Implantation Trial on implantable cardioverter defibrillator indication trends. *Am J Cardiol* 1999;**83**:79D–82D (not a systematic review, meta-analysis or RCT).

Kron J, Herre J, Renfroe EG, Rizo-Patron C, Raitt M, Halperin B, *et al*. Lead- and device-related complications in the antiarrhythmics versus implantable defibrillators trial. *Am Heart J* 2001;**141**:92–8 (comparison data not reported).

Lee KL, Hafley G, Fisher JD, Gold MR, Prystowsky EN, Talajic M, *et al*. Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. *Circulation* 2002;**106**:233–8 (*post hoc* subgroup MUSTT).

Nademanee K, Veerakul G, Mower M, Likittanasombat K, Krittayapong R, Bhuripanyo K, *et al*. Defibrillator Versus Beta-blockers for Unexplained Death in Thailand (DEBUT): a randomized clinical trial. *Circulation* 2003;**107**:2221–6 (wrong participants).

Nisam S, Henry S, Wilber DJ. Implementation of MADIT and MUSTT in clinical practice: results of an international survey. *Ann Noninvas Electrocardiol* 2002;**7**:399–405 (not a systematic review, meta-analysis or RCT).

Russo AM, Hafley GE, Lee KL, Stamato NJ, Lehmann MH, Page RL, *et al*. Racial differences in outcome in the Multicenter UnSustained Tachycardia Trial (MUSTT): a comparison of whites versus blacks. *Circulation* 2003;**108**:67–72 (*post hoc* subgroup MUSTT).

Appendix 10

Data extraction of economic evaluations

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: Kupersmith *et al*., 1995[49] Country: USA Setting: inpatient Language: English Study design: Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: to establish the cost-effectiveness of epicardial and endocardial ICD versus EP-guided drug therapy Dates: 1985 to 1988 Modelling: Markov model	Treatment intervention: ICD Type of intervention: ☒ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: Electrophysiological-guided drug therapy	Eligibility criteria: high-risk patients with VT/VF Numbers involved: cohort of 218 patients Disease: Baseline characteristics: cohort mean age 56.6 ± 12.8 years, mean EF 0.346 ± 0.16; 77% had coronary artery disease, 15% cardiomyopathy, 8% other underlying heart disease, 55.4% VF, 44.6% VT	Clinical effectiveness outcome measures: Primary outcomes used: Secondary outcomes used: Length of follow-up:

Methods

Direct costs:
- ☐ Marginal costs
- ☒ Charges
- ☒ Discounting (5%)
- ☐ Costs of secondary consequences
- ☐ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☒ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
- ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
- ☐ don't know
- ☒ Base year (1989 to 1992)
- ☒ Reflated costs (by 6% to 1989)
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

Currency: US dollars

Measures of benefits: (free text below)
- ☒ Life-year gained
- ☐ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

continued

Results

Cost results:

Intervention: base-case charges were $146,797

Control: base-case charges were $93,340

Base case benefit used:

ICD effectiveness was an increase in discounted mean life expectancy of 1.72 years

Synthesis of costs and benefits:

Base-case cost-effectiveness was $31,100 per life-year saved

Statistical analysis of costs or CIs:

Reducing the base-case assumption that 100% of first appropriate ICD discharges would have been the time of death without the ICD: at <38%, cost-effectiveness (CE) becomes more favourable
Perioperative mortality rate: at 1% CE $31,000; at 7.2% CE $31,900; at 9.6% CE $33,900
Battery life at 2 years: CE $41,800
Lead replacement: at 1 year CE $31,150; at 4 years CE $31,150
Discount: at 0% CE $28,000; at 3% CE $29,900; at 10% CE $40,300
Antiarrhythmic use: any CE $27,600; amiodarone CE $37,500
Published ICD survival curves: Kupperman *et al.*[51] CE $32,900; Larsen *et al.*[52] CE $31,500
Repeat hospitalisations (high/low):
ICD: year one $34,400/$28,900; subsequent years $34,500/$31,100; all years $37,800/$28,900
EP therapy: year one $20,100/$37,100; subsequent years $27,700/$39,500; all years $16,800/$45,400
EF: <0.25 CE $44,000 and ≥ 0.25 CE $27,200
ICD without preimplant EP study: CE $18,100
Endocardial ICD: base case CE $25,700; 3.4% operative mortality $26,400; first shock = death: 78% $23,200; 54% $27,300; 22% $25,400; requiring epicardial ICD (1%/11.8%): $26,100/$26,700; initial hospitalisation ± SE $28,800/22,700; lead replacement (1%/4%) $25,700/25,700; EF (<0.25/≥ 0.25): $33,700/$22,400; ICD, no EP $14,200

Conclusions and critical comments

Authors' conclusions:

Results, made with conservative assumptions indicate that the cost-effectiveness of the ICD is comparable to that of other technologies. It remains so under a variety of reasonable assumptions in sensitivity analysis and further can be considerably improved under certain circumstances

Reviewers' commentary:

Early study with data from 1989–92. Cyclic Markov model

Implications of the study:

Very limited implications for UK

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Yes
2. Is there a clear description of alternatives?	Yes
3. Are data used from a reasonable study type?	No (not an RCT)
4. Are relevant costs and consequences identified?	
(a) Healthcare resources (adverse events)	No (no patient costs)
(b) Patient/family resources	No (some guessed)
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	
6. Are the costs and consequences valued credibly?	No (some guessed)
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	No
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	Yes

continued

	Score (yes/no/unclear)
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Reference and design	**Intervention**	**Participants (if trial based)**	**Outcomes (if trial based)**
Study: Kuppermann *et al*., 1990[51] Country: USA Setting: inpatient Language: English Study design: Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: to present the results of a study of the cost-effectiveness of ICD with secondary data, expert opinion and techniques of decision analysis Dates: 1986 and 1991 Modelling: Markov model	Treatment intervention: ICD Type of intervention: ☐ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: Drug therapy (as treated before the general availability of ICDs)	Eligibility criteria: survivors of cardiac arrest, not associated with MI and inducible VT/VF Numbers involved: Disease: Baseline characteristics:	Clinical effectiveness outcome measures: Primary outcomes used: Secondary outcomes used: Length of follow-up:

Methods

Direct costs:

- ☐ Marginal costs
- ☒ Charges
- ☒ Discounting (5%)
- ☐ Costs of secondary consequences
- ☐ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☒ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☐ don't know
- ☒ Base year
- ☒ Reflated costs (1986)
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

continued

Currency: US dollars
Measures of benefits: (free text below)
- ☒ Life year gained
- ☐ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

Results

Cost results:

Intervention: total expected cost $121,540

Control: total expected cost $88,990

Base-case benefit used:

ICD total life expectancy 5.1 years, comparison patients' total life expectancy 3.2 years

Synthesis of costs and benefits:

1986 scenario leads to a cost-effectiveness of ICD of $17,100 per life-year saved (reports $17,400 in text and $17,100 in table)

Statistical analysis of costs or CIs:

Mortality: decreasing the probability of arrhythmic death in the ICD group from 0.04 to 0.01 during year 1 led to a CE ratio of $17,260 per life-year saved. Increasing the rate to 0.04 led to a CE ratio of $17,670 per life-year saved

