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Rapid review

Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review

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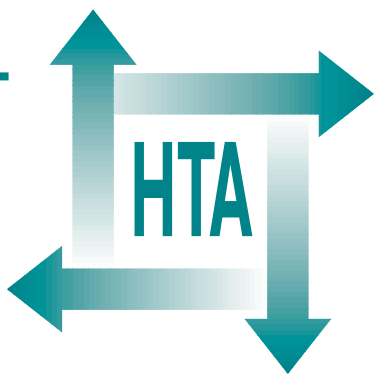
NHS R&D HTA Programme



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Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review

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The research reported in this monograph was commissioned by the HTA programme (project number 00/07/01) on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources. Any views expressed in this rapid review are therefore those of the authors and not necessarily those of the HTA programme, NICE or the Department of Health.

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Contents

Glossary and list of abbreviations

ARR	absolute risk reduction. The subtracted difference between event rates*
Arrhythmia	an abnormality in the rate or rhythm of the heart, caused by a defect in the generation or conduction of electrical impulses
AVID	Antiarrhythmic Versus Implantable Defibrillator
CABG Patch	Coronary artery Bypass Graft Patch Trial
Cardioversion	a carefully timed direct-current shock applied to the heart to treat an arrhythmia
CASH	Cardiac Arrest Study Hamburg
Catheter ablation	application of energy (radio frequency) to site generating arrhythmia, thereby destroying it
CI	confidence interval. The 95% CI is the range of values in which it is 95% certain that the true value lies for the whole population
CIDS	Canadian Implantable Defibrillator Study
CRD	Centre for Reviews and Dissemination
Defibrillator	an apparatus used to terminate fibrillation usually by cardioversion or pacing
EPS	electrophysiological study of the electrical activity of the heart
ESVEM	Electrophysiologic Study Versus Electrocardiographic Monitoring
Fibrillation	rapid chaotic activity of the heart muscle
ICD	implantable cardioverter defibrillator
ITT	intention to treat*
LVEF	left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implications Trial
MI	myocardial infarction*
MUSTT	Multicenter UnSustained Tachycardia Trial
NICE	National Institute for Clinical Excellence
NNT	number needed to treat. The number of patients who need to be treated to achieve one additional favourable outcome*
QALY	quality-adjusted life-year
RCT	randomised controlled trial

*Used only in tables

continued

continued

RR	relative risk. The ratio of the risk in the intervention group relative to the risk in the control. Hazard ratio can be read as a relative risk*
RRR	relative risk reduction. The proportional reduction in rates of bad events between experimental and controls participants in a trial. If there were an increase in the rate of bad events the term would then be the relative risk*
SCD	sudden cardiac death
SWORD	Survival With Oral Sotalol (study)
SVT	supraventricular tachycardia. An abnormally rapid heart rate caused by impulses originating in the atria/upper chambers of the heart
Tachycardia	an abnormally rapid heart rate
Tachyarrhythmia	a rapid and abnormal heart rate
VF	ventricular fibrillation. The rapid and chaotic activity of the lower chambers of the heart
VT	ventricular tachycardia. The abnormally rapid heart rate caused by ventricular activity

Executive summary

Proposed service

The service proposed is the use of implantable cardioverter defibrillators (ICDs) in the management of risk factors leading to sudden cardiac death (SCD). ICDs are similar in size to a pacemaker and are intended to prevent death due to life-threatening ventricular tachyarrhythmias.

Epidemiology and background

SCD 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. Standard treatments for those at high risk have been anti-arrhythmic drugs, catheter ablation or surgery and, increasingly, vasodilating beta-blockers.

Methods

Electronic databases were searched for the period 1980–99. In addition, bibliographies of related papers were assessed for relevant studies, and experts were contacted to identify additional published and unpublished references.

Studies were included if they were systematic reviews, meta-analyses or randomised controlled trials (RCTs) comparing ICDs with conventional therapy in people at high risk of SCD.

Number and quality of studies and direction of evidence

Seven RCTs on effectiveness the majority of which were of good quality, eight cost-effectiveness analyses most of which were older studies and based on non-UK data, and two good-quality literature reviews one of which was a critical appraisal of the literature of effectiveness and cost-effectiveness of ICD therapy, and the other a review of the cost-effectiveness of ICD therapy. These showed changes in absolute risk of total mortality ranging from an increase of 1.7% to a reduction of 22.8% (relative risk reductions of –7% to +54%).

Summary of benefits

Estimated benefits from RCT data are 0.23–0.8 additional years of life with ICD therapy compared with anti-arrhythmic drug therapy.

Costs

Unit cost of ICDs (based on 1999/2000 prices), ranges from £12,500 to £22,000. Total discounted costs for 3 years range from £20,000 to £29,000.

Cost-effectiveness

Cost-effectiveness estimates in the literature identified range from $11,000 to $146,000 per life-year saved. Using UK cost data from three hospitals and trial survival data from one RCT, the estimate of cost-effectiveness from this review ranges between £20,250 and £87,000 per life-year saved.

Cost–utility

Cost per quality-adjusted life-year is estimated by the authors of this review at £21,300 to £108,800 (using survival data from one trial and quality-of-life indices derived from clinical opinion). These figures remain speculative until quality-of-life data from ongoing trials are available to inform future UK cost-effectiveness/utility analyses.

Implications

If implemented for indications supported by evidence from RCTs, ICDs may cost the NHS in excess of £24 million per annum.

Future research

Future research should include the use of British Pacing and Electrophysiological Group registries to assess the use of different types of ICD and current service provision.

Chapter 1

Aims and background

Aim of the review

The aim of the review is to provide a rapid review of the clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators (ICDs) compared with conventional therapy, in patients at risk of sudden cardiac death (SCD) from arrhythmias.

By addressing this aim we hope to provide answers to the following policy-relevant questions:

- Are ICDs effective (or cost-effective) in reducing mortality, preventing tachyarrhythmia and improving quality of life?
- Are ICDs more effective (or cost-effective) as first-line therapy or in patients for whom drugs do not work?
- Can a subset of patients be identified for whom ICDs are more effective (or cost-effective)?

Background

Evidence is accumulating on the use of ICDs in the management of SCD in particular patient groups, including prophylactic use in patients at high risk of SCD.[1] Until recently the standard treatment has been with anti-arrhythmic drugs, catheter ablation or surgery, treatment of ischaemia, electrolyte supplements and increased use of vasodilating beta-blockers. The development of ICDs over the past 20 years has offered a new alternative. Recent editorials in peer-reviewed journals[2,3] have recommended that patients at high risk of sustained ventricular tachycardia (VT) or following successful resuscitation from ventricular fibrillation (VF) should be considered for ICD as first-line treatment. As the cost of each ICD can be as high as £29,000 per device, there is concern about the cost-effectiveness of the ICD, as well as the overall cost to the NHS. There is an increasing demand for the service within cardiology, making its affordability and cost-effectiveness a local, regional and national issue.

Description of underlying health problem

SCD occurs in approximately 70,000 to 100,000 people annually in the UK and represents over half of the deaths attributable to cardiovascular disease[4,5] (*Table 1*). Coronary artery disease is the leading cause of mortality and morbidity in the UK, with 20% of coronary heart disease presenting as ventricular tachyarrhythmia. The number of patients potentially eligible for this treatment may become substantial. However, consideration should be given to the declining age-specific incidence of coronary artery disease in the UK.

SCD has been defined as death occurring unexpectedly within 1 hour of onset of symptoms.[8] SCD is often due to ventricular tachyarrhythmia[7] and 80% occur in patients with ischaemic heart disease. Unlike coronary heart disease, the mortality rates for SCD do not appear to be falling.[1] Outcomes of out-of-hospital resuscitation 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,[9,10] and 40% will die within 2 years.[11] In the UK, fewer than 5% of people survive the initial cardiac arrest (J Morgan: personal communication, January 2000).

Subgroups of patients with the highest relative risk for SCD (e.g. survivors of cardiac arrest, patients with low left ventricular ejection fraction (LVEF)) are a small proportion of the total population burden of SCD, making identification of those patients that could potentially benefit

TABLE 1 *Deaths in England and Wales, 1997*

	Males	Females	Total
Coronary heart disease[6]	78,500	73,500	152,000
SCD[4,5]	39,000–52,000	36,000–48,000	75,000–100,000
Ventricular tachyarrhythmia[7]	29,000–39,000	27,000–36,000	56,000–75,000

most from ICD difficult.[12,13] The risk of SCD in the general population is 2 per 1000 persons per year,[14] making population screening for risk factors a current challenge. Risk stratification using techniques such as ambulatory electrophysiological study (EPS), signal-averaged ECGs and heart rate variability have been used, though the evidence base for these is often not strong.[15,16] Research is ongoing into the effectiveness of these techniques.

Risk factors for SCD are those risk factors associated with coronary heart disease (80% of SCD), for example smoking, hypertension, exercise, raised cholesterol, genetic factors, diabetes mellitus, cardiomyopathies (10–15% of SCD), other structural heart defects (< 5% of SCD) and molecular structure defects (e.g. long QT syndrome). Transient risk factors are drugs, electrolyte inbalance, and ischaemia.[1,16]

Current service provision

Patients with tachyarrhythmias may experience a wide range of outcomes, some may be well controlled and others not. For those patients presenting with tachyarrhythmias with or without symptoms, management may include drug therapy, ICD, catheter ablation therapy, or surgery. The latter two options apply to a very small patient group with specific pathology that is amenable to these treatments. The majority of patients will be treated with drugs. Class I anti-arrhythmic drugs increase SCD,[17] and there are inconsistent results using *d*-sotalol as seen in the Survival With Oral Sotalol (SWORD) and Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trials.[18,19] Beta-blockers may improve survival in patients with chronic heart failure.[20] Of anti-arrhythmic 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.[21] Amiodarone reduced risk similarly in patients after myocardial infarction, with heart failure, or with clinically evident arrhythmia. In a population of patients post-myocardial infarction or chronic cardiac failure, an additional meta-analysis has shown that prophylactic amiodarone has a 13% reduction on total mortality (95% CI, 1% to 22%; $p = 0.3$) and a 29% reduction in arrhythmic deaths (95% CI, 15% to 41%; $p = 0.0003$).[22] However, typically about 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.[22]

Description of new intervention

ICDs are similar in size to a pacemaker (30–40 cm^3 in capacity), weigh less than 80 g, and are placed under the skin in the pectoral region. The latest devices offer graded responses to a sensed ventricular arrhythmia (see appendix 1). 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 5–8 years before replacement is required. Device longevity is gradually being extended with advances in technology. Implantation mortality rates with pre-pectoral subfascial position of ICD under conscious sedation have decreased from 3–5% to no more than 1%.[23] ECG storage provides a retrievable record of the onset and termination of the arrhythmia.

EPS is sometimes used to identify the origins of an arrhythmia and programmed electrical stimulation of the heart may be used in stimulating the heart to induce the arrhythmia. Drugs or electrical equipment can then be used to suppress the abnormal arrhythmia. EPS is sometimes used prior to implantation of ICD in order to confirm need for ICD or diagnostic work-up.

Since the first ICD was implanted in 1980,[24] more than 240,000 ICDs have been implanted worldwide. It has been estimated that in 1996, 262 patients in the UK received an ICD, which is half the average for Western Europe and less than 10% of the rate in the USA.[2]

There have been no agreed UK guidelines for use of ICD therapy. For local districts there has been an agreed number of ICD per head of population that was derived from debate and consensus between cardiologists locally and the health authorities. Most authorities are operating at ten per million population (for a typical health authority of 500,000 this represents approximately five annually). This practice is lower than other European countries and North America (*Table 2*).

Provision of electrophysiologists 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.[25] This may lead to implications for service provision should the rate of implantation of

TABLE 2 *Frequency and number of ICDs implanted*[*]

Region/ country	Estimated no. of ICD inserted	Approximate ratio of ICD per million population
USA	16,900	169
Germany	4890	60
Quebec, Canada	175	48
Denmark	140	27
Sweden	180	23
Australia	525	20
Italy	1010	20
The Netherlands	230	15
Spain	645	15
UK	645	10
France	565	9

[*] *J Morgan: personal communication, 1998 data*

ICD increase in this country, and adds to the debate on the present service provision for arrhythmia management in the UK, and the optimum number of specialist cardiologists who may be required to provide this service.

Chapter 2
Methods

Methods for reviewing effectiveness

The review was undertaken as systematically as time allowed, following the general principles outlined in the NHS Centre for Reviews and Dissemination (CRD) Report 4.[26] Sources of information, including databases searched and key search terms, can be found in appendix 2.

Inclusion criteria

Studies were included if they were systematic reviews, meta-analyses or RCTs comparing ICDs with conventional therapy (such as anti-arrhythmic drugs, catheter ablation or surgery), in people at high risk of SCD usually due to ventricular tachyarrhythmia. These studies also included published evaluations of cost-effectiveness.

Three main patient outcomes measures were reduction in mortality, prevention of tachyarrhythmias and improvement in quality of life.

Studies identified by the search strategy were assessed for inclusion through three stages (*Figure 1*). Over 4000 titles and abstracts were screened for inclusion by one reviewer, and then the full text of the 74 studies chosen for inclusion were examined for inclusion by the same reviewer.

Data extraction strategy

Data extraction was undertaken by one reviewer and checked by a second reviewer, with any disagreements being resolved through discussion.