Varying the year 1 arrhythmic mortality for the non-defibrillator group from base rate of 0.22 to 0.4 or 0.44 changes the CE ratio to $14,770 and $18,560, respectively, per life-year saved

Increasing arrhythmic mortality in subsequent years from 0.08 to either 0.04 or 0.16 reduces the CE of the comparison groups to $15,670 and $18,470 per life-year saved, respectively

Varying the arrhythmic mortality in subsequent years from 0.02 to either 0.04 to 0.01 reduces the CE of the ICD group from $19,200 to $17,700 per life-year saved, respectively

Initial hospitalisation: varying the initial hospitalisation cost for ICD implantation from $49,830 to either $45,000 or $52,000 worsens the CE ratio to $14,810 and $18,550 per life-year saved, respectively

Varying the cost of the initial hospitalisation in the non-defibrillator group from $13,680 to either $12,000 or $42,000 decreases the CE ratio to $18,290 and $2,260 per life-year saved, respectively

Rehospitalisation: varying rehospitalisation rates in the first year for the ICD group changed the CE ratios from $15,580 to $20,910. Varying the rehospitalisation rates in the first year for the non-defibrillator group increases the CE ratio from $7,020 to $22,980 per life-year saved. Varying rehospitalisation rates in subsequent years for the ICD group changes the CE ratios from $17,100 to $22,280. Varying the rehospitalisation rates in subsequent years for the non-defibrillator group increases the CE ratio from $12,640 to $29,604 per life-year saved

Probability of ICD patients using antiarrhythmic medication: changing from 0.57 to 0.75 leads to a CE ratio of $18,050; reducing to 0.20 reduces the CE ratio to $16,020 per life-year saved

Projecting into the future with replacement of ICD at 5 years and programmable devices and a transvenous approach CE ratio estimated at $74,00 per life-year saved.

Conclusions and critical comments

Authors' conclusions:

Results suggest that the cost-effectiveness of ICD lies between $15,600 and $29,600 per life-year saved. The CE of ICDs is well within the range of currently accepted life-saving technologies

Reviewers' commentary:

Very early American study. Method sound with the data available, but expert panel was used for large part of data

Implications of the study:

Very limited relevance for the NHS

continued

Quality assessment for economic evaluations	
	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	No
2. Is there a clear description of alternatives?	No
3. Are data used from a reasonable study type?	Unclear
4. Are relevant costs and consequences identified?	No (no patient costs)
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	No (some guessed)
6. Are the costs and consequences valued credibly?	No (some guessed)
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	No
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	Yes
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Unclear
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Reference and design	**Intervention**	**Participants (if trial based)**	**Outcomes (if trial based)**
Study: Larsen *et al*., 1990[52] Country: USA Setting: inpatient Language: English Study design: Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: to perform a cost-effectiveness analysis of ICD, compared with both conventional antiarrhythmic therapy and amiodarone therapy Dates: 1985 to 1988 Modelling: Markov model	Treatment intervention: ICD Type of intervention: ☒ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: 1. Amiodarone 2. Conventional therapy (antiarrhythmic therapy but with inducible arrhythmia)	Eligibility criteria: model based on patients with VT/VF, aged 45, 55 and 65 years, with a 24-month ICD replacement Numbers involved: Disease: Baseline characteristics:	Clinical effectiveness outcome measures: Primary outcomes used: Secondary outcomes used: Length of follow-up:

continued

Methods

Direct costs:

- ☒ Marginal costs (variable hospital costs)
- ☒ Charges
- ☒ Discounting (5%)
- ☐ Costs of secondary consequences
- ☐ Patient or society costs

  Estimation of the quantities was one or more of the following:

  - ☐ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☐ don't know
- ☐ Base year
- ☒ Reflated costs (1989)
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

Currency: US dollars

Measures of benefits: (free text below)

- ☒ Life year gained
- ☐ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

    Speculation about the influence of QALYS

Results

Cost results:

Intervention: average cost for a 45-year-old $93,182; for a 55-year-old $89,592; for a 65-year-old $83,640

Amiodarone: average cost for a 45-year-old $25,074; for a 55-year-old $24,790; for a 65-year-old $24,250

Conventional: average cost for a 45-year-old $16,200; for a 55-year-old $16,156; for a 65-year-old $16,071

Base case benefit used:

Life expectancy with ICD was 6.1 years, with amiodarone 3.9 years, with conventional treatment 2.5 years

Synthesis of costs and benefits:

For a 45-year-old: the marginal cost-effectiveness of amiodarone compared with conventional therapy is $6509 per life-year saved. The marginal cost-effectiveness of the ICD compared with amiodarone is $27,561 per life-year saved

For a 55-year-old: the marginal cost-effectiveness of amiodarone compared with conventional therapy is $6635 per life-year saved. The marginal cost-effectiveness of the ICD compared with amiodarone is $29,244 per life-year saved

For a 65-year-old: the marginal cost-effectiveness of amiodarone compared with conventional therapy is $6892 per life-year saved. The marginal cost-effectiveness of the ICD compared with amiodarone is $32,674 per life-year saved

Statistical analysis of costs or CIs:

ICD battery life: if 36 months the CE ratio is $21,800 per life-year saved; at 60 months the CE ratio is $16,500; at 96 months the CE ratio is $13,800

Amiodarone efficacy: would have to decline from its baseline value of 69% to 15% for its marginal CE ratio to become higher than that of ICD therapy. If none of the efficacy of amiodarone is due to complete suppression of arrhythmia and all patients treated with amiodarone require repeat admission, the marginal CE ratio of ICD is still greater than that of amiodarone ($28,900 vs $7,300 per life-year saved)

QoL: amiodarone QALYs need to be <40% of ICD in order for ICD to dominate over amiodarone

ICD QALYs need to be <65% of amiodarone, in order for amiodarone to be preferred over ICD therapy

Cost per life-year saved of amiodarone therapy: to overstep that of ICD it would have to decrease in efficacy from 69% to 15%

continued

Conclusions and critical comments

Authors' conclusions:

Results show that the marginal cost-effectiveness of treatment with ICD versus amiodarone is highly dependent on the longevity of the ICD power supply; as battery life improves, CE improves dramatically. Even at present levels of battery life, the CE in these patients is comparable to that of other accepted medical treatments and is not affected substantially by the patients' age

Reviewers' commentary:

Very early American study. Method sound with the data available, but expert panel had to be used for large part of data

Implications of the study:

Very little relevance for the NHS

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Yes
2. Is there a clear description of alternatives?	Yes
3. Are data used from a reasonable study type?	No
4. Are relevant costs and consequences identified?	No
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Unclear
6. Are the costs and consequences valued credibly?	Unclear
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	No
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	Yes
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Unclear
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	Unclear

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: Larsen *et al*., 2002[42] Country: USA Setting: inpatient Language: English Study design: data from AVID RCT Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: not reported Dates: study dates AVID were 1992–97 Modelling: not applicable	Treatment intervention: ICD Type of intervention: ☐ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: amiodarone	Eligibility criteria: brief patients who had been resuscitated from near-fatal VF, sustained VT with syncope or sustained VT with an EF of ≤ 0.40. See Appendix 7, p. 65. Numbers involved: 1016 in trial (as above). Of these, 8 were excluded from economic study because they had not completed their initial hospitalisations at the time of the trial termination Baseline characteristics: see Appendix 7, p. 66)	Clinical effectiveness outcome measures: Primary outcomes used: all-cause mortality Secondary outcomes used: Length of follow-up: average 1.49 years for all 1008 patients

Methods

Direct costs:

- ☐ Marginal costs
- ☒ Charges
- ☒ Discounting (3%)
- ☐ Costs of secondary consequences
- ☒ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☐ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☒ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☐ don't know
- ☐ Base year
- ☒ Reflated costs (prices were standardised to 1997 prices)
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

Currency: US dollars

Data collection was divided into two basic types: all patients had data collected on hospital bills and antiarrhythmic drug use; all other data were collected on a subset of patients (n = 237) only

Measures of benefits: (free text below)

- ☒ Life-year gained
- ☐ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

    Bootstrap procedure used to obtain 95% CIs

Results

Cost results:

Intervention: $87,479 with no discounting, $85,522 with discounting of 3% per annum

Control: $73,564 with no discounting, $71,421 with discounting of 3% per annum

Base-case benefit used:

Survival with ICD 0.21 years longer than AAD

continued

Synthesis of costs and benefits:

At 3 years of follow-up, the expected survival for patients treated with ICD was 0.21 years longer than for AAD at an incremental cost of $14,101, yielding a cost-effectiveness ratio of $66,677 per life-year saved (95% CI $30,761 to $154,768)

Statistical analysis of costs or CIs:

Shorter initial hospitalisation length of stay: reducing the baseline hospitalisation stay might save $1328 per day. The differential change of one day's length of stay would alter the CE ratio by $6281 ($1328 differential costs/0.21 years, the survival differential). If the mean length of stay was dropped 3 days compared with patients treated with AAD, the CE ratio would fall from $66,677 to $47,834

Extended time horizons: two models used: (1) relative hazard = 1 after 6 years, (2) survival modelled on Weinbull distributions after 6 years

Out to 6 years, the costs and survival differences using either survival model are the same and the CE estimate is $79,291

From 6 to 20 years, however, the CE ratio differs slightly from $68,378 with model (1) and $80,358 with model (2)

Projected lifetime survival: model (1) predicts that the CE ratio will drop by $12,160 ($67,131), whereas model (2) yields a lifetime CE ratio of $211,128 per life-year saved

Differences:

CE ratio at 3 years:

Those with VF (n = 453): $55,163, p = 0.49

Those with VT (n = 555): $82,889

Those with EF ≤ 35% (n = 695): $60,967, p = 0.48

Those with EF >35% (n = 306): $536,106

Those aged <60 years (n = 266): $72,917, p = 0.50

Those aged 60–69 years (n = 374): $77,829

Those aged ≥ 70 years (n = 368): $65,041

Those with CAD (n = 822): $74,932, p = 0.48

Those with other cause (n = 186): $–9513

Conclusions and critical comments

Authors' conclusions:

The AVID economic substudy base-case CE ratio suggests that a year of life saved by ICD implantation compared with AAD therapy is moderately cost-effective. However, most costs associated with the treatment of both groups were for in-hospital care

Reviewers' commentary:

Recent publication. Cost of technology more reliable than early studies. Methodology sound and of general importance

Implications of the study:

American setting, with charges as costing basis makes the study of limited detailed UK importance.

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	No
2. Is there a clear description of alternatives?	Yes
3. Is data used from a reasonable study type?	Yes
4. Are relevant costs and consequences identified?	Yes
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Yes
6. Are the costs and consequences valued credibly?	Yes
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	Yes
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	N/A

continued

	Score (yes/no/unclear)
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: Mushlin, 1998[44] MADIT trial Country: Germany and USA Setting: inpatient Language: English Study design: RCT Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: Dates: trial December 1990 to March 1996 Modelling:	Treatment intervention: ICD Type of intervention: ☒ Primary prevention ☐ Secondary prevention ☒ Treatment Control intervention: conventional medical treatment	Eligibility criteria: VT, prior MI, LVEF <0.35 and inducible VT (see Appendix 8, p. 83) Numbers involved: ICD group 95, conventional therapy group 101 (as above); cost-effectiveness on 181 Disease: MI Baseline characteristics: Age (years): medical 64 ± 9, ICD 62 ± 9 Gender (M/F): medical 92/8, ICD 92/8 Cardiac history (%): ≥ 2 prior MI: medical 29, ICD 34 (see Appendix 8, p. 84)	Clinical effectiveness outcome measures: Primary outcomes used: total mortality Secondary outcomes used: adverse events Length of follow-up: average 27 months

Methods

Direct costs:
- ☐ Marginal costs
- ☒ Charges (used 'charge-to-cost' ratios)
- ☒ Discounting (3%)
- ☐ Costs of secondary consequences
- ☐ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☒ a guess (some derived from self reports from patients)
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☒ don't know
- ☐ Base year
- ☒ Reflated costs (1995)
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

Currency: US dollars

Measures of benefits: (free text below)
- ☐ Life-year gained
- ☒ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

continued

Results

Cost results:

Intervention: initial costs $44,600. Total costs per month for surviving patients $1384. The net present value in 1995 dollars for treating patients with ICD during the 4 years of the trial was estimated at $97,560

Control: initial costs $18,900. Total costs per month for surviving patients $1915. The net present value in 1995 dollars for treating patients with conventional therapy during the 4 years of the trial was estimated at $75,980

Base-case benefit used:

Average survival over 4 years was 3.66 years for the ICD group and 2.80 years for the conventionally treated group

Synthesis of costs and benefits:

The incremental cost-effectiveness ratio (ICER) is $27,000 (95% CI 0.2, 68.2) per life-year saved

Statistical analysis of costs or CIs:

If a transvenous ICD is used the ICER is $22,800 per life-year saved
If generators are only replaced every 4 years the ICER is $12,500 per life-year saved
Reducing the cost of the device by 25% reduces the ICER to $13,100 per life-year saved
Reducing the cost of the device by 50% reduces the ICER to $3300 per life-year saved
Reducing the cost for transplant/dialysis to a maximum of $40,000 increases the ICER to $32,900
Dropping four patients who had transplant/dialysis from the calculation increases the ICER to $39,600
Analysing the data without patients who crossed over increased the ICER to $32,900
Correcting the data for the sequential stopping rule used in MADIT which could lead to biases in secondary survival analysis increased the ICER to $29,300
Extrapolating results to 8 years decreases the ICER to $16,900

Conclusions and critical comments

Authors' conclusions:

Analysis indicates that when an ICD is used for the prevention of SCD in selected high-risk patients, this therapeutic strategy is cost-effective

Reviewers' commentary:

Costing made in an aggregated bottom-up fashion although with cost-to-charge technique, which basically leads to relatively detailed information

Implications of the study:

American setting, with charges as costing basis makes the study of limited detailed UK importance