Quality assessment strategy

Included studies were assessed using the critical appraisal criteria and standard checklists such as those developed by the Critical Appraisal Skills Programme and CRD. Primary studies were scored using the Jadad[27] scale and secondary studies were scored using the CRD Review Score scale (see appendix 3).

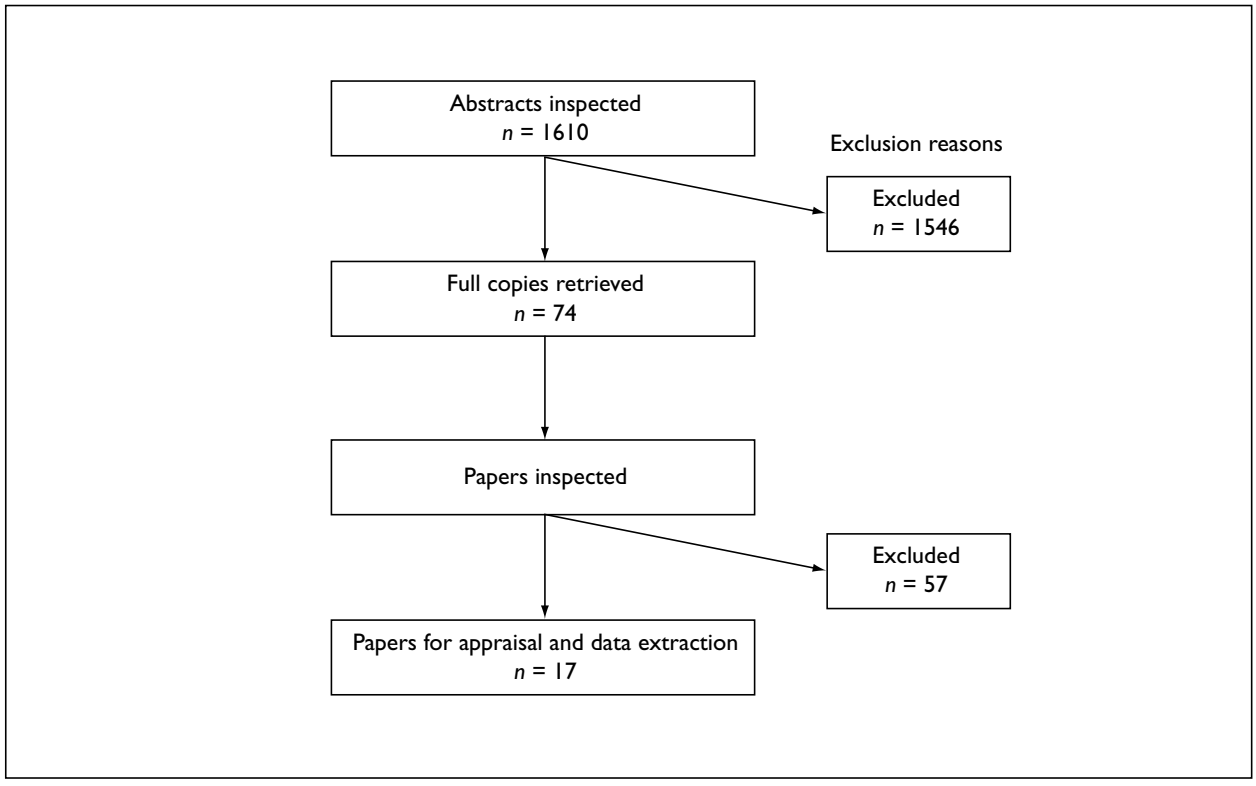

FIGURE 1 *Flowchart of identification and inclusion of studies for ICD review*

Quality assessment was undertaken by one reviewer and checked by a second reviewer, with any disagreements being resolved through discussion.

Data analysis/synthesis

Data are presented as a narrative review with full tabulation of results of all included studies. Formal meta-analysis was not undertaken due to lack of time.

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

Cost-effectiveness studies identified by the search strategy were data-extracted and quality-assessed by one reviewer and checked by a second reviewer. Any differences in opinion were resolved through discussion. Studies were critically appraised using standard criteria for decision analysis and economic evaluations.[28]

Quality-of-life information to estimate quality-adjusted life-years (QALYs) was obtained from the literature and through consultation with experts. Costs were sought from Southampton General Hospital (a regional centre) and at least two other centres in England. Cost per QALY was estimated by combining effectiveness information from the trials and QALYs. Sensitivity analysis was performed to determine how robust estimates are to the assumptions made.

Chapter 3

Effectiveness

Quantity and quality of research available on effectiveness

One systematic review (*Table 3*; appendix 4) and seven RCTs (*Table 3*; appendix 5) met the inclusion criteria for the review.

In the systematic review of the outcomes from the use of ICDs,[16] 34 studies are cited, three of which were RCTs, 12 were observational studies and 19 were descriptive studies. The review is of good quality and is thorough and rigorous (the NHS CRD Quality Score was 4). It contains a methods section identifying the findings of relevant trials and assessment of validity. Explicit methods were used to determine which articles were selected, and assessment of primary studies is reproducible and free from bias. The review has not been widely peer-reviewed. Unpublished research was not searched for.

There are seven RCTs that have studied the effectiveness of ICD on total mortality. Six of these trials are published in peer-reviewed journals, and one is presently in the public domain as published preliminary results and conference proceedings.[29,30]

Internationally recognised convention in this field is to divide the trials into primary prevention trials (to prevent SCD from first incident of VT/VF) and secondary prevention trials (to prevent recurrence of VT/VF). The studies in *Table 4* are separated in this way.

Assessment of effectiveness

From the retrieved literature the effectiveness of ICD needs to be assessed against three main outcomes:

- Do ICDs reduce total mortality?
- Do ICDs stop tachyarrhythmias?
- Do ICDs improve quality of additional life?

Evidence from secondary research

Hider's 1997 systematic review (CRD Quality Score 4/6)[16] assessed 4000 abstracts and retrieved, assessed and summarised 500 relevant articles. The review concluded the following.

- ICDs have consistently shown to be effective at terminating ventricular arrhythmias and reducing the incidence of SCD to less than 1% annually in recipients.
- Effects of ICD therapy on overall survival were found to be uncertain due to lack of evidence from RCTs published at the time of writing the review.
- Only a few trials have examined the effects of ICD on recipient quality of life. Generally the studies have shown that quality of life can be preserved among recipients but that there is often some initial impairment just after insertion.
- Alternative therapies to ICD have a limited ability to improve survival. Amiodarone has been shown to be effective but up to 24% need to withdraw from treatment due to side-effects. Only a small number of patients are suitable for surgery or catheter ablation.

TABLE 3 *Summary of review of the effectiveness of ICDs to reduce SCD*

Study	Results	Disbenefits
Hider, 1997[16] Intervention: ICD vs other therapies Subjects: Coronary heart disease	ICD consistently shown to be effective at terminating VT and therefore reducing the incidence of SCD in recipients. Uncertainty exists about whether overall survival is enhanced. Most appropriate for cardiac arrest survivors and patients at high risk of malignant tachyarrhythmias with underlying ischaemic heart disease and/or LVEF	Mortality < 1%, lead displacement 1–10%, infection < 4%, wound problems 0–16%, thrombosis 1–16%, perforation < 1%

TABLE 4 *Summary of RCTs of the effectiveness of ICD versus medication to reduce SCD*

Study	Results	Disbenefits
Primary prevention of VT/VF		
Moss *et al.*, 1996[31] MADIT **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial Intervention: Prophylactic ICD vs conventional tiered therapy (anti-arrhythmic drugs) 27 months' follow-up 47% transthoracic, 53% transvenous Patients: MI ≥ 3 weeks before entry, with documented asymptomatic unsustained VT unrelated to MI; LVEF ≤ 0.35, with inducible VT not suppressed by procainamide; NYHA Functional Class I, II or III; and no indications for CABG/angioplasty within 3 months Excluded patients with past history of malignant VT *n* = 196	Absolute mortality: ICD: 15.8% Conventional therapy: 38.6% ARR: 22.8%. RR ICD arm: 0.46 (95% CI, 0.26 to 0.82; $p = 0.009$) RRR: 54% NNT: 5 (3–10)	ICD: 19/95 patients with adverse events: two pneumothorax, two infection, seven lead problems, seven rhythm problems Conventional therapy: 12/101 patients with adverse events: five unexplained syncope, seven VT/VF; amiodarone discontinued in 46% patients
Buxton *et al.*, 1993,[32] 1999[33] MUSTT **M**ulticenter **U**n**S**ustained **T**achycardia **T**rial Intervention: Conservative (ACE-inhibitor and/or beta-blocker when tolerated with no other anti-arrhythmic therapy) or EP-guided treatment (tiered anti-arrhythmic drug therapy until non-inducible/haemodynamic stable tachyarrhythmia on EPS; with ICD implanted if drug test on EPS unsuccessful) Transvenous Median follow-up 39 months Patients: Coronary heart disease, non-sustained VT; LVEF < 40% and EP-diagnosed inducible sustained VT *n* = 704	Absolute all-cause mortality: Conservative: 48% EP-guided: 42% ARR: 6% RRR: 13% NNT: 17 Total mortality in EP-guided arm (non-randomised comparison): ICD: 24% Drug therapy: 55% ARR: 31% RRR: 56% NNT: 3	Complications occurred in five patients with inducible sustained VT (0.7%) non-fatal; one patient died after infection complicating revision of lead system 18 months after initial ICD implantation

ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; CABG, coronary artery bypass graft; ARR, absolute risk reduction; RR, relative risk; RRR, relative risk reduction; NNT, number needed to treat; EP, electrophysiological

continued

TABLE 4 contd *Summary of RCTs of the effectiveness of ICD versus medication to reduce SCD*

Study	Results	Disbenefits
Bigger, 1997[34] CABG Patch **C**oronary **A**rtery **B**ypass **G**raft Patch Trial Intervention: ICD vs control (no ICD) Transvenous Average follow-up 32 months ± 16 (SD) Patients: Patients having CABG with LVEF < 0.36 and abnormalities of signal-averaged ECG *n* = 900	Absolute mortality (at 32 months): ICD: 22.6% Control: 20.9% ARR in control group: 1.7% RR in ICD arm: 1.07 (p = 0.64) NNH: 58 (14–∞)	Significantly different complications in ICD: 12.3% infection, 8.5% pneumonia, deep sternal wound infection 2.7% Control: 4.2% MI
Secondary prevention of VT/VF		
AVID Investigators, 1997[35] AVID **A**ntiarrhythmic **V**ersus **I**mplantable **D**efibrillator Intervention: Drug (amiodarone or sotalol) (*n* = 509) vs ICD (*n* = 507) Transvenous 45 months, mean follow-up 27 months Patients: Cardiac arrest survivors and/or symptomatic tachyarrhythmia with LVEF ≤ 40% *n* = 1016	Absolute mortality: ICD: 10.7% (1 year), 18.4% (2 year), 24.6% (3 year) Drug: 17.7% (1 year), 25.3% (2 year), 35.9% (3 year) ARR: 7% (1 year) 6.9% (2 year), 11.3% (3 year) Relative reduction in total mortality (adjusted) in ICD arm ± 95% CI: 37 ± 22% (1 year), 24 ± 22% (2 year), 29 ± 23% (3 year) NNT: 9 (95% CI, 6 to 18)	Drug: 5% pulmonary toxic (one death), 16% required thyroid replacement medication at 2 years ICD: 1% bleeding, 2.6% requiring re-operation/ transfusion, 2% infection, 1.6% pneumothorax, one cardiac perforation
Siebels, 1993[30] CASH **C**ardiac **A**rrest **S**tudy **H**amburg ('preliminary results' only published) Intervention: ICD vs anti-arrhythmic drug (amiodarone/metoprolol/propafenone) Transthoracic pre-1990 Transvenous post-1990 11 months (propafenone arm deleted) and 24 months' follow-up Patients: Survivors of cardiac arrest *n* = 230	Total mortality: ICD: 11.5% Propafenone: 29.3% Trial stopped Absolute total mortality (at 2 years): ICD: 19.6% Amiodarone/metoprolol: 12.1% ARR: 7.5% (p = 0.047) RRR: 37% NNT: 14 (6–∞)	Propafenone: 12/56 side-effects, drug stopped; 2/59 ICD explantation (infection)

CABG, coronary artery bypass graft; ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat; NNH, number needed to harm

continued

TABLE 4 contd *Summary of RCTs of the effectiveness of ICD versus medication to reduce SCD*

Study	Results	Disbenefits
Connolly *et al.*, 1993,[36] 2000[37] CIDS **C**anadian **I**mplantable **D**efibrillator **S**tudy Intervention: ICD vs amiodarone First 33 transthoracic remaining 277 transvenous 36–60 months' follow-up Patients: Survivors of cardiac arrest, tachyarrhythmias with symptoms, with LVEF < 35% *n* = 600	At 5 years Absolute mortality: ICD: 23% Amiodarone: 27% ARR: 3.7% RRR: 19.7% with ICD (p = 0.142) NNT: 24 (10–∞)	At 3 years Amiodarone: 22% stopped, 19.6% pulmonary toxic, 5.1% hepatic, 8.8% thyroid, CNS 26% ICD: 5.1% infection, 2.6% lead fracture, 11.9% pulmonary toxic, 0.9% hepatic, 1.8% thyroid, 8.5% CNS
Wever *et al.*, 1995[38] Intervention: ICD vs conventional (tiered drug therapy/late ICD) Transthoracic apart from three transvenous 27 months' follow-up Patients: Survivors of cardiac arrest *n* = 60	Absolute mortality (at 2 years): Early ICD: 14% Conventional group: 35% ARR: 21% RR of death in ICD arm: 0.27 (95% CI, 0.09 to 0.85; p = 0.02) NNT: 5 (3–∞)	ICD: migration of lead in one patient, infection in one patient; 4.4% perioperative mortality rate Conventional: 16/31 received late ICD (15 pre-discharge; 52%)

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat

- A small number of studies examine cost-effectiveness, and they generally concluded that ICD treatment is associated with increased cost to the funding organisation, and that ICD therapy can be considered to be a cost-effective intervention for treating arrhythmias compared with alternatives.