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Unclear
2. Is there a clear description of alternatives?	Yes (in trial data)
3. Are data used from a reasonable study type?	Yes
4. Are relevant costs and consequences identified?	No (no patient costs)
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Unclear (some guessed)
6. Are the costs and consequences valued credibly?	Unclear (some guessed)
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	Yes
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	N/A

continued

	Score (yes/no/unclear)
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: O'Brien *et al*., 1992[50] Country: UK Setting: inpatient Language: English Study design: Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: a preliminary assessment of the economics of ICD treatment in the UK Dates: Modelling: Markov model	Treatment intervention: ICD Type of intervention: ☒ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: amiodarone	Eligibility criteria: patients at high risk of SCD Numbers involved: Disease: Baseline characteristics:	Clinical effectiveness outcome measures: Primary outcomes used: Secondary outcomes used: Length of follow-up:

Methods

Direct costs:
- ☐ Marginal costs
- ☒ Charges
- ☒ Discounting (6%)
- ☐ Costs of secondary consequences
- ☐ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☒ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☐ don't know
- ☐ Base year
- ☐ Reflated costs
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

Currency: pound sterling

Measures of benefits: (free text below)
- ☒ Life-year gained
- ☐ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

continued

Results

Cost results:

Intervention: total discounted cost to 20 years: £28,400 adjusted mortality; £32,200 unadjusted mortality
Net cost of ICD treatment: £26,100 adjusted mortality; £30,200 unadjusted mortality

Control: total discounted cost to 20 years: £2300 adjusted mortality; £2100 unadjusted mortality

Base-case benefit used:

Estimated life expectancy was 11.1 and 6.7 years with ICD and amiodarone, respectively

Synthesis of costs and benefits:

Net cost-effectiveness of ICD with adjusted mortality: £15,400 per life-year gained
Net cost-effectiveness of ICD with unadjusted mortality: £8,200 per life-year gained

Statistical analysis of costs or confidence intervals:

Cost of ICD implantation reduced by 50% to £1500: £14,590 per life-year gained (adjusted); £7769 per life-year gained (unadjusted)
Device generator life increased to 6 years (from 4 years): £13,029 per life-year gained (adjusted); £6890 per life-year gained (unadjusted)
Follow-up frequency reduced to 6-monthly (from 3-monthly): £14,776 per life-year gained (adjusted); £7784 per life-year gained (unadjusted)
Amiodarone management costs increased by £1000 per year: £12,954 per life-year gained (adjusted); £7221 per life-year gained (unadjusted)

Conclusions and critical comments

Authors' conclusions:

Study shows that, compared with management with amiodarone, the CE of ICD treatment lies in the range £8200–15,400 per life-year gained

Reviewers' commentary:

Early UK study. Limitations in secondary data make results uncertain

Implications of the study:

Early and uncertain cost results. Important background study

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Unclear
2. Is there a clear description of alternatives?	No
3. Are data used from a reasonable study type?	No
4. Are relevant costs and consequences identified?	No
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	No (some guessed)
6. Are the costs and consequences valued credibly?	No (some guessed)
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	No
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	N/A
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	Yes
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	Yes
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

continued

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: O'Brien *et al*., 2001[43] and Sheldon *et al*., 2001[53] CIDS study Country: Canada Setting: inpatient Language: English Study design: RCT Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: (1) to estimate the cost per life-year gained with ICD therapy compared with drug therapy with amiodarone; (2) to determine whether ICD in patients with ≥ 2 risk factors is economically attractive Dates: enrolment October 1990 to January 1997 Modelling: not applicable	Treatment intervention: ICD Type of intervention: ☒ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: amiodarone	Eligibility criteria: resuscitated VF or VT or with unmonitored syncope (see Appendix 7, p. 75) Numbers involved: clinical effectiveness: ICD 328, amiodarone 331; cost-effectiveness: ICD 212, amiodarone 218 Disease: see Appendix 7, p. 75 Baseline characteristics: see Appendix 7, p. 76	Clinical effectiveness outcome measures: Primary outcomes used: all-cause mortality Secondary outcomes used: Length of follow-up: 2310 days (6.3 years)

Methods

Direct costs:
- ☐ Marginal costs
- ☒ Charges
- ☒ Discounting (3%)
- ☐ Costs of secondary consequences
- ☐ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☐ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☐ don't know
- ☒ Base year (1999)
- ☐ Reflated costs
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

Currency: Canadian dollars

Measures of benefits: (free text below)
- ☒ Life-year gained
- ☐ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

Results

Cost results:

Intervention: hospital and physician services costs of implanting an intravenous ICD estimated at Can$39,093, of which Can$22,000 was the cost of the device. Replacement procedures cost Can$29,012 including the device. Total cost per patient (initial hospitalisation, drugs, follow-up, etc.) = Can$87,715

Control: amiodarone Can$2.06. Total cost per patient (initial hospitalisation, drugs, follow-up, etc.) = Can$38,600

continued

Base-case benefit used:

Life expectancy for the ICD group was 4.58 years and for the control group 4.35 years, difference 0.23 years (95% CI –0.09 to 0.55)

Synthesis of costs and benefits:

The incremental cost-effectiveness of ICD therapy was Can$213,543 per life-year gained [additional cost Can$49,115/0.23 (gain in life expectancy)]. The lower bound of the bootstrap 95% CI for cost-effectiveness was Can$88,187 per life-year gained; the upper bound was arbitrarily large as the CI included a region in which amiodarone was dominant

Statistical analysis of costs or CIs:

If the cost of the ICD were Can$16,000 the CE falls to Can$191,929 per life-year gained, when costs are Can$26,000 the CE rises to Can$231,137

At an extreme of 1-day hospital stay, CE is still high at Can$170,284 per life-year gained, at 5 days Can$195,082, at 10 days Can$195,082 and at 15 days Can$208,859

When costs are discounted to present value at 3% per year but effects are not discounted, CE is Can$191,383. When costs and effects are discounted at 6% the CE is Can$240,760

When LVEF <35% CE is Can$108,484, when LVEF is ≥35% amiodarone is dominant

Extrapolating to 12 years beyond the trial: if benefit continues CE is Can$99,420, if benefit is equivalent CE is Can$118,668, if benefit declines CE is Can$149,710

Differences:

From Sheldon *et al*. paper:[53]

ICER in patients with 0 risk factors was dominated, ICER in patients with 1 risk factor was Can$238,388, with 2 risk factors Can$96,718 and with 3 risk factors Can$23,344. Risk factors were age ≥70 years, LVEF ≤35%, NYHA functional class III

ICERs for two groups: those 'unlikely to benefit' (having < two risk factors) ICER was Can$916,659 (95% CI: 120,869, dom); those 'likely to benefit' (having ≥ two risk factors) ICER was Can$65,195 (95% CI: 31,456, dom). Sensitivity analysis on these two groups (all Can$):

Those 'unlikely to benefit':

ICD costs Can$26,000 ICER = 992,237; ICD costs Can$16,000 ICER = 828,569

Length of initial stay 15 days ICER = 897,237; 10 days ICER = 840,282; 5 days ICER = 782,595, 1 day ICER = 736,445

Discount rate 0% effects, 3% costs ICER = 1,042,639; 6% costs and effects ICER 771,590

Extrapolation to 12 years, If benefit continues ICER is 322,240; If benefit is equivalent ICER is 400,983; If benefit declines ICER is 549,030

Those 'likely to benefit':

ICD costs Can$26,000 ICER = 71,395; ICD costs Can$16,000 ICER = 57,849

Length of initial stay 15 days ICER = 63,497; 10 days ICER = 58,733; 5 days ICER = 53,969, 1 day ICER = 50,158

Discount rate 0% effects, 3% costs ICER = 70,693; 6% costs and effects ICER 58,069

Extrapolation to 12 years, If benefit continues ICER is 40,604; If benefit is equivalent ICER is 46,094; If benefit declines ICER is 52,715

Conclusions and critical comments

Authors' conclusions:

Our estimates of CE of ICD therapy bring into question whether this technology is good value for money in survivors of VF/VT. However, ICD appears to be relatively more cost-effective in patients with low EF, whether as primary or secondary prevention. Estimates of CE are clearly sensitive to the time horizon of analysis, and 'within-trial' analyses need to be interpreted with caution

From Sheldon *et al*. paper:[53] ICE therapy relative to best medical therapy is more economically attractive when treating patients with ≥ 2 risk factors compared with treating patients with <2 of these factors

Reviewers' commentary:

Methods sound. Conclusions should be considered

Implications of the study:

Canadian setting, with costing basis slightly different than in UK. Makes the study of limited detailed importance

continued

Quality assessment for economic evaluations	
	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Yes
2. Is there a clear description of alternatives?	Yes (in trial data)
3. Are data used from a reasonable study type?	Yes
4. Are relevant costs and consequences identified?	No (no patient costs)
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Yes
6. Are the costs and consequences valued credibly?	Yes
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	Yes
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	N/A
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: Owens *et al*., 1997[48] Country: USA Setting: inpatient Language: English Study design: N/A Economic evaluation/type: cost–utility analysis Hypothesis/study question: to estimate the cost-effectiveness of ICD relative to amiodarone treatment for the prevention of SCD in patients at high or intermediate risk Dates: Modelling: Markov model	Treatment intervention: ICD only Type of intervention: ☐ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: amiodarone only; amiodarone–ICD	Eligibility criteria: Numbers involved: Disease: Baseline characteristics: base cases were aged 57 years (range 45–75 years) who had survived previous cardiac arrest and were thus at high risk of SCD. Also a population at intermediate risk of SCD (where the rate of arrhythmia and non-arrhythmic cardiac death was approximately half the base-case rate)	Clinical effectiveness outcome measures: Primary outcomes used: Secondary outcomes used: Length of follow-up:

Methods

Direct costs:
- ☒ Marginal costs
- ☒ Charges
- ☒ Discounting (3%)
- ☐ Costs of secondary consequences
- ☒ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☐ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☐ don't know
- ☐ Base year
- ☒ Reflated costs (1995)
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

Currency: US dollars

Measures of benefits: (free text below)
- ☒ Life-year gained
- ☒ QALY
  - ☒ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

Results

Cost results:

Intervention: total costs not reported. Costs for ICD implantation $44,600, annual costs $7700, general replacement $24,000

Control: total costs not reported. Initial hospitalisation $14,000, annual costs $4000

Base-case benefit used:

Treatment with ICD would reduce total mortality rate by 20–40% at 1 year compared with amiodarone

continued

Synthesis of costs and benefits:

Expenditures per life-year gained are reported but not data extracted here

In high-risk patients, the marginal cost-effectiveness of treatment with an ICD relative to treatment with amiodarone alone ranges from $74,400 per QALY (if ICD reduces total mortality by 20%) to $37,300 per QALY (if ICD reduces total mortality by 40%). If ICD reduces total mortality by 30% it costs $49,300 per QALY gained relative to amiodarone therapy. In intermediate-risk patients, if ICD use reduces the mortality rate by 20%, ICD use is $76,800 per QALY; if it reduces the mortality rate by 40%, the CE ratio is $36,300

In high-risk patients, the CE ratio of ICD compared with amiodarone–ICD with an RRR of 20% is $71,300 and with an RRR of 40% it is $36,300. In intermediate-risk patients, the CE ratio of ICD compared with amiodarone–ICD with an RRR of 20% is $74,300 and with an RRR of 40% it is $35,500

In high-risk patients, the CE ratio of amiodarone–ICD compared with amiodarone only with an RRR of 20% is $126,300 and with an RRR of 40% it is $54,900. In intermediate-risk patients, the CE ratio of amiodarone–ICD compared with amiodarone only with an RRR of 20% is $138,900 and with an RRR of 40% it is $55,200

Statistical analysis of costs or CIs:

Sensitivity analysis for amiodarone only versus ICD only groups:
Risk reduction: at an RRR of 10% CE is $158,700 per QALY; at an RRR of 15% CE = $100,600 per QALY; at an RRR 50% CE = $30,200 per QALY
Generator replacement: if replaced every 5 years (rather than 4 years in model) CE = $63,800 per QALY
If QoL in amiodarone group is 0.65 and ICD remains at 0.75 (base case) the CE = $43,300 per QALY. If QoL in ICD is 0.65 and QoL in amiodarone is 0.75, CE = $447,700 per QALY
A discount rate of 5% reduces CE estimate to $85,900 per QALY
Reduction of perioperative mortality from 1.8% to 0.5% improves CE to $69,900 per QALY

Conclusions and critical comments

Authors' conclusions:

Analysis suggests that using an ICD to prevent SCD will cost more than $500,000 per QALY unless the device reduces all-cause mortality by ≥ 30%. Study suggests that the use of ICDs may be less cost-effective than was estimated in previous studies

Reviewers' commentary:

Methods sound. Data from a specified set of literature makes the interpretation transparent

Implications of the study:

American setting, with charges as costing basis makes the study of limited detailed UK importance

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Yes
2. Is there a clear description of alternatives?	Yes
3. Is data used from a reasonable study type?	No
4. Are relevant costs and consequences identified?	Yes
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Yes
6. Are the costs and consequences valued credibly?	Yes
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	No
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	Yes

continued

	Score (yes/no/unclear)
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	Yes

Reference and design	**Intervention**	**Participants (if trial based)**	**Outcomes (if trial based)**
Study: Owens *et al*., 2002[46] Supersedes Owens *et al*., 1997[48] Country: USA Setting: Language: English Study design: Economic evaluation/type: cost–utility analysis Hypothesis/study question: to develop a risk stratification of candidates for ICD implantation Dates: Modelling: decision model (previously developed model was adapted to estimate the cost and benefits associated with use of an ICD or amiodarone), Markov model	Treatment intervention: ICD Type of intervention: ☐ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: amiodarone	Eligibility criteria: N/A Numbers involved: N/A Disease: N/A Baseline characteristics: N/A	Clinical effectiveness outcome measures: N/A Primary outcomes used: N/A Secondary outcomes used: N/A Length of follow-up: N/A

Methods

Direct costs:
- ☐ Costs
- ☒ Charges (Medicare)
- ☒ Discounting (3%)
- ☐ Costs of secondary consequences
- ☒ Patient or society costs