The review concluded that there was general recognition that ICD is most appropriate for patients in one of two high-risk groups for SCD: cardiac arrest survivors (number needed to treat, 4.8), and patients at high risk of malignant tachyarrhythmias on the basis of spontaneous or inducible arrhythmia, without an arrest, who are not eligible or have failed other medical or surgical treatments and who usually have underlying ischaemic heart disease and/or a low LVEF.

Hider's review was completed before the results of several of the included RCTs were available, and so the conclusions drawn were based on evidence, that did not take account of these data.

Evidence from primary studies

Six studies found a favourable survival advantage for patients treated with ICD.[30,31,33,35,37,38] There are several generic methodological issues that have been raised in the context of the included trials that will be addressed here. Comparison of a drug (subject to compliance issues) and a device (whose interaction with the patient is involuntary and requires removal which is more difficult and more easily measurable than compliance measurement) may lead to an over- or underestimate of effect of therapy. Recent trials have found that between 20% and 53% of patients with ICDs require anti-arrhythmic medication to suppress supra-ventricular tachycardia (SVT), to treat underlying ischaemic heart disease, and to reduce the false-positive firing of the ICD. However, these drugs may interfere with the functioning of the device, and may influence the estimate of effectiveness of

ICD therapy. The differential use of beta-blockers in the ICD groups in the trials has been implicated in an overestimate of effectiveness of the ICD, as beta-blockers may have an effect on mortality in this patient group. Subanalyses from some trials and multivariate analysis from unpublished pooled data of three trials have shown that beta-blockers did not convey a survival advantage to the patients in the trials.

Primary prevention studies

MADIT[31] (Jadad Quality Score 3/5)
This was the first trial to assess the prophylactic use of ICD in patients at risk for SCD. Its limitations were that selection bias may have occurred (see appendix 5 for details). The inclusion criteria were very limiting. The number of potentially preventable deaths if all eligible people determined by this trial were given ICD would be small, 1–2% of post-myocardial infarction population and fewer than 10% of all cardiac-related deaths.

MUSTT[32,33] (Jadad Quality Score 1/5)
Conclusions drawn are that the population of patients in the trial (LVEF ≤ 40%, asymptomatic unsustained VT, inducible sustained VT) have substantial mortality due to arrhythmias, and that the use of ICD therapy in patients with inducible sustained VT reduced mortality rate. Thus, EP testing should be considered for this subset of patients, and ICD therapy considered if sustained VT is inducible in clinical settings similar to those in the trial. The comparison between outcomes of those patients receiving ICD therapy compared with anti-arrhythmic therapy is not randomised, thus introducing the potential for bias and confounding of results. Therefore, the size of the benefit of ICD therapy that is shown should be interpreted with caution. Two further *post hoc* analyses of MUSTT were carried out, and demonstrated consistent benefit for ICD therapy.[39,40] Most patients discharged receiving anti-arrhythmic drugs were treated with class I agents. Greater use of class III agents may have improved outcomes among patients treated with anti-arrhythmic drug therapy thereby over-estimating the effect size of ICD therapy. The financial implications of the number of patients (estimated at 20,000–40,000 in the USA) who could fit the inclusion criteria and would appear to potentially benefit from ICD, are significant.

CABG Patch study[34] (Jadad Quality Score 3/5)
There was no significant difference in overall survival between patients receiving ICD therapy and usual therapy. Patients were included in the trial if they had an LVEF of less than 36%, had abnormalities on signal-averaged ECG and were scheduled for CABG. Patients were allocated at time of CABG to ICD or to control. The group recruited to this trial was lower risk compared with AVID and MADIT. CABG may reduce the risk of SCD, which may influence the results.

Secondary prevention studies

AVID study[35] (Jadad Quality Score 2/5)
This large trial compared ICD with class III drugs, amiodarone or sotalol. The potential of selection bias has been examined via a study on the registry of recruited patients who met the study entry criteria.[41] This substudy found that there was no difference in clinical characteristics, cardiac history and presenting arrhythmias in those patients eligible for inclusion in the trial and those who were actually randomised. There was a high cross-over rate in the trial (33.7% ICD group receiving amiodarone and 24.3% amiodarone group receiving ICD at 3 years), which may have reduced the power of the study, and compromised the intention-to-treat analysis. There was a statistically significant difference between the two groups in the number of patients receiving beta-blockers after 2 years of follow-up. The percentage in the ICD therapy group was 40% compared with 10% in the amiodarone group. In addition, the severity of cardiac failure differed in the two comparison groups – those in the amiodarone group having worse disease. Concern has been raised that some of the survival benefit from ICD therapy may have been due to beta-blocker therapy or poorer outcomes in drug arm due to their more severe cardiac failure. However, subgroup analysis of AVID data have demonstrated that beta-blocker use conveyed no survival benefit to patients receiving either amiodarone or ICD therapy.[42]

There are eight substudies based on AVID data at the time of writing, (seven published and one unpublished). The results of these that are not mentioned elsewhere in the text are summarised in appendix 6.

Initial cost data have been communicated via personal communication and will be presented in the economic evaluation section (chapter 4, *Economic analysis*).

CASH[29,30]
This trial has only recently finished and the final results had not been published at the time of writing, though they were presented at the 1999 meeting of the North American Society of Pacing and Electrophysiology. The 5-year results showed

a continuing trend toward benefit from ICD compared with drug therapy. Comparison between metoprolol and amiodarone showed no difference in mortality, though this arm was underpowered. Recruitment occurred over 9 years, and influences of secular trends may have resulted in changes in clinical outcomes. Improved performance of the fourth-generation devices and reduction of perioperative risks may have led to an underestimate of true effect.

CIDS[36,37] (Jadad Quality Score 3/5)
At 3 years 21% of ICD patients were also receiving amiodarone and 18% of amiodarone patients had received an ICD. This rate of cross-over plus the rate of beta-blocker treatment (30% of ICD patients receiving beta-blockers at 5 years compared with 22% of patients receiving amiodarone), expose this trial to similar potential biases as AVID. Unlike the AVID authors however, CIDS authors report that an adjustment analysis for this imbalance is not valid and the degree to which beta-blockade accounts for some of the benefits of ICD therapy is uncertain, as the distribution of the co-interventions is not random. 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 compared with the AVID study. AVID and CIDS trials have similar design and patient inclusion and exclusion criteria, and the overlapping CIs on effect size may indicate that these differences in RRRs between the trials are due to chance. Authors state that the true benefit probably lies between the two values (relative risk reduction 20% and 29%). Quality-of-life data and cost data have not yet been published.

***Wever* et al.**[38] (Jadad Quality Score 2/5)
In this small study, the randomisation method is not reported, reducing the overall quality of the trial. The use of class I anti-arrhythmics among the medication arm may have increased the mortality risk of patients. The small number of patients who received beta-blockers in the medication arm may also have confounded the findings leading to an overestimate of the survival advantage for ICD recipients.

Results from three of the trials (AVID, CASH and CIDS) have been combined in a meta-analysis but this remains unpublished. It exists in the public domain only as a conference proceeding.[43] It showed a strongly significant benefit of ICDs, with a relative risk reduction of 27% for total mortality. This was mainly due to a more than 50% reduction in arrhythmic deaths. There was virtually no difference in non-arrhythmic deaths between the two groups. This may mean that the CIDS and CASH trials were underpowered to detect any significant difference in overall mortality. The meta-analysis shows that patients with an LVEF of less than 35% had a marked benefit from ICD and patients with an LVEF of at least 35% had virtually no benefit from ICDs. This difference was statistically significant, suggesting that LVEF may be an important determinant of ICD effect. The analysis found that the benefit of ICDs was independent of beta-blockade use. Further combination of results was not possible due to the heterogeneity of patient characteristics. No *p*-values or CIs were reported in the conference proceedings.

Assessment of adverse effects

The three main disbenefits of ICD relate to peri-insertion complications, device failure and effects on quality of life. The evidence summarised below comes mostly from the review by Hider.[16]

Peri-insertion complications

- **Mortality** This is now reported to be less than 1% with transvenous compared with transthoracic insertion of devices.
- **Inability to insert** The smaller device size, and transvenous approach have reduced the number of patients in whom insertion of ICD is not possible. Most series report over 90% of patients have been able to receive an ICD. With new, smaller devices this figure reaches 98%.
- **Lead dislodgement** This is related to the experience of the operator implanting the ICD, and is the most common of the perioperative complications. Hider cites 20 studies that assessed this outcome with a range of 1% to 10%.
- **Infection** This is reported as less than 4% with the transvenous approach, and is usually apparent within 60 days of implantation. Hider cites 12 studies with a range of 0.8% to 4%.
- **Haematomas and bleeding** Hider notes a wide range of wound-related problems after insertion (0.5–16% in nine studies assessed in his review). This may be due to differences in definitions between studies. The use of concurrent anti-coagulation, the muscular pocket used to implant the device and use of subcutaneous leads seems to have an association with this disbenefit.
- **Thromboembolic events** Hider assessed 13 studies that reported this complication, and found a discrepancy in those studies that reported clinically significant outcomes (0.6%), and those reporting thrombotic vegetations

on leads (15.7%). The consensus from the literature is that while vegetations are relatively common they embolise infrequently.
- **Perforation of heart and lungs** This was reported as very uncommon with less than 1% in most of the 11 studies reporting this outcome.

Device failure

- **Proarrhythmia** The production of an iatrogenic arrhythmia is a recognised complication of ICD. The evidence is from small numbers of patients (8–40), and has led to considerable variation in reported frequency (0–43%).[16] Many of these iatrogenic arrhythmias are terminated by the ICD. This can have deleterious effects on patients, who experience a series of uncomfortable additional shocks after the ICD has induced arrhythmia. There are at least three reported fatalities in the literature.
- **Failure to detect an arrhythmia/inappropriate intervention** ICD cannot easily differentiate between VTs and SVTs and may be activated inappropriately by the latter. Hider found that literature suggests that 10% to 30% of recipients per year receive inappropriate shocks. These in turn may cause an arrhythmia, cause the patient discomfort and psychological harm, and reduce the battery life. This complication is reduced by the use of dual-chamber sensing devices in the most recent ICD but this increases the initial cost of the device.
- **Lead fracture** There were 17 studies that assessed this outcome in the review by Hider. This reduces the effectiveness of the ICD and ranges from 0.4% to 5%.

Adverse effects of amiodarone

Hypothyroidism is the most common adverse experience (odds ratio, 7.3). Hyperthyroidism is statistically more common in patients receiving amiodarone than those receiving placebo in controlled trials (odds ratio, 2.5). Thyroid dysfunction along with peripheral neuropathy (odds ratio, 2.8), bradycardia (odds ratio, 2.6), liver dysfunction (odds ratio, 2.7) and lung infiltrative disease (odds ratio, 3.1) are major adverse experiences associated with early permanent drug discontinuation in placebo controlled trials.[22]

Effects on quality of life

There are a number of quality-of-life studies in patients receiving ICD therapy, including one literature review, and three from randomised evidence, which are considered in more detail below.

Quality-of-life data from three of the effectiveness RCTs are in the public domain, one published [44] and two unpublished (AVID, MADIT). The CABG Patch Trial showed that patients in the ICD group at 6 months had lower levels of psychological well-being, reported feeling less healthy and had reduced physical and emotional role functioning compared with controls. For patients with ICD, shocks are a likely explanation for lower mental health scores. A published preliminary analysis from AVID data has revealed difficulties in data collected before and after randomisation.[45] The abstract of AVID trial data on quality of life shows that sporadic defibrillator shocks are associated with a significant independent reduction in self-perceived mental well-being and an increase in patient concerns.[46]

Recent preliminary unpublished data on quality of life from the MADIT trial showed no difference in quality of life between ICD and controls, and quality-of-life scores negatively correlated with number of shocks received. Overall, the quality of life with ICD showed mild-to-moderate disability. Mushlin suggests that added life-years in the study would likely be of reasonable quality with ICD.[47]

There are a number of problems with these studies, including:

- small sample sizes
- selection bias
- non-standardised assessment measures
- lack of baseline assessment
- lack of long-term follow-up data, and
- confounding by the patient's reactions to suffering major illness and near-death experiences.

The issue of quality of life is crucial to the overall assessment of cost–utility of ICDs, and the results of large rigorous studies underway at Stanford (CARDPORT) and CIDS results may help to clarify issues (see appendix 7 for details of relevant ongoing studies).