  Estimation of the quantities was one or more of the following:
  - ☐ a guess
  - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
  - ☒ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
  - ☒ don't know
- ☐ Base year
- ☒ Reflated costs (to 1999)
- ☐ Indirect costs included
  - ☐ transferred
  - ☐ productivity loss

continued

Currency: US dollars

Measures of benefits:
- ☐ Life-year gained
- ☒ QALY
  - ☐ Time trade-off
  - ☒ Standard gamble
  - ☒ Other (visual analogue scale)

Results

Cost results:

Intervention: for example, at a total annual cardiac mortality rate of 12% and a ratio of SCD death to non-SCD of 1.0, treatment with ICD led to costs of $129,600 and 5.24 QALYs

Control: under the same example: treatment with amiodarone resulted in expenditures of $82,000 and 4.39 QALYs

Base-case benefit used:

At a total mortality rate of 12% and a ratio of SCD to non-SCD of 1.0, treatment with amiodarone associated with 4.39 QALYs. Treatment with ICD led to 5.24 QALYs

Synthesis of costs and benefits:

Incremental cost of $54,700 per QALY gained

The cost-effectiveness of the ICD was influenced strongly by the total annual cardiac mortality rate and by the proportion of deaths that were sudden. There was a U-shaped relation between the cost-effectiveness of the ICD and the total annual cardiac mortality rate, with the cost-effectiveness becoming unfavourable at both low and high total cardiac mortality rates. In addition, at any given annual cardiac mortality rate, the CE of the ICD improved significantly as the ratio of SCD to non-SCD increased. For example, with an annual total cardiac mortality rate of 12% the CE of the ICD varies from $36,000 per QALY gained when the ratio of SCD to non-SCD is 4 to $116,000 per QALY gained when the ratio is 0.25

Statistical analysis of costs or CIs:

If the efficacy of the ICD were <25% the CE became less favourable. For example, at a total annual cardiac mortality rate of 12% and a ratio of SCD to non-SCD of 1.0, the CE ratio of ICD increased from $54,700 to $64,000 per QALY gained when the assumed efficacy of the ICD was decreased from 25% to 20%

If survival with an ICD is unchanged but the efficacy of amiodarone is only 5%, then the use of ICD costs $49,400 per QALY gained relative to treatment with amiodarone

If the costs of the ICD device were reduced by 30% (with ICD efficacy of 25%, total cardiac mortality rate of 12% per year, and equal rates of SCD and non-SCD), the CE of the ICD implantation improved from $54,700 to $40,500 per QALY gained

If the entire cost of the initial hospitalisation for ICD were reduced by 30%, implantation cost $32,900 per QALY gained

If the QoL with an ICD improved relative to that of amiodarone, the ICD became more cost-effective. Conversely, if the QoL with an ICD decreased relative to amiodarone, the costs-effectiveness of the ICD became less favourable compared with amiodarone

Conclusions and critical comments

Authors' conclusions:

In patients with high rates of SCD but low rates of non-SCD, the ICD provides a large benefit at a reasonable cost. In contrast, when used in patients who have lower ratios of SCD to non-SCD, the benefit of the ICD is substantially diminished: these patients have a high mortality rate even if SCDs are effectively prevented

Reviewers' commentary:

Methods sound. Data from a specified set of literature makes the interpretation transparent. Risk stratification strategies must provide information about both the likelihood of SCD and non-SCD if they are to identify successfully patients for whom use of the ICD is economically attractive

Implications of the study:

American setting, although excluding overhead costs as costing basis makes the study of some detailed UK importance

continued

From Owens *et al.*, 1997[48] ($) ICD only compared with amiodarone only:		
	RRR 40%	**RRR 20%**
High-risk patients		
Per life-year saved	27,300	54,000
Per QALY	37,300	74,400
Low-risk patients		
Per life-year saved	26,700	56,000
Per QALY	36,300	76,800
ICD only compared with amiodarone-to-ICD regimen:		
	RRR 40%	**RRR 20%**
High-risk patients		
Per life-year saved	26,600	50,400
Per QALY	36,300	71,300
Low-risk patients		
Per life-year saved	26,200	54,100
Per QALY	35,500	74,300
Amiodarone-to-ICD compared with amiodarone only regimen:		
	RRR 40%	**RRR 20%**
High-risk patients		
Per life-year saved	40,700	89,600
Per QALY	54,900	126,300
Low-risk patients		
Per life-year saved	41,000	101,900
Per QALY	55,200	138,900

Quality assessment for economic evaluations	
	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Yes
2. Is there a clear description of alternatives?	Yes
3. Are data used from a reasonable study type?	No
4. Are relevant costs and consequences identified?	Yes
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Yes
6. Are the costs and consequences valued credibly?	Yes
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	Yes
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	Yes
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: Sanders *et al*., 2001[47] Country: USA Setting: inpatient Language: English Study design: Economic evaluation/type: cost–utility analysis Hypothesis/study question: evaluated the level of efficacy needed to make prophylactic therapy with and ICD or amiodarone in patients stratified by LVEF Dates: Modelling: Markov model	Treatment intervention: 1. ICD 2. Amiodarone Type of intervention: ☒ Primary prevention ☐ Secondary prevention ☒ Treatment Control intervention: no treatment	Eligibility criteria: patients with past MI without sustained ventricular arrhythmia. Patients stratified into 3 groups: LVEF ≤ 0.3, 0.31–0.4 and >0.4 Numbers involved: LVEF ≤ 0.3 $n = 293$; LVEF 0.31–0.4 $n = 482$; LVEF >0.4 $n = 2149$. No details of numbers within intervention group Disease: not reported Baseline characteristics: no detailed characteristics within intervention groups; only reported in the subgroups based on LVEF	Clinical effectiveness outcome measures: Primary outcomes used: survival, cardiac death, inpatient costs Secondary outcomes used: Length of follow-up: 3 years

Methods

Direct costs:

- ☐ Marginal costs
- ☒ Charges (using 'cost-to-charge ratios', not given)
- ☒ Discounting (3%)
- ☐ Costs of secondary consequences
- ☒ Patient or society costs
  - Estimation of the quantities was one or more of the following:
    - ☐ a guess
    - ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
    - ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
    - ☐ don't know
- ☐ Base year
- ☒ Reflated costs (1999)
- ☒ Indirect costs included 'patient travel and inconvenience'
  - ☐ transferred
  - ☐ productivity loss

Currency: US dollars

Measures of benefits: (free text below)

- ☐ Life-year gained
- ☒ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☒ Other (comments below)
    - Assumed that 1 year of life in the post-MI health state was equal to 0.88 year (~10.5 months) in optimal health. This was based on data collected on a cohort of 67 patients

Results

Cost results:

Intervention: EF ≤ 0.3, low efficacy $119,600, moderate efficacy $123,700, high efficacy $128,100
EF 0.31–0.4, low efficacy $129,500, moderate efficacy $131,400, high efficacy $133,400
EF >0.4, low efficacy $150,300, moderate efficacy $151,500, high efficacy $152,600