A literature review, which includes qualitative studies, examined the psychosocial impact of ICD and found five studies with pre- and post-assessment of psychosocial adjustment in recipients of ICD and 18 studies of post-implantation assessment.[48] This review concluded that ICD specific fears (fear of shock, fear of death, fear of embarrassment) are commonly experienced by recipients, along with lifestyle changes (e.g. driving restrictions, concerns about sexual activity and social interactions). Symptoms of anxiety

are widely reported by ICD recipients, with 13–38% of recipients reporting diagnosable levels of anxiety. Depressive symptoms are reported at the same rate as other cardiac populations.

Patients reported feeling fearful and anxious before receiving the ICD and that the anxiety and depression persisted after implantation but generally diminished over time. In one study, one-third had clinical anxiety and depression, which persisted, with 40–63% of this group continuing to have difficulties after 1 year.[49] Anxiety about the ICD firing was closely linked to occurrence of depression, as was avoidance of activities.[49] Psychosocial adjustment risk profiles indicate that younger ICD recipients (< 50 years) and those with high discharge rates may experience the most adjustment difficulties.[50]

In four of the included studies a reported 75–93% of patients with ICDs had a positive attitude to the ICD regarding it as a 'life extender' and very important to their life.

In one study 62% of patients resumed employment, and these were more likely to be educated and less likely to have had a history of myocardial infarct. Comparison of groups of patients with ICDs and a similar group with coronary artery disease found that the quality of life did not differ between the groups, but patients with ICDs were less anxious. However, with increasing number of shocks the percentage of psychologically distressed patients rose from 10% to over 50%, with patients having lower quality-of-life scores.[51]

Chapter 4

Economic analysis

Quantity and quality of research available on cost-effectiveness

Eight cost-effectiveness studies were identified and one literature review. Details are shown in *Tables 5* and *6* and appendix 8.

Evidence from primary studies

- The studies are similar in methodology in that they have all used standard hospital costs, obtained by different methods. Most take the viewpoint of the funder, though Owens[57] takes a view from society, but does not include indirect costs. In all studies the majority of the intervention cost is due to the high price of the device.
- In all but two of the studies (Wever *et al*.[56] and Mushlin[58]), data were collected retrospectively and so the two populations used may not be comparable.
- In the MADIT cost-effectiveness analysis[58] costs were collected from randomisation and did not include the screening process, which is an important element in a primary prevention trial. This may have led to a more favourable cost-effectiveness ratio than is justified.
- In the majority of models it has been assumed that the first appropriate discharge of the device is life saving. This cannot be presumed as some tachyarrhythmias are self-limiting, or arrhythmias other than VT/VF can trigger the ICD.
- Sensitivity analyses were carried out in all of the studies.
- The mode of implantation of the ICD is important in that transthoracic implantation is less favourable in cost-effectiveness studies as it is associated with older models of ICD, which have a shorter battery life, higher insertion costs and higher incidence of complications.
- Owens and co-workers[57] and O'Brien and co-workers[54] have attempted a cost–utility analysis, deriving a cost for ICD per QALY.
- The generalisability of these studies is limited. This is because most used US cost data and US system charges, both of which will be different from the UK. The UK study is useful but out of date. However, all studies consider that the marginal cost-effectiveness ratio for ICD to be favourable for the cardiac arrest survivors and patients with VT/VF, and in one study for high-risk post-myocardial infarction patients. Authors have arrived at different conclusions about which population has a lower cost-effectiveness ratio. Kupersmith and Holmes-Rovner[55] found it more cost-effective to implant ICDs in patients with a better LVEF because more people would die in the poorer LVEF group regardless of the intervention. Owens and co-workers[57] concluded that when the occurrence of sudden death was lower, costs were higher and thus the ratio remained relatively the same despite the mortality risk of the population.
- In a sensitivity analysis, Owens found that early implantation is more cost-effective than delayed implantation. Reductions in total mortality from insertion of the ICD gave an exponentially increasing marginal cost-effectiveness ratio[57] (*Table 6*). Using a discount rate of 5% reduced the cost-effectiveness of ICD from $74,400 to $85,900 per QALY. Treatment for patients who received ICD therapy subsequent to amiodarone was found to be expensive, and resulted in a small incremental benefit (0.01) relative to amiodarone alone, while still having a relatively high mortality rate.
- An analysis of costs before and after implantation showed rates of hospitalisation were reduced, and calculated that the payback for ICD insertion was 19 months.[60]
- A cost-analysis model using UK cost and observational study data published in 1993,[61] estimated the cost per life-year saved in different populations. Results varied from £22,400 in highest-risk group (LVEF < 30%, inducible non-suppressible VT/VF) to £57,000 in all survivors of cardiac arrest. The latter could potentially have greatest impact as the highest-risk group accounts for approximately only 27% of recurrent cardiac arrest. A widening of high-risk group criteria patients with inducible non-suppressed VT with high/low LVEF and non-inducible low LVEF increases the potential for prevention of SCD to 56% at a cost of £23,600 per life-year saved. Authors conclude that ICD is expensive and adoption of strategies suggested by trials available at this time, could cost £2 million to £100 million

TABLE 5 *Summary of cost-effectiveness studies of ICD*

Study	Method of evaluation	Marginal effectiveness of ICD (years of life saved)	Marginal cost-effectiveness per year of life saved
Kuppermann *et al.*, 1990[52] USA Intervention: ICD vs anti-arrhythmics Transthoracic implantation Patients: Cardiac arrest survivors, inducible VT/VF	Markov model	+1.9 years	$17,100
Larsen *et al.*, 1992[53] USA Intervention: ICDs vs amiodarone vs conventional anti-arrhythmics Transthoracic Patients: High-risk patients from past history of recurring arrhythmia	Modelling	+2.2 years	$39,400
O'Brien *et al.*, 1992[54] UK Intervention: ICD vs amiodarone Transthoracic Patients: Cardiac arrest survivors	Markov model	+1.7 years	£15,400
Kupersmith & Holmes-Rovner, 1995[55] USA Intervention: ICD vs anti-arrhythmics Transthoracic Patients: Cardiac arrest survivors, patients with VT/VF	Markov model	+1.72 years	$25,700
Wever *et al.*, 1996[56] The Netherlands Intervention: ICD vs anti-arrhythmics Transthoracic Patients: Cardiac arrest survivors	Markov model		$11,315

continued

TABLE 5 contd *Summary of cost-effectiveness studies of ICD*

Study	Method of evaluation	Marginal effectiveness of ICD (years of life saved)	Marginal cost-effectiveness per year of life saved
Owens *et al.*, 1997[57] USA Intervention: ICD vs amiodarone vs amiodarone to ICD Transvenous Patients: Cardiac arrest survivors	Markov model	+0.5 years	$30,500–47,700 per life-year saved and $37,300 (if total mortality rate reduced by 40%) to $74,400 (if reduced by 20%) per QALY
Mushlin, 1998[58] Germany and USA Intervention: ICD vs anti-arrhythmics Transvenous and transthoracic Patients: Post-MI, non-symptomatic VT, LVEF < 35% and inducible VT not suppressed by procainamide	Clinical trial (MADIT) with costs	+0.8 years	$23,000
O'Brien *et al.*, 2000[59] Canada unpublished data from conference abstract Intervention: ICD vs amiodarone Patients: Survivors of cardiac arrest, tachyarrythmias with symptoms, with LVEF < 35%	Clinical trial (CIDS)	0.23 years	Can$213,543 (US$146,180, UK £93,000) sensitive to longer follow-up with suggested improved cost-effectiveness of ICD

TABLE 6 *Marginal cost-effectiveness of ICD – sensitivity analysis[57] (ICD only regimen compared with amiodarone only regimen)*

	RRR[a] 40%	RRR[a] 20%
High-risk patients: Expenditures per life-year saved	$27,300	$54,000
Intermediate-risk patients: Expenditures per life-year saved	$26,700	$56,000

Discounting at 3%, costs represent life-time costs are expressed in 1995 US$

[a]*RRR is the reduction in total mortality from ICD relative to amiodarone therapy*

per annum. Future technological developments may lead to improvement of cost-effectiveness. Screening tests are limited and restriction of ICD therapy to those groups at highest risk, will only make a small impact on overall mortality from SCD.

- Many studies have predicted a cost-effectiveness ratio on the premise that device price would be reduced in the future. This has not occurred yet, perhaps due to continued tech-

TABLE 7 *Summary of secondary cost-effectiveness analysis (Stanton & Bell)[62]*

Economic analysis	Break-even (year)	ICD follow-up/ life expectancy (years)	Savings $[a]	Incremental cost per life-year saved $ base case
Wever	1.0	2.4 follow-up	33,733	
Mushlin[b]	2.9	3.7 follow-up	8928	28,751
Kuppermann[b]	2.9	5.1 life expectancy	54,426	32,910
Kuppersmith[b]	1.0	3.8 life expectancy	27,991	36,257
Larsen	Does not break even	6.1 life expectancy	Nil	45,922
Owens	Does not break even	5.6 life expectancy	Nil	57,502
AVID	Insufficient data	Insufficient data	Insufficient data	Insufficient data

All conducted with costs restated in 1997 dollars based on medical cost component of Consumer Price Index

[a]If the average patient on anti-arrhythmic drugs survived as long as the average patient implanted with ICD

[b]Updated scenarios ≥ 4 years battery life, non-thoracotomy insertion or insertion without pre-implant EP study

nical development. It is currently anticipated that price will fall in the next few years, with increased longevity of the device influencing cost-effectiveness. A basic ICD device with a limited number of shocks and no additional features (so-called lifeboat/safety net ICD) is being developed, which should further reduce unit cost.

- Little work has yet been done on quality of life post-implantation, which will allow cost–utility analysis to be performed. Data from CIDS and AVID have been collected. This is clearly an important aspect of cost-effectiveness studies that awaits elaboration. Initial unpublished results of the AVID cost data have been communicated by the authors and state that based on the preliminary presentations, a small benefit favouring ICD was found for a couple of quality-of-life constructs and the cost per year of life saved (from 3 years' follow-up) was estimated at approximately $125,000 per annum (AP Hallstrom: personal communication, August 1999). These preliminary results are not expected to change much with more complete data and more careful analyses, but the final word will have to await completion and publication of the analysis. The costs may be an overestimate as the trial was terminated early at 3 years.

Evidence from secondary research

Stanton & Bell[62]

A literature review of cost-effectiveness of ICD therapy in the management of ventricular fibrillation and tachycardia has been published[62] (CRD Quality Score 4/6). Secondary synthesis of data has been performed (*Table 7*). Novel elements presented in the Stanton review are discussed. An estimate of the break-even time (expected number of months or years before initial cost disadvantage of a therapy has been offset by its continuing costs) has been calculated from the cost data from the included studies comparing ICD and anti-arrhythmic therapies. Also, costs presented in the included economic analyses were updated to 1997 dollars with the use of the medical cost component of the Consumer Price Index, and discounting continuing therapy costs and life expectancy at a rate of 5%. The validity of this methodology is not discussed.

Stanton concludes that advances in ICD technology over the past 3–5 years (such as transvenous insertion, pectoral implant, extended battery life, endocardial ICD systems), as well as clinical practice shifts (such as elimination of pre-implant EP, pre-discharge device tests and use of conscious sedation rather than general anaesthesia), have allowed ICD therapy to become more cost-effective.

Estimation of net benefits

To estimate the benefit in terms of life-years gained we have used the results from the AVID trial because it is the largest study, powered to detect a difference in overall survival, and appears to be the most generalisable. This showed that overall survival with ICD was 89.3% compared with 82.3% with drug therapy at 1 year; 81.6% compared with 74.7% at 2 years; and 75.4% compared with 64.1% at 3 years. Using survival curve analysis, this equates to 20 additional years of life for every 100 patients treated for 3 years with ICD (see appendix 9, *Table 16*).

In the absence of published quality-of-life data we estimated utility gain associated with ICD therapy after consultation with UK expert clinical opinion (see appendix 9). This suggests that quality of life may improve from 0.86 to 0.94 on the Index of Health-related Quality of Life Scale after ICD, which gives a gain of 0.08. Using a gain of 0.08 in quality of life and survival curve analysis, a maximum of 0.38 QALYs may be gained over 3 years with ICD treatment over drug therapy (see appendix 9, *Table 18*). However, this is speculative and other data may show that there may be no gains in quality of life attributable to ICD. In the MADIT study, preliminary results suggest that there is no difference in quality of life between ICD and conventional therapy, and that quality-of-life scores correlate with the number of shocks received from the defibrillator and overall quality of life in these patients showed mild-to-moderate disability. One study assigns a quality of life of 0.75 to both anti-arrhythmic drug therapy and ICD therapy cohorts.[52]

Estimation of net costs

Unit ICD cost is the largest single factor in the estimation of total costs as can be seen in *Table 8*. ICD costs and hospital costs were obtained from three regional centres. Drug costs for treatment with amiodarone are taken from the British National Formulary (1999) and are shown in *Table 9*. Example total costs associated with treatment with amiodarone are derived from one hospital only and are shown in *Table 9*. In both *Tables 8* and *9* total costs are calculated for treatment with amiodarone and with ICD therapy over a 3-year period, with and without discounting at 6%.

The additional cost of ICD therapy over amiodarone is £11,600, taking the average of three hospitals discounted at 3 years.

Estimated cost to the NHS

Table 10 compares the estimated cost to the NHS if various criteria for the use of ICD were

TABLE 9 *Amiodarone-associated costs (£) taken from one hospital*

	Cost
Amiodarone 400 mg/day	190
Eight outpatient visits annually	480
Re-admission 7 days six times annually	2562
One emergency resuscitation	850
Total cost first year	**4082**
Total cost for 3 years	**12,246**
Discounted at 6% over 3 years	**11,600**

TABLE 8 *ICD-associated costs (£) in three UK hospitals*

	Hospital A	**Hospital B**	**Hospital C**
One-time costs			
Lab. session 1 hour	244	244	150
Theatre 2 hours	155	155	300
ICD[a]	22,000	14,688	12,500
Hospital stay	2135	1220	2205
Hospital overheads	62	65	(included in hospital stay)
Cost per case	**24,596**	**16,372**	**15,155**
Ongoing costs per year			
Five outpatient visits annually	300	300	1035
Re-admissions 0.5 per patient per year at 3 days	1065	1065	440
Adjunctive therapy	190	190	190
Total ongoing costs per year	**1555**	**1555**	**1665**
Total cost first year	**26,151**	**17,927**	**16,820**
Total cost for 3 years	**29,261**	**21,037**	**20,150**
Discounted at 6% over 3 years	**29,000**	**20,800**	**19,700**

[a]*Range of costs due to variation in sophistication of ICD and hospital contracts*

TABLE 10 *Estimated cost to the NHS of ICD use in different patient groups*

Patient group/trial	Approximate no. of patients in the UK per annum	Approximate cost if device available to all eligible patients	Approximate no. of patients reduced by 25% (50%)[a]	Approximate cost if device available to 25% (50%) fewer patients
All survivors of cardiac arrest	4000[b]	£100 million	3000 (2000)	£75 million (£50 million)
AVID trial[35]	1000	£24.1 million	750 (500)	£18 million (£12 million)
MUSTT trial[33]	1400	£50 million	1050 (700)	£37.5 million (£25 million)

Adapted from Anderson & Camm, 1993[61] (using 1998 average costs)

[a]Number of survivors reduced by 25% for possible non-eligibility due to co-morbidity, life expectancy and neurological issues affecting these patients, which would preclude them from having an ICD, and a further 25% for non-referral of patients (J Morgan: personal communication, January 2000); [b]Based on 8.3 survivors of cardiac arrest per 100,000 people

to be followed, and ranges from £12 million to £100 million.

The American College of Cardiology and American Heart Association guidelines[63,64] for the implantation of ICD are shown in appendix 11. These guidelines illustrate the basis for the hundreds of millions of dollars that are expended annually on ICD in the USA.

Estimation of cost-effectiveness and cost–utility

Our cost-effectiveness analysis concentrates on the secondary prevention strategy because there is more evidence for this approach. It is also a more feasible management strategy because it does not involve the screening programme implied with the primary prevention strategy.

Moreover, because the baseline risk is higher, it may be that ICDs will produce greater benefits and so give a better cost-effectiveness ratio.

Using survival curve analysis based on AVID data, for every 100 patients treated for 3 years with ICD therapy, 20 years of life may be gained. Using UK costs, which suggest that the additional cost ranges from £810,000 to £1,740,000 per 100 people treated, the estimated cost per life-year saved is between £40,500 and £87,000.

An estimate of cost–utility per patient can be made using 0.38 QALYs gained over 3 years with the additional cost of between £8400 and £17,400, which gives the cost per additional QALY gained with ICD ranging from £21,300 to £45,800.

Sensitivity analyses are shown in appendix 9.

Chapter 5
Conclusions

Aim of the review

The aim of the review was to provide a rapid review of the clinical effectiveness and cost-effectiveness of ICDs compared with conventional therapy, in patients at risk of SCD from arrhythmias. By addressing the objectives stated in chapter 1, we have addressed the following policy-relevant questions.

Are ICDs effective (or cost-effective) in reducing mortality, preventing tachyarrhythmia and improving quality of life?

- ICD therapy is effective in treating ventricular arrhythmias.
- ICD therapy is effective in reducing total mortality in patients with life-threatening ventricular tachyarrhythmias compared with anti-arrhythmic drug therapy.
- Changes in absolute risk of mortality range from an increase of 1.7% to a reduction of 22.8%, and relative risk reductions of –7% to +54%.
- Marginal effectiveness of ICD therapy from the literature ranges from 0.23 to 2.2 years of life saved.
- Cost per life-year saved calculated by the authors of the current review may vary from £20,250 to £87,000 per year of life saved. (From the literature from a saving of US$11,315 to Can$213,543 (US$146,180) per year of life saved.)
- Cost per QALY, calculated by authors of the current review, is estimated as ranging from £21,300 to £108,800.
- There are no published cost–utility analyses using UK data, and few good studies on quality of life.
- There is no evidence that one make of ICD has an advantage over another.
- The recent advances in dual-chamber devices offer advantages to a possible 50% of patients eligible for ICD therapy.

Are ICDs more effective (or cost-effective) as first-line therapy or in patients for whom drugs do not work?

- ICD therapy is effective as first-line management of patients at high risk for SCD due to ventricular tachyarrhythmias. The evidence for this is derived from RCTs that have compared first-line use of ICD therapy versus first-line use of drug therapy.

Can a subset of patients be identified for whom ICDs are more effective (or cost-effective)?

- The particular subgroups of patients that may benefit from ICD therapy identified by RCTs (secondary prevention) are those at high risk of SCD from ventricular tachyarrhythmias not due to a reversible cause. These can be further elaborated as:
  - patients surviving cardiac arrest
  - patients having symptomatic sustained ventricular tachyarrhythmias
  - patients with symptomatic sustained ventricular tachyarrhythmias and LVEF no greater than 40%.
- The subgroups of patients that may benefit from ICD therapy identified by two primary prevention trials are those at high risk of SCD from ventricular tachyarrhythmias not due to a reversible cause. These can be further elaborated as:
  - those patients having underlying coronary heart disease with unsustained VT and inducible sustained VT on EPS
  - patients post-myocardial infarction with unsustained VT, LVEF no greater than 35% with inducible VT not suppressed by procainamide with no indications for coronary artery surgery within 3 months.
- The optimal strategy for the identification of a subgroup of patients who could benefit from ICD is not clearly established. An LVEF of 35% or less has been shown to be an important factor to consider (except for those patients with normal LVEF who are at very high risk of SCD, such as long QT syndrome and Brugada syndrome).
- Ongoing trials into treatment of cardiac failure with ICD, and elaboration of quality-of-life outcomes in those treated with ICD therapy, may produce evidence that may have implications for those subgroups of patients in whom ICDs are effective.
- Patients with rarer conditions, such as long QT syndrome, Brugada syndrome and hypertropic cardiomyopathy have been shown to benefit from ICD.

Factors relevant to NHS policy

The policy implications of ICDs are considerable. Demand for ICD therapy would rise by 2.5 times if patient criteria used in the AVID trial were to be applied. On the basis of data collected in the Midlands in the MAVERIC trial,[65] 52% of patients presenting to coronary care units with sustained ventricular arrhythmia not related to myocardial infarction would satisfy the AVID criteria.

If the AVID criteria were to be introduced in the UK, 1000 patients per year would receive ICD at a cost to the NHS of £24 million (an increase from 10 to 18 ICD per million of population). If **all** of those patients presenting to the coronary care unit in the MAVERIC trial were to receive ICD, the annual implant rate would be 35 per million. This would cost almost double that anticipated for the AVID criteria. If the AVID number needed to treat of 8.85 is used (that is over a 3-year period, for every 8.85 people treated with ICD therapy one life is saved), and current costs of ICD therapy over 3 years may range between £20,000 and £29,000 (excluding replacement costs), then an investment per typical health authority over 3 years would be between £177,000 (at the lower cost of ICDs) and £256,650 (at the higher cost of ICDs) for each life saved (or an additional £74,336 to £153,982 over amiodarone therapy).

Any unmet need for ICD therapy is likely to be hidden within the entire chain of referral. Patients with ischaemic heart disease may never be referred to their district general hospital. For those that do present to the secondary services, dispersal of care among the medical services who may not have sufficient knowledge of ICD and its indications, may lead to eligible patients not receiving ICD. Long waiting times to see cardiac electrophysiologists/specialist cardiologists may also result in reduced uptake of ICD therapy. If there is an increased rate of implantation of ICDs there is likely to be a requirement for an increase in the established pool of general cardiologists and specialist cardiac electrophysiologists and specialist cardiology services.

The numbers of patients eligible for ICDs may be increased by raised awareness of coronary artery disease by the implementation of the *National Service Framework for Coronary Artery Disease.*[66] Also the recent national initiative to provide external defibrillators for rescusitation within the community, increasing paramedic ambulances and trained members of the public, may contribute to an increase.

Statement of principal findings and implications

- SCD is a significant public health issue. The majority of these patients die from ventricular arrhythmias. Published RCTs have shown changes in absolute risk of total mortality ranging from an increase of 1.7% to a reduction of 22.8%, and relative risk reductions of –7% to +54%, (excluding the observational arm of MUSTT study).The meta-analysis of three of these trials with similar patient populations confirms the direction of effect and shows a relative risk reduction of 27%. The CABG Patch trial had a greater increase in non-arrhythmic death, but had similar percentage of arrhythmic death. It may be that surgery has an effect on SCD itself.
- The evidence cited in this report points to consistent clinically relevant effectiveness in those patients who have survived cardiac arrest due to sustained VT/VF, patients with symptomatic VT with a LVEF of 35% or less. Only a small number of patients are thought to fit these criteria, and concern has been raised as to equity in the broader context of the NHS. In 1998 the American College of Cardiology issued guidelines for implantation of ICD, which considerably widened the indications for ICD treatment.[64] The Canadian Cardiovascular Society has recently developed guidelines for ICD therapy and their consensus document will soon be published. The *National Service Framework for Coronary Artery Disease,* published by the Department of Health[66] mentions ICD therapy in the heart failure chapter: “the few people who have survived an episode of VF not associated with an acute myocardial infarction may benefit from assessment for an ICD”, and cites evidence from AVID. The implementation of this service framework may lead to a decrease in number of patients eligible for ICDs through the better application of primary and secondary prevention strategies.
- Risk stratification remains contentious as recent evidence has suggested that EPS does not reliably predict SCD.[15,67] Similarly, signal-activated ECG has not been found to be helpful. Modelling work by Owen’s team[68,69] found that strategies to identify those high-risk patients in whom use of an ICD is cost-effective should estimate rates of non-sudden cardiac death and SCD and that echocardiography did not provide a risk stratification tool. AVID substudies cited in chapter 3 (*Assessment of effectiveness*) have explored the use of LVEF

and location of index arrhythmia as risk stratification strategies.
- The effectiveness of ICD on total mortality has been strongly suggested but cost-effectiveness remains a barrier. Eligible patients and their families may expect this treatment to be offered, perceiving it as a life-saving benefit, and may seek redress if refused on an individual basis. There remains the tension between a utilitarian approach (greatest good for greatest number) and the right to rescue for the individual. The consensus from the literature on cost-effectiveness is that ICD therapy is associated with an increased expenditure for funding organisations, with initial costs of the device and insertion being an expensive outlay, but continuing costs of ICD therapy are proving to be less than alternative therapies. Changes in device costs and in clinical practice may reduce the overall costs of ICD therapy in the future.

Strengths and limitations of the review

This rapid review has certain strengths.

- The review brings together the evidence for the effectiveness of ICDs and the evidence for the cost-effectiveness, applying consistent methods of critical appraisal and presentation.
- The review was guided by the principles for undertaking a systematic review. The methods were set out in the research protocol, which defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of review.
- An advisory panel of experts provided invaluable advice through comments on drafts of the report.

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

- Due to time restrictions placed upon the review, no formal meta-analysis has been undertaken. As such, the narrative review presents outcome measures reported in the studies with no additional analysis.
- 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/drop-outs, it could be criticised for excluding other elements that may cause bias (e.g. not including the level of withdrawal/drop-out). It has also been pointed out that the Jadad scale "gives more weight to the quality of reporting than to actual methodological quality".[26,27]
- The calculation of QALY gain due to ICD therapy is speculative. In the absence of published data on utilities, estimation was dependent on clinical judgement.

Implications for research

In undertaking the rapid review of ICDs, certain implications for research have become evident.

- Longer-term cost-effectiveness data may yield answers to remaining questions that surround dilemmas of increasing costs to NHS. As the majority of cost occurs in initial treatment, it may be that cost-effectiveness will become more favourable as patients survive longer, as battery life of ICD extends beyond 10 years, patient acceptability increases, cost of device is reduced and improvements to efficacy occur.
- There is substantial crossover from drug therapy to ICD therapy and the outcomes from this population of patients have not been separately reported in the published literature. This may require further sub-analysis of primary data.
- Further RCT research on effectiveness of ICD therapy is unlikely to be funded because of lack of equipoise in the clinical community. However, one research recommendation that could be pursued is the use of British Pacing and Electrophysiological Group registries to monitor the diffusion and effectiveness of different types of ICD and current service use. These registries could be used to supply epidemiological data and data to inform natural history of underlying conditions in the UK.
- The Health Technology Assessment (HTA) programme has prioritised a systematic review with modelling of the literature to assess the cost-effectiveness of ICD versus anti-arrhythmic drugs. This will be able to include results of ongoing studies due for publication in the near future, which were not available as full publications for this rapid review. It should also develop a new model for UK practice, using NHS cost and activity data to further inform practice and cost-effectiveness in the UK.