Amiodarone: EF ≤ 0.3, low efficacy $82,700, moderate efficacy $86,200, high efficacy $90,100
EF 0.31–0.4, low efficacy $94,100, moderate efficacy $96,800, high efficacy $99,700
EF >0.4, low efficacy $111,100, moderate efficacy $113,200, high efficacy $115,100

continued

Control: EF ≤ 0.3, low efficacy $70,100, moderate efficacy $70,100, high efficacy $70,100
EF 0.31–0.4, low efficacy $78,300, moderate efficacy $78,300, high efficacy $78,300
EF >0.4, low efficacy $91,700, moderate efficacy $91,700, high efficacy $91,700
For low efficacy ICD reduces SCD by 40% and amiodarone reduces total mortality by 4%; for moderate efficacy ICD reduces SCD by 60% and amiodarone reduces total mortality by 11%; for high efficacy ICD reduces SCD by 80% and amiodarone reduces total mortality by 19%

Base-case benefit used:
Utilities: current health 0.88 (0.6–1); ICD 0.88 (0.6–1); amiodarone 0.88 (0.6–1)

Synthesis of costs and benefits:
Amiodarone vs no treatment:
EF ≤ 0.3, low efficacy $191,600 life-year, $221,200/QALY; moderate efficacy $37,800/life-year, $43,100/QALY; high efficacy $24,100/life-year, $27,400/QALY
EF 0.31–0.4, low efficacy $/life-year dominated, $/QALY dominated; moderate efficacy $58,300/life-year, $66,500/QALY; high efficacy $32,600/life-year, $37,100/QALY
EF >0.4, low efficacy $/life-year dominated, $/QALY dominated; moderate efficacy $115,600/life-year, $132,500/QALY; high efficacy $56,200/life-year, $64,100/QALY

ICD vs no treatment:
EF ≤ 0.3, low efficacy $78,000/life-year, $88,600/QALY; moderate efficacy $52,700/life-year, $59,800 $/QALY; high efficacy $40,600/life-year, $46,100/QALY
EF 0.31–0.4, low efficacy $164,000/life-year, $186,300/QALY; moderate efficacy $102,800/life-year, $116,800/QALY; high efficacy $75,600/life-year, $85,900/QALY
EF >0.4, low efficacy $421,700/life-year, $479,200/QALY; moderate efficacy $227,800/life-year, $258,800/QALY; high efficacy $157,200/life-year, $178,600/QALY

ICD vs amiodarone
EF ≤ 0.3, low efficacy $64,900/life year, $73,700/QALY; moderate efficacy $63,300/life year, $71,800/QALY; high efficacy $63,300/life year, $71,700/QALY
EF 0.31–0.4, low efficacy $113,200/life year, $128,100/QALY; moderate efficacy $173,400/life year, $195,700/QALY; high efficacy $463,800/life year, $517,100/QALY
EF >0.4, low efficacy $183,000/life year, $206,400/QALY; moderate efficacy $501,500/life year, $557,900/QALY; high efficacy $/life year dominated, $/QALY dominated

Statistical analysis of costs or CIs:
Sensitivity analyses presented in figures. Data from text only reported here
In patients with EF ≤ 0.30, the ICD had to prevent 70% and 35% of SCD to reach the cost-effectiveness thresholds of $50,000 and $100,000 per QALY gained, respectively. In the cohort with EF of 0.31–0.4, the ICD had to prevent 70% of SCD to reach $100,000 per QALY gained. In the cohort with EF >0.4, amiodarone had to reduce total mortality by 9% and 6% to reach $50,000 and $100,000 per QALY gained, respectively
In the cohort with EF ≤ 0.30, even with the most optimistic estimate of the efficacy of amiodarone, an ICD would cost $100,000 per QALY gained if it prevented 70% of deaths
If the underlying cardiac mortality rate of the population were reduced by ≥ 25%, the cost-effectiveness of both the ICD and amiodarone compared with no treatment would be far less favourable. If the population risk were 25% or higher, both amiodarone and ICD would be more economically attractive
When moderate efficacy is assumed, if the cost of ICD were reduced from $25,000 to $10,000 the ICER of the ICD relative to amiodarone would improve from $71,800 to $29,200 per QALY gained in patients with EF ≤ 0.3, from $195,700 to $59,600 per QALY gained in those with EF 0.31–0.40 and from $557,900 to $168,900 per QALY gained in those with EF >0.4
QoL: if EF ≤ 0.3, if patients were assumed to have low symptom severity after ICD implantation and QoL utilities were amiodarone 0.73, ICD 0.76, current health 0.80, then the ICER of ICD relative to no treatment is $97,600 per QALY, ICD compared with amiodarone $70,000 per QALY and amiodarone compared with no therapy $1,239,600 per QALY. If, however, the patients experienced severe ICD symptoms (decreasing the utility of ICD to 0.64), then ICD would be dominated by both amiodarone and no treatment

continued

Differences:

Probabilistic sensitivity analysis which simultaneously varied the values of each of the input variables (demographics, mortality, costs) except QoL:

If EF ≤ 0.3 amiodarone dominated ICD in 2.6% of simulations. Implantation of ICD was more effective, yet more costly, in the remaining 97.4% of simulations (median ICER is $83,2000 per QALY). In 0.02% of simulations, ICD was dominated by no treatment; in the remaining 99.98% it had a median ICER of $67,700 per QALY compared with no treatment. Amiodarone was dominated by no antiarrhythmic therapy in 0.07% of the simulations and had a median ICER of $47,000 per QALY in the remaining 99.93%

Conclusions and critical comments

Authors' conclusions:

Analysis indicates that in patients with past MI and severely depressed LVEF function, use of ICD or amiodarone may provide substantial clinical benefit at an acceptable cost

Reviewers' commentary:

Recent study, makes cost results relevant. Modelling relies to a large extent on unpublished data

Implications of the study:

American setting, with charges as costing basis, although scaled down to compensate for excess overhead part of cost, makes the study of limited detailed UK importance

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Yes
2. Is there a clear description of alternatives?	Yes
3. Are data used from a reasonable study type?	?
4. Are relevant costs and consequences identified?	Yes
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Yes
6. Are the costs and consequences valued credibly?	Yes
7. Is differential timing considered? (discounting)	Yes
8. Was an incremental analysis performed?	Yes
9. Was a sensitivity analysis performed?	Yes
10. Was the model conducted reasonably?	Yes
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Reference and design	Intervention	Participants (if trial based)	Outcomes (if trial based)
Study: Wever *et al*., 1996[45] Country: The Netherlands Setting: inpatient Language: English Study design: randomised study Economic evaluation/type: cost-effectiveness analysis Hypothesis/study question: to demonstrate the cost-effectiveness of ICD implantation as first-choice therapy versus a tiered EGT strategy Dates: study between April 1989 and April 1993	Treatment intervention: ICD Type of intervention: ☐ Primary prevention ☒ Secondary prevention ☒ Treatment Control intervention: EGT drug therapy	Eligibility criteria: postinfarct survivors of out-of-hospital cardiac arrest caused by documented VT or VT Numbers involved: 60 consecutive patients, 29 allocated to early ICD and 31 to drug therapy Disease: Baseline characteristics: mean age ± SD (years): ICD 59 ± 11, drug 57 ± 10 Male gender, *n* (%): ICD 26 (90), drug 28 (90) Index arrhythmia, *n* (%): VF: ICD 24 (83), drug 27 (87) VT: ICD 5 (17), drug 4 (13)	Clinical effectiveness outcome measures: Primary outcomes used: total mortality Secondary outcomes used: outcomes reflecting QOL: major non-fatal events, functional NYHA, exercise tolerance, LVEF, hospitalisation, number of invasive procedures, changes in antiarrhythmic therapy Length of follow-up: median 2 years

Direct costs:
- ☐ Marginal costs
- ☒ Charges
- ☐ Discounting
- ☐ Costs of secondary consequences
- ☐ Patient or society costs

Estimation of the quantities was one or more of the following:
- ☐ a guess
- ☒ based on actual data, i.e. based for example on one unit of analysis or a sampling technique or on published information from other studies (e.g. clinical trial)
- ☐ derived using modelling studies. In the case above the source of quantity/cost data will be recorded
- ☐ don't know

- ☒ Base year (1990 and 1993)
- ☐ Reflated costs
- ☒ Indirect costs included
  - ☒ transferred
  - ☐ productivity loss

Currency: US dollars

Measures of benefits: (free text below)
- ☒ Life-year gained
- ☐ QALY
  - ☐ Time trade-off
  - ☐ Standard gamble
  - ☐ Other (comments below)

Results:

Cost results:

Intervention: total costs for the entire study period $56,067 per patient (1992 scenario)

Control: total costs for the entire study period $63,032 per patient (1992 scenario)

continued

Base-case benefit used:
Based on 4 deaths in the ICD group and 11 deaths in the EGT group

Synthesis of costs and benefits:
The CE ratio based on median values was $63 and $94 per patient per day alive in the early ICD and EGT groups, respectively (1992). The difference would relate to a net CE ratio of $11,300 (saved costs) per patient per life-year saved

Conclusions and critical comments

Authors' conclusions:
Early ICD implantation is superior to serial drug testing and subsequent non-pharmacological EGT as used in postinfarct SCD survivors

Reviewers' commentary:
Median costs were used as input into the calculations, which makes the study of uncertain quality compared with most studies, which use mean values. Billing costs to insurance companies also include some financial overhead, which makes results too high compared with marginal cost calculations

Implications of the study:
Although an insurance-based healthcare system, Dutch costs are more comparable to the UK system than the US. In spite of this, data are collected from the early 1990s, which makes costing of limited importance to the UK

Quality assessment for economic evaluations

	Score (yes/no/unclear)
Internal validity	
1. Is there a well-defined question?	Yes
2. Is there a clear description of alternatives?	Yes
3. Are data used from a reasonable study type?	Unclear
4. Are relevant costs and consequences identified?	No
(a) Healthcare resources (adverse events)	
(b) Patient/family resources	
(c) Social care sector resources	
(d) Patient benefits	
(e) Carer benefits	
5. Are the costs and consequences measured accurately?	Yes
6. Are the costs and consequences valued credibly?	Yes
7. Is differential timing considered? (discounting)	No
8. Was an incremental analysis performed?	No
9. Was a sensitivity analysis performed?	No
10. Was the model conducted reasonably?	N/A
External validity	
11. Are the patients in the study similar to those of interest in England and Wales?	Yes
12. Are the healthcare systems/settings comparable?	No
(a) Comparable alternatives available	
(b) Similar levels of resources	
(c) No untoward supply constraints	
(d) Institutional arrangements comparable	
13. Are resource costs comparable between study and setting/population of interest?	No
14. Are marginal costs used, does this make a difference, and are there real cost savings?	No

Appendix 11

Review of manufacturers' submission

Southampton Health Technology Assessment Centre (SHTAC) review of the industry submission for assessment of ICD for the treatment of arrhythmias

Clinical effectiveness

This submission is a joint submission by the ABHI CRM Special Interest Section (Biotronik, ELA, Guidant, Medtronic and St Jude).

The submission comprises five main sections: background, technology improvements, clinical effectiveness, QoL and cost-effectiveness.

The submission is an update of published literature, technology, practise patterns and implant trends since the NICE guidance in September 2000.

No details of the search strategy are given; however, these may have been previously reported in the submission in 2000. It is not clear how primary studies were assessed for inclusion, and eligibility criteria are not reported. No assessment of study quality has been performed. As such, it appears to be a non-systematic review of the evidence.

One study in patients with idiopathic dilated cardiomyopathy (Grimm and colleagues, 2002[59]) is discussed in the submission that did not meet the inclusion criteria of the SHTAC systematic review. This study was not an RCT and did not involve a comparison of ICDs.

Other studies used in the submission relate to heart transplant studies and heart failure studies. The participants in these studies do not meet the inclusion criteria of the SHTAC systematic review and have not been included. No further review of these studies is given here.

No additional studies were identified within the submission that met the inclusion criteria of the SHTAC review.

Cost-effectiveness

This submission is a joint submission by the ABHI CRM Special Interest Section (Biotronik, ELA, Guidant, Medtronic and St Jude) and an economic evaluation study of ICDs by the University of York, Health Economics Consortium.

ABHI CRM Special Interest Section model

This was a summary of the full economic submission (see below) which looked at ICD versus AAD and used cost per QALY gained. A Markov model was used which was based on clinical effectiveness studies and resource use and cost data for the UK. A 12-year time horizon was used with discounting at 6% and 1.5%.

The incremental costs of an ICD compared with AADs was £22,842 and £24,761 for secondary and primary prevention studies, respectively. Incremental QALYs were 0.82 and 0.622, respectively. The ICERs were £25,887 for secondary prevention studies and £39,385 for primary prevention studies.

The manufacturers state that they use parts of the appendix by the York group. The manufacturers' analysis is considerably more favourable to ICD than the appendix. It is not possible to review the bases to the differences, since the results are given without references for instance to the high QoL scores used in the evaluation.

York Health Economics Consortium

This submission reports an economic evaluation of ICD versus AAD in terms of costs per QALY gained. A Markov model was used which was based on clinical effectiveness studies and resource use and cost data for the UK. Health outcomes were discounted at 1.5% and costs at 6.0%, and a 12-year time horizon was used.

The incremental costs of an ICD compared with AADs was £15,762 and £15,608 for secondary and primary prevention studies, respectively. Incremental QALYs were 0.32 and 0.19, respectively. The ICERs were £47,191 for secondary prevention studies and £82,703 for primary prevention studies.

The manufacturers' submission relied on data from the literature. The effectiveness data in both the manufacturers' and the York group's analyses

were based mainly on the meta-analysis by Connolly and colleagues[31] for their secondary prevention model. The primary prevention models they used were MADIT and COMPANION, the latter of which did not meet the inclusion criteria. It is not clear where QoL utility data were obtained. Also, a number of assumptions have been introduced about the standard costs of treatment, and also to facilitate a probabilistic model, such as a beta distribution for probabilities and gamma distributions for costs.

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We look forward to hearing from you.

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