- Patient-derived quality-of-life indices for those people receiving ICD therapy compared with those receiving drug therapy based on UK data are needed to generate more accurate and generalisable UK-based cost–utility analyses. This would add a most important dimension to the cost-effectiveness evidence available to policy makers.

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Appendix 1

Types of ICD and potential usage

There have been various technological advances in ICD over the past 15 years. These have resulted in smaller size, easier implantation and improved detection, therapy and stored diagnostic information. The first-generation devices required a transthoracic approach with general anaesthesia, leading to a higher morbidity and mortality. They were capable of recognising VF only and delivered high-energy shock therapy. Their use was reserved for individuals who had survived two episodes of cardiac arrest. Recently, a dual-chamber, rate-responsive pacemaker with mode-switching capability was incorporated into an ICD capable of antitachycardia pacing, low-energy cardioversion or high-energy defibrillation for ventricular arrhythmias.[70] These devices help to prevent inappropriate shock delivery without loss of efficacy and to allow a more individualised therapy. With improvements in lead systems, almost all devices are being implanted with non-thoracotomy leads in the pectoralis region. Continued developments are likely to produce smaller and lower-output devices. However, there is concern that with smaller devices, there may be less efficient capacitor charging.

One RCT that compared two transvenous defibrillator models found no statistically significant difference in the VF detection times between a dual chamber type and control device.[71] The study concluded that the dual-chamber model had a similar effectiveness to sense, detect and treat VF compared with the single-chamber device. Also there was no difference in the efficacy rates of appropriate post-shock bradycardia pacing and sensing between the two devices. One study[72] has shown that clinically important charge times exist between three types of ICD studied. Capacitor charging takes up most of the time between tachycardia detection and therapy delivery and prolonged charge times may result in syncope in patients with poorly tolerated tachyarrhythmias. However, the study was small, short term, based on retrospective data, did not consider detection times and is not generalisable to other types of device.

The RCTs that compare ICDs with alternative therapy do not identify differences in ICD types. For example, in the AVID trial many different types of ICD were used, and there was no standard programming of devices for antitachycardia pacing. However, there is no evidence that one device is better than another in preventing death, and antitachycardia pacing protocols selected by physicians in the AVID trial were similar among devices and institutions.

Results of clinical trials have expanded indications for primary and secondary prevention of SCD, though potential indications for dual chamber are still controversial. A retrospective study[73] on the potential usage of dual-chamber pacing has been conducted which analysed all patients who received a non-thoracotomy ICD at the Mayo clinic from March 1991 to October 1996 in order determine the proportion of patients in whom a dual-chamber pacing ICD may be indicated. Definitions used were:

- definitely indicated = pacemaker present at ICD implant or NASPE Class I pacing indication
- probably indicated = NASPE Class II pacing indication, NYHA Functional Class III or IV, or history of systolic congestive heart failure
- possibly indicated = history of paroxysmal atrial fibrillation or ejection fraction of 20% or less.

The results showed that dual chamber would have been definitely indicated in 11% of the study group, probably indicated in 28%, and possibly indicated in 14%. The addition of dual-chamber pacing to ICDs stands to potentially benefit approximately half (53%) of ICD recipients.

Appendix 2

Databases searched and search strategy

A literature search was performed to ascertain the evidence of the effectiveness and cost-effectiveness of ICD therapy. Evidence was extracted from trials on the effectiveness and from economic evaluations on the cost-effectiveness of this therapy.

Electronic databases searched

(ft) = free text
(mh) = MeSH heading

- **Cochrane Library 1999 no. 3**
- **MEDLINE 1980–99**

Search terms used

implantable cardiac defibrillator
implant* defib* (ft)
implant* defib* (ft)
ventricul* Arrythm*(ft)
cardi* arrest*(ft)
defibrillators implantable(mh)
ventricular fibrillation(mh)
heart arrest(mh)
quality of life (mh)
implant* and defibrill* (mh)
sudden cardiac death (mh)
vent* arrhy* (mh)
clinical trial (pt)
english (lg)

- **Embase 1980–99**

MeSH terms as for MEDLINE

- **BIDS Science Citation index**
- **National Research Register**

MeSH terms as for Cochrane

- **International Network of Agencies for Health Technology Assessment**
- **NHS Economic Evaluation Database**

Other search strategies

- To identify RCTs, the Lefebvre strategy was used.[74]
- To identify economic evaluation the CRD high sensitivity strategy was used.[74]
- The Yahoo search engine on the Internet was used to locate any relevant sites, such as conference proceedings at which several of the recently completed RCTs were presented in abstract form.
- Reference lists were searched and relevant articles retrieved. Search terms were added following initial searches as appropriate.
- Studies were graded according to the level of evidence. Due to limitations of time, only those studies of higher level of evidence, systematic review, meta-analysis and RCT, were located and appraised. Economic evaluations have been located and appraised.
- Authors of two retrieved RCTs (Zipes,[35] Hallstrom,[75] and Connolly[37]) and one ongoing trial (Htlatky) were contacted to answer queries or to seek further information/data.

Appendix 3

Methods for assessing the quality of systematic reviews and RCTs

Criteria for assessing good-quality systematic reviews[26]

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

1. **Does the review answer a well-defined question?** A good review should focus on a well-defined question, making the objectives of the review easy to understand. The most important components in a review question include the target population, healthcare intervention and outcomes of interest.
2. **Was a substantial effort made to search for all the relevant literature?**
3. **Are the inclusion/exclusion criteria reported and are they appropriate?** Criteria for the inclusion of individual studies in a review have two major dimensions: relevance and validity. A relevant study should be useful to answer review questions in terms of patients, intervention and outcomes. The validity issue is related to the methodological standard of an individual study.
4. **Is the validity of included studies adequately assessed?**
5. **Is sufficient detail of the individual studies presented?** Details of the individual studies included in a review include study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate, effectiveness results and side-effects. The importance of the study details may differ for different review topics.
6. **Have the primary studies been combined or summarised appropriately?**

If at least four of the criteria are met the paper will be considered to be of good quality.

Instrument to measure the likelihood of bias in RCTs[27]

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 drop-outs?

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 1 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 1 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 term '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. (Note: It should be noted that in the RCTs included in this study no Jadad Score exceeds 3 because insertion of an ICD is virtually impossible to double blind.)

Withdrawals and drop-outs

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 4

Systematic review of effectiveness of ICDs

TABLE 11

Study	Research question	Inclusion criteria	Search strategy
Hider, 1997[16] New Zealand Health Technology Assessment Group NHS CRD Quality Score: 4/6	To determine health outcomes from the use of ICDs, including effectiveness, comparison with other therapies, identification of patients who would most benefit, and cost-effectiveness	Descriptive, observational, and RCT reviewing the efficacy, cost-effectiveness, indications or complications related to the use of ICD Sample size ≥ 50 Follow-up period ≥ 3 months Trial gave explicit description of study design, results and analysis ITT analysis in RCT was performed English language All articles examining the indications or prioritisation for ICD were reviewed	MEDLINE and EMBASE were searched from 1993 using an explicit strategy Cochrane Library and INAHTA database were searched using an explicit strategy Relevant sites on the Internet were searched using the same terms

Results

- ICD consistently shown to be effective at terminating ventricular arrhythmias and therefore reducing the incidence of SCD in recipients
- Uncertainty exists about whether overall survival is enhanced by the device, due to lack of evidence from RCTs. Case-control and cohort studies have found that ICDs are associated with reduced overall mortality. However, these studies are prone to significant problems with selection bias and difficulties with effects of confounding. Patient populations have varied and bias has been introduced in definitions of SCD and inappropriate shock. Temporal disparity and questionable validity in using appropriate shock as a valid end-point further limit the results of these studies
- Only a few trials have examined the effects of ICD on recipient quality of life. These have had small sample sizes and confounded by examining the effect of a device on quality of life among patients with serious illness. Generally the studies have shown that quality of life can be preserved among recipients but that there is often some initial impairment just after insertion. Most recipients are grateful for the ICD and adapt to the major changes in their functioning, work ability and psychological state that result from having a cardiac arrest and receipt of ICD
- Alternative therapy to ICD has a limited ability to improve survival. Amiodarone has been shown to be effective but up to 24% need to withdraw from treatment due to side-effects. Only a small number of patients are suitable for surgery or catheter ablation
- A small number of studies examine cost-effectiveness, and generally concluded that ICD treatment is associated with increased cost to the funding organisation. However most have also concluded that the ICD is a cost-effective intervention for treating arrhythmias compared with alternatives. In addition, some authors suggest the cost-effectiveness of the ICD compares favourably with many other established treatments for other conditions
- Indications for insertion of ICD are difficult to derive. This is due to inconsistency in research surrounding patients selected for the intervention as well as relative inability to identify those patients most at risk from SCD
- General recognition that ICD most appropriate for patients in one of two high risk for SCD: cardiac arrest survivors (NNT = 4.8) and patients at high risk of malignant tachyarrhythmias on basis of spontaneous or inducible arrhythmia, without an arrest, who are not eligible or in whom other medical or surgical treatments failed and who usually have underlying ischaemic heart disease and/or a low LVEF

Comments

- The review contains a methods section identifying the finding of relevant trials and assessment of validity
- Explicit methods were used to determine which articles to include
- Selection and assessment of primary studies is reproducible and free from bias
- Quality of studies was appraised using valid, explicit schedules
- Differences in individual studies were adequately explained
- Reviewers' conclusions were supported by the data cited
- Results were not combined
- Generalisability limited by the predominance of North American studies especially in cost-effectiveness studies
- The review has not been widely peer-reviewed
- Unpublished research was not searched for

INAHTA, International Network of Agencies for Health Technology Assessment

Appendix 5

Summary of RCTs of ICDs

TABLE 12 *Primary prevention trials*

Study	Intervention	Subjects	Outcome measures
Moss *et al.*, 1996[31] MADIT **M**ulticentre **A**utomatic **D**efibrillator **I**mplantation **T**rial Prospective RCT; randomisation stratified according to interval between most recent MI and enrolment (≤ 6 months or ≥ 6 months) and according to centre	Patients randomly assigned to prophylactic insertion of ICD or conventional medical therapy, prescribed by the attending physician; anti-arrhythmic drugs could be used by either arm	Patients with MI ≥ 3 weeks before entry, with documented asymptomatic unsustained VT unrelated to MI, with an LVEF ≤ 0.35, with inducible VT on EPS not suppresssed by procainamide, and were in NYHA Functional Class I, II, III and had no indications for CABG/angioplasty within 3 months Excluded patients with past history of malignant VT *n* = 196 (98 in transthoracic stratum: 50 in ICD and 48 in conventional therapy; 98 in transvenous stratum: 50 in ICD and 48 in conventional therapy)	All-cause mortality 5-year follow-up; average length of follow-up 27 months

Results

- Hazard ratio comparing risk of death per unit of time in ICD group with that in conventional therapy group was 0.46 (95% CI, 0.26 to 0.82; $p = 0.009$)
- RRR = 0.59; ARR = 22%; NNT = 4.4
- During average follow-up of 27 months crude deaths in ICD arm = 15 (11 from cardiac causes) and 39 in conventional therapy arm (27 from cardiac causes)
- Mortality from cardiac causes was 12% vs 27% in ICD group and conventional medical therapy group. respectively; RRR = 0.57; ARR = 15%
- Regression analyses revealed no evidence that anti-arrhythmic medication or other cardiac medication being given 1 month after enrolment or any of 11 preselected baseline variables (e.g. cardiac history) had any influence on hazard ratio
- 16 crossovers occurred 11 patients in conventional therapy group received ICD; five of the ICD group did not receive ICD and two were inactivated
- Therapy-related adverse events reported: 12 with conventional therapy 19 with ICD

Comments

- Randomisation method not reported; ITT analysis performed and all patients accounted for
- There were a higher number of beta-blockers in the ICD group: 30% vs 8.6% at 1 month and 31% vs 6% at last contact. Similarly a higher number of patients on digoxin in ICD group: 62% vs 41% at 1 month and 66% vs 37% at last contact. This may have resulted in confounding and an overestimate of the effect of ICD. A mathematical model was used in an attempt to adjust for these potential biases, and the authors conclude that there was no significant effect on the results. No details were given.
- True denominator from which study population was drawn or the size of the selection bias that may have occurred during enrolment is not known
- Selection bias may also have occurred in that patients were selected for randomisation if they had not responded to procainamide, introducing a potential bias against the medication arm
- Very prescribed inclusion criteria and recruitment over 5 years, limiting the generalisability of the results to populations other than defined by the study
- Potentially preventable deaths are small: 1–2% of post-MI population, and < 10% of all cardiac-related deaths
- A significant number of patients with ICD still require treatment with anti-arrhythmic drugs for underlying SVT or cardiac problems and these may interfere with the proper functioning of the ICD

Quality assessment (Jadad Score)

Question	Score
Was the study described as randomised?	1 + 1
Was the study described as double blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Three patients lost to follow-up (two conventional, one ICD)

continued

TABLE 12 contd *Primary prevention trials*

Study	Intervention	Subjects	Outcome measures
Buxton *et al*., 1993,[32] 1999[33] MUSTT (**M**ulticentre **U**n**S**ustained **T**achycardia **T**rial)	Randomised to conservative treatment (no anti-arrhythmic therapy) or EP-guided therapy tiered and sequential drug/drug/ICD/drug	Coronary heart disease, LVEF < 40%, non-sustained VT, inducible sustained VT on EPS	Primary: cardiac arrest or arrhythmic death Secondary: total mortality

Results

- The enrolled patients with non-sustained VT, LVEF < 40% and coronary artery disease all had EPS to determine if they had inducible VT and if so were randomised to either conservative treatment (no additional anti-arrhythmic), or EP-guided therapy using a tiered round beginning with class II drug then ICD with patients proceeding to next round if a repeat EPS showed induced VT. Median duration of follow-up was 39 months
- Of the 351 patients in intervention arm 45% (158) were discharged on anti-arrhythmic drugs, 26% of which was amiodarone. 46% (161) of intervention patients received ICD therapy. After discharge 12% of patients on drug therapy swapped to ICD therapy, and 17% had a change in their drug therapy. At the last follow-up 58% (202) of patients in intervention arm had received ICD and 29% (103) were receiving drug therapy. In the control arm 3% of patients had received ICD and 10% received drug therapy without having had a cardiac arrest, sustained VT or syncope. Atrial fibrillation was indication for drug therapy in over half of these cases
- The arrhythmic death/cardiac arrest rate at 24- and 60-month follow-up showed the intervention group (12% and 25%, respectively) and the conservative group (18% and 32%); $p = 0.043$; RR = 0.73; RRR = 23%; ARR = 7% at 5 years
- The all-cause death rate at 24- and 60-month follow-up showed intervention group (28% and 42%, respectively) and the control (28% and 48%); $p = 0.6$; RRR = 13%; ARR = 6% at 5 years
- The cardiac death rate at 60 months was 34% vs 40% in intervention and control, respectively; RRR = 15%; ARR = 6%
- Spontaneous sustained VT at 60 months was 20% vs 21% in intervention and control, respectively; $p = 0.9$; RRR = 5%; ARR = 1%
- Death from cardiac arrest/arrhythmia in intervention arm was 9% vs 37% in patients with ICD therapy compared with those not receiving an ICD; $p < 0.001$; RRR = 76%; ARR = 28%
- All-cause death at 60 months in intervention arm was 24% vs 55% in those patients receiving ICD therapy compared with those who did not; RRR = 56%; ARR = 31%
- Adjusted RR of arrhythmic events in patients in intervention arm receiving ICD compared with those who did not is 0.24 (95% CI, 0.13 to 0.45), and an adjusted RR of overall mortality of 0.40 (95% CI, 0.27 to 0.59)
- The secondary outcome of total mortality did not reach statistical significance, though the trend was toward better performance in the intervention group
- Subgroup analysis patients receiving ICD performed better than any other group: 92% alive at 60 months, and when this group removed from the anti-arrhythmic group, no significant difference between conservative group and anti-arrhythmic drug group

Comments

- This was a trial of EP-guided therapy vs no anti-arrhythmic therapy (apart from beta-blockers). The comparison between outcomes of those patients receiving ICD therapy compared with anti-arrhythmic therapy is not randomised, and can be regarded as an observational study. Therefore, the size of the benefit of ICD therapy that is shown should be interpreted with caution
- Extensive adjustment analyses made for prognostic factors that could have influenced outcomes still show a better survival for ICD group of intervention arm than those patients in intervention arm receiving anti-arrhythmic drug therapy
- The study supports the conclusion it draws that the population of patients in the trial (LVEF ≤ 40%, asymptomatic unsustained VT), inducible sustained VT have substantial mortality due to arrhythmias, and that use of ICD therapy in patients with inducible sustained VT reduced mortality rate. Thus, EP testing should be considered for this subset of patients, and ICD therapy considered if sustained VT is inducible in similar clinical settings as the trial
- 2002 enrolled in study but 704 had an inducible VT and were randomised. Those that were not, entered a registry and had a better outcome than those in trial. EPS selecting a population at high risk for arrhythmic death
- The EP-guided therapy patients frequently ended up with an ICD when EPS testing did not reveal an anti-arrhythmic drug that suppressed the inducible VT

Quality assessment (Jadad Score)

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

continued

TABLE 12 contd *Primary prevention trials*

Study	Intervention	Subjects	Outcome measures
Bigger, 1997[34] CABG PATCH Trial **C**oronary **A**rtery **B**ypass **G**raft Patch Trial Multicentre (USA and Germany) Prospective RCT	Randomisation in two schedules – above and below LVEF 0.20, and patients allocated at time of CABG to ICD and to the control (usual treatment)	All patients scheduled to have CABG who were < 80 years, LVEF of < 0.36, and had abnormalities on signal-averaged ECG Patients excluded if sustained VT or VF, poorly controlled diabetes, life expectancy < 2 years *n* = 900 (446 to ICD group and 454 to control)	Overall mortality Average follow-up 32 ± 16 months (SD)

Results

- Hazard ratio comparing risk of death per unit time in the ICD group with that in the control group was 1.07 (95% CI, 0.81 to 1.42)
- Regression model stratified according to LVEF and clinical centre yielded hazard ratio of 1.02 (95% CI, 0.76 to 1.35)
- Separate Cox regression analyses with each of ten prospectively identified covariates showed no significant interaction with ICD
- During an average follow-up of 32 months there were 101 deaths (22%) (71 cardiac cause) in ICD group and 95 (20.9%) (72 cardiac cause) in control
- After 4 years of follow-up actuarial mortality in ICD was 27% and in control group, 24%; $p = 0.64$
- 57% of patients with ICD received a shock within the first 2 years after implantation
- Significantly more postoperative infections were reported in ICD group and more MI in long-term follow-up in control group
- At 42 months cumulative rate of crossover to the control group was 10%, and the cumulative rate of crossover to the ICD group was < 5%
- Use of cardiac drugs similar in two groups at time of discharge, and rates of use of class II and class III similar in both groups

Comments

- Randomisation method reported
- Surgeon had option at randomisation not to have a patient randomly assigned to a treatment group if they thought that ICD would be too risky for that patient. This is a pragmatic approach but may reduce external validity
- ITT analysis was performed and all patients randomised accounted for
- Groups treated equally apart from the intervention
- Groups appear to be similar at baseline especially in beta-blockade, which is less for the ICD group than the control
- Patients recruited into trial represent a high-risk group but compared with AVID trial (actuarial mortality at 24 months, 24%) and MADIT (32%) and CABG Patch (18%) sample was lower risk
- Inclusion criteria for CABG Patch was ECG abnormalities and non-inducible VT (MADIT) or spontaneous VT (AVID) and it may be that occurrence of sustained VT is a better marker than ECG changes of high risk of sudden death that may be prevented by prophylactic insertion of ICD
- It may be that CABG decreases the risk of sudden death
- The use of German and US hospitals limits the applicability of the results to the UK

Quality assessment (Jadad Score)

Question	Score
Was the study described as randomised?	1 + 1
Was the study described as double blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Crossover rate to control group was 10%, crossover rate to ICD < 5%

TABLE 13 *Secondary prevention trials*

Study	Intervention	Subjects	Outcome measures
AVID Investigators, 1997[35] AVID **A**nti-arrhythmic **V**ersus **I**mplantable **D**efibrillators Multicentre prospective RCT	ICD or class III drugs (further randomisation to sotalol or amiodarone in the drug arm if no contra-indications to sotalol)	Patients resuscitated from near-fatal VF, or cardioverted due to sustained VT; patients with VT with syncope or other serious cardiac symptoms and patients with LVEF of ≤ 0.40 *n* = 1017 (507 ICD) 153 of drug arm further randomly assigned: 79 to amiodarone and 74 to sotalol	Overall mortality Cost Quality of life Mean follow-up 18.2 ± 12.2 months (premature termination of trial by data and safety monitoring board as difference in overall mortality between two groups had crossed statistical boundary for early termination)

Results

- Reductions in mortality (unadjusted) with ICD 39 (95%CI, 19 to 59) at 1 year, 27 (95% CI, 6 to 48) at 2 years and 31 (95% CI, 10 to 52) at 3 years
- Absolute mortality: ICD 10.7% (1 year), 18.4% (2 years), 24.6% (3 years); drugs 17.7% (1 year), 25.3% (2 years), 35.9% (3 years)
- Overall survival (unadjusted): 89.3 % in ICD vs 82.3 % in drug arm at 1 year, 81.6% vs 74.7% at 2 years, 75.4% vs 64.1% at 3 years; $p \leq 0.02$
- Average adjusted length of additional life associated with ICD was 2.7 months at 3 years
- Nine people would need to be treated for 3 years to save one life
- 20% of patients crossed over to or added the other therapy by 24 months; crossover rate highest in those initially assigned to therapy
- Patients with ICD hospitalised sooner ($p = 0.04$); at 1 year 59.5% of ICD and 55.6% of drugs re-hospitalised; at 3 years 83.3% of ICD and 75.5% of drugs re-hospitalised
- Hazard ratio = 0.62; hazard ratios calculated for subgroups of patients and did not differ significantly from overall population
- Complications: no serious complications of ICD; one death from pulmonary toxicity in amiodarone group; 16% of amiodarone group on thyroid replacement by 2 years; bleeding requiring transfusion or re-operation in six patients in ICD group; and serious haematomas in 13. 9 patients had insertion problems (pneumothorax, cardiac perforation); ten patients had infections
- Quality-of-life results (unpublished conference abstract data): ≥ 1 vs 0 shocks: Short Form-36 (SF-36) Mental Score –1.96 (95% CI, –3.81 to –0.12; $p < 0.05$); patient concerns quality of life 1.47 (95% CI, 0.39 to 2.54; $p < 0.05$). ≥ 3 vs < 3 shocks: SF-36 Mental Score –4.91 (95% CI, –8.06 to –1.76; $p < 0.001$); patient concerns quality of life 2.16 (95% CI, 0.15 to 4.17; $p < 0.05$). Conclusion that shocks are associated with a significant, independent reduction in self-perceived mental well-being and an increase in patient concerns. Not significantly associated with altered physical functioning

Comments

- Has adequate power to detect an improvement in survival
- Randomisation method not mentioned
- Drug treatment arm contains a disproportionate number of patients with more severe cardiac failure and AF/flutter, and the ICD arm contained a significantly higher percentage of patients receiving beta-blocker medication, raising possibility that some of survival differences between therapies may have been influenced by these factors
- Trial was terminated half way through recruitment as an interim analysis revealed difference in mortality between the two arms that crossed pre-set statistical criteria for ending the trial

Quality assessment (Jadad Score)

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

continued

TABLE 13 contd *Secondary prevention trials*

Study	Intervention	Subjects	Outcome measures
Siebels *et al.*, 1993[30] (1999[29]) CASH **C**ardiac **A**rrest **S**tudy **H**amburg Prospective multicentre RCT	Randomised to receive: amiodarone (loading dose 1000 mg/day for 7 days and 400–600 mg/day after day 8); metoprolol (initial dose 12.5–25 mg/day up to 200 mg/day as tolerated); propafenone (450 mg/day initially to 900 mg/day as tolerated); or transthoracic insertion of ICD	Survivors of cardiac arrest due to VF/VT unrelated to MI *n* = 230 Mean age 57 ± 11 years	Total mortality Cardiac arrest recurrence Incidence of new arrhythmias Drug withdrawal Heart transplantation requirement Minimum follow-up of 2 years

Results

- No significant difference at 11 months in total mortality among those patients on amiodarone, metoprolol and ICD
- Significant higher mortality in propafenone arm compared with ICD (12% sudden death and 23% sudden death and cardiac arrest on propafenenone vs 0% in ICD; $p = 0.05$
- An interim analysis was performed in March 1992. At that time, patients assigned to the propafenone treatment arm had a significantly greater risk of mortality compared with the ICD arm (29.3% vs 11.5%, respectively; $p = 0.0121$; RR = 2.61; 95% CI, 1.1 to 7.6); enrolment into the propafenone arm was discontinued at that time
- Final results were analysed in December 1997. Baseline characteristics for those receiving ICD, amiodarone, and metoprolol were similar; approximately 75% of patients in each of the three groups had documented coronary artery disease; there was a 7.5% reduction in overall mortality among those assigned to the ICD treatment arm (12.1% vs 19.6%) when compared with those receiving amiodarone or metoprolol ($p = 0.047$); the mortality data comparing amiodarone and metoprolol were similar
- There was a significant decrease in SCD in patients treated with ICD compared with medical management (2% vs 11%; $p < 0.001$)
- Patients receiving the transvenous ICD systems had an overall better survival rate compared with those receiving epicardial systems ($p = 0.037$), because mortality-related transvenous placement was significantly lower than that associated with open thoracotomy

Comments

- The propafenone arm of this trial was discontinued due to the excessive number of sudden deaths
- No randomisation method mentioned, but groups appear similar at baseline
- Recruitment duration was very long (1987–96); influences of secular trends may result in changes in clinical outcomes; advances in ICD technology and reduction in perioperative risks and improved functioning of the device may have led to an underestimate of effect
- Patients assigned to ICD received a transthoracic device if enrolled before July 1990 and transvenous lead system if enrolled after July 1990
- Preliminary data only are published, though a 2-year 39% reduction of all-cause mortality in the ICD arm compared with the drug arm recently presented at the 1999 Annual Scientific Sessions of North American Society of Pacing and Electrophysiology
- Use of a one-tailed test to compare two treatment strategies prevents the testing of the potential deleterious effects of ICD

Quality assessment (Jadad Score)

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

continued

TABLE 13 contd *Secondary prevention trials*

Study	Intervention	Subjects	Outcome measures
Connolly *et al.*, 1993,[36] 2000[37] CIDS **C**anadian **I**mplantable **D**efibrillator **S**tudy Multicentre RCT	Randomisation to insertion of ICD (the first 33 via transthoracic route, remaining 277 via transvenous) or to treatment with amiodarone (1200 mg/day for first week in hospital, followed by ≥ 400 mg/day for at least 10 weeks, followed by ≥ 300 mg/day for long-term treatment	Patients with documented VF, out-of-hospital cardiac arrest, presentation of VT at a rate ≥ 150 beats/minute causing presyncope or angina in the patient with LVEF ≤ 35% or unmonitored syncope with subsequent documentation of either spontaneous or inducible VT Patients excluded if MI < 3 days prior to randomisation, intolerant of amiodarone or having received amiodarone for 6 weeks or more in the past *n* = 600 (310 in ICD arm)	Total all-cause mortality Arrhythmic deaths Non-fatal recurrence of VF or sustained VT Cause-specific mortality Follow-up 3–5 years minimum 1 year

Results

- 28% of patients receiving ICD were also receiving amiodarone; of those in amiodarone group 22% had received subsequent ICD insertion
- Beta-blocker treatment was four times greater in patients randomised to ICD group compared with those in the amiodarone group
- After 5 years of follow-up the patients randomised to ICD group had a 19.7% RRR in all-cause mortality compared with those in amiodarone group (not statistically significant; $p = 0.142$); NNT = 24; RRR in arrhythmic death was 32.8% (not significant; $p = 0.094$); 23.3% mortality in ICD group compared with 27% in amiodarone group after 3 years of follow-up
- Mortality difference was not affected significantly by subgroup analysis of age, entry criteria or LVEF
- Complications of ICD therapy were infrequent: infection 4.6%; lead fracture 2.4%; transvenous approach improved perioperative mortality (0.3% 30-day mortality compared with 3.3% when using the thoracotomy approach)
- Amiodarone was well tolerated: after 5 years of follow-up 85% of patients started on amiodarone continued therapy; adverse effects noted more frequently in those patients randomised to amiodarone group; increased rates of pulmonary (11.9% ICD group vs 19.6% in amiodarone group), thyroid (1.5% vs 8.8%), hepatic (0.9% vs 5.1%) and CNS (8.5% vs 26.0%) toxicity

Comments

- The primary outcome was changed in 1995 to all-cause mortality
- Cost analyses are not published and quality-of-life results not yet in public domain

Quality assessment (Jadad Score)

Question	Score
Was the study described as randomised?	1 + 1
Was the study described as double blind?	0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	30% crossover to amiodarone, 22% crossover to ICD

continued

TABLE 13 contd *Secondary prevention trials*

Study	Intervention	Subjects	Outcome measures
Wever *et al.*, 1995[38] Dutch study Prospective RCT	Randomised to ICD or conventional therapy; in the conventional arm the efficacy of class IA, Ic and III drugs was evaluated; non-responders to drugs were assessed for catheter ablation, which if not possible ICD was implanted	Patients with cardiac arrest secondary to VT or VF, MI ≥ 4 weeks in past and inducible ventricular arrhythmia at electrical stimulation *n* = 60 (31 in conventional arm) Mean age 57 ± 10 years	Total mortality Prolonged syncope with circulatory arrest Pump failure requiring heart transplantation Changes in functional class Exercise duration LVEF Duration of hospitalisation Changes in anti-arrhythmic drug

Results

- 35% died in conventional therapy arm and 14% in ICD
- 42% total number of main outcome events in conventional arm compared with 13.8% in ICD
- All-cause mortality RR for ICD 0.27 (95% CI, 0.09 to 0.85; $p = 0.02$)
- NNT = 4.8
- 61% of conventional arm failed tests of drug efficacy
- 45% of conventional arm received a late ICD

Comments

- Small number of patients in trial
- Randomisation method not reported
- ITT analysis performed and all patients accounted for
- Use of class I drugs in the conventional arm may have increased the mortality risk in the conventional arm and confounded the study finding of a survival advantage for ICD group
- Only a small number of patients in conventional therapy arm received beta-blockers increasing the mortality risk in this group and potentially an overestimate in effect of ICD
- Generalisability may be limited

Quality assessment (Jadad Score)

Question	Score
Was the study described as randomised?	1
Was the study described as double blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Four patients died in ICD group, 11 patients died in conventional group

Appendix 6

Subgroup analyses from the AVID trial

In the AVID trial, beta-blocker use was independently associated with improved survival in patients with VF or symptomatic VT who were not treated with specific anti-arrhythmic therapy, but a protective effect was not prominent in patients already receiving amiodarone or a defibrillator.[42] (In other studies it has been noted that the effects of amiodarone may be potentiated by beta-blockers, so underestimating the effect size difference between amiodarone therapy and ICD therapy.[77,78])

Based on proportional hazards modelling, a sextile of patients were identified who appeared to derive virtually no benefit from ICD therapy. The clinical features identifying patients in this low-risk sextile were; an index arrhythmia of VF, absence of cerebral vascular disease, absence of prior arrhythmia, and either an LVEF more than 27%, or a history of revascularisation.[75]

When the LVEF was less than 35%, the benefit of ICD therapy compared with anti-arrhythmic drug therapy was considerably greater than if the LVEF was greater than 35%. In patients with an LVEF greater than 35% there was no difference in survival between drug therapy and ICD therapy. The same size of benefit was seen in subgroups with LVEF less than 20% and 20–34%. This difference in benefit was not statistically significant between the two groups. Further subdividing the LVEF into three groups did not improve the specificity of the analysis. This was taken to suggest that there is a low-risk patient group with a well-preserved LVEF, which may not benefit particularly from ICD.[79]

Out-of-hospital presentation of life-threatening ventricular arrhythmias not due to a reversible cause had a better long-term prognosis than those patients presenting with their index ventricular arrhythmias in hospital. This was found to be an independent predictor for long-term outcome.[80]

All registry patients (who had life-threatening VT/VF or unexplained syncope that could be considered for ICD or anti-arrhythmic drug therapy) had a similar and poor prognosis whether they were eligible ('higher risk'), or ineligible ('low or unknown-risk' VT/VF) for inclusion in AVID. The authors suggest that present risk stratification may not be sensitive and that treatment options for the whole broader range of patients need to be considered.[81]

A cohort of eligible patients from the registry not included in the AVID trial was followed to determine those patient characteristics that might influence whether a patient receives ICD therapy. Those patients who are older, have minority status and co-morbidity and without VF as an index of arrhythmia were less likely to be treated with ICD therapy.[82]

ICD therapy is more effective than anti-arrhythmic drugs in reducing arrhythmic cardiac death while non-arrhythmic cardiac death is unchanged. Arrhythmic death still constitutes 38% of all cardiac deaths despite treatment with ICD therapy. ICD therapy remains superior to anti-arrhythmic drug therapy in prolonging survival after life-threatening ventricular arrhythmias.[83]

Appendix 7

Ongoing studies

- CARDPORT is a large non-randomised study being undertaken at Stanford University. It will have more than 1000 patients with ICD and will undertake regular functional, psychological and quality-of-life analyses and will document patient preferences for ICD and other treatment options. It will provide evidence that will determine reliable methods of risk stratification in patients with ischaemic heart disease and the clinical predictors of individual risk of SCD. It is due to finish in late 1999. No published reports have been found on searching electronic databases and relevant Internet websites (May 2000). http://www.stanford.edu/group/cardport
- The Midlands trial of empiric Amiodarone Versus ElectRophysiologically guided Intervention and Cardioverter implant in ventricular arrhythmias (MAVERIC). A population-based study where patients with sustained ventricular arrhythmia are randomised to empirical amiodarone or EP-guided treatment which may be one or a combination of anti-arrhythmic drugs or coronary revascularisation or ICD. Quality-of-life and cost data, including indirect costs, will be collected and total mortality is the primary outcome. Data on crossover and referral for EPS will be collected. A total of 200 patients will be recruited over 2 years, and the trial began in February 1997. Inclusion criteria are resuscitated VT/VF, sustained non-syncopal VT and resuscitated SCD. Exclusion criteria are myocardial infarction within 48 hours, prognosis of less than 6 months from a non-arrhythmic cause and pregnancy. Natural history and incidence of ventricular arrhythmias will be studied. This is now finished and results were presented at the NASPE conference on 20 May 2000. (Dr M Griffith: personal communication, 10 May, 2000).
- Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Patients with Class I or Class II heart failure will be randomised to receive placebo, amiodarone or ICD. Primary outcome is total mortality, and it should define the role of anti-arrhythmic prophylaxis in reducing total mortality as well as relative effectiveness of amiodarone and ICD. Trial began in 1997, and is now almost fully recruited.
- MADIT II (RCT, USA). Trial patients are post-myocardial infarction with LVEF of less than 30%. It uses sequential analysis as MADIT I and is due to finish enrolment in 3–6 months.
- DEFINITE where the study population are patients with cardiomyopathy, low LVEF, and some ventricular arrhythmia.
- DINAMIT (RCT, Germany/Canada) where the study population are patients with acute myocardial infarction and LVEF of 35% or less and decreased heart rate variability.

Appendix 8

Summary of economic evaluations of ICDs

TABLE 14

Study	Intervention	Subjects	Outcome measures/ sensitivity analysis
Kuppermann *et al.*, 1990[52] USA Markov model data from literature (non-RCT) expert opinion	ICD compared with drug therapy	Survivors of cardiac arrest, not associated with MI and inducible VT/VF	Outcome measures: Effectiveness Initial hospitalisation cost Re-hospitalisation Concurrent drug treatment with ICD
Results • 1.9 years of life saved in ICD group (5.1 vs 3.2) • $17,100 per life-year saved (range depending on assumptions used $15,600 to $29,600) • Projecting into future with replacement at 5 years and programmable devices and transvenous approach estimate of $7400 per life-year saved; at best may become cost saving • 5% discount rate used			
Comments • Clear question, using secondary data, expert opinion and decision analytic modelling • Compared with drug therapy only • Assumed that cardiac-related care other than that relating to therapies in question was the same in both groups of patients • Used data collected on ICD insertion via transthoracic route, which has higher perioperative morbidity and mortality and length of hospital stay • Patient population is heterogeneous and selected • It is likely that initial hospital costs for non-ICD group were underestimated • Conservative estimate of readmission every 2 years for ICD group likely to be underestimate • No cost–utility analyses presented • US data limit generalisability			

continued

TABLE 14 contd

Study	Intervention	Subjects	Outcome measures/ sensitivity analysis
Larsen *et al.*, 1992[53] USA Markov model Based on literature historical controls	ICD vs amiodarone vs conventional therapy (patients on anti-arrhythmic drugs who still have inducible arrhythmia) Transthoracic implantation	VT/VF patients aged 55 years *n* = 64	Sensitivity analysis: Life of device QALY Efficiency of amiodarone
Results • ICD most expensive alternative • Marginal effectiveness of ICD 2.2 years of life saved • Cost-effectiveness ICD vs amiodarone $39,400 per life-year saved • Cost-effectiveness amiodarone vs conventional therapy $8900 per life-year saved • Cost-effectiveness ICD vs conventional therapy £26,600 per life-year saved • In sensitivity analysis, life of device had important influence • Amiodarone QALYs need to dip below 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% • 5% discount rate used			
Comments • US data limit generalisabilty • Old devices with transthoracic approach • Assumed no crossovers • Assumed each group identical apart from therapy			
O'Brien *et al.*, 1992[54] UK Markov model	Incremental cost-effectiveness of ICD compared with amiodarone	Patients at high risk of SCD Model constructed from published data and other secondary sources; differences in patient survival from two US studies	Outcome measures: Cost-effectiveness of ICD over 20 years discounted at 6% Sensitivity analysis: Alternate estimates of patient survival Initial cost of ICD implantation Alternative treatment assumptions (e.g. amiodarone costs, life span of ICD)
Results • In the 20-year study period, range of 1.7 to 3.7 discounted life-years gained from ICD • Cost-effectiveness of ICD £15,400 per life-year gained • Unadjusted survival series cost-effectiveness ratio of £8200 • Analysis assuming a reduction in start-up costs of ICD treatment result in cost-effectiveness of £14,500 per life-year gained • Sensitivity analysis shows cost-effectiveness most sensitive to alternative estimates of patient survival (i.e. the size of the mortality benefit attributable to ICD)			
Comments • UK data used to produce the cost-effectiveness figures • Comparison of well-defined alternative courses of action used • No specified view point stated • Evidence cited not RCT and predominantly observational or descriptive studies; costs based on management protocols and interviews with physicians • No indirect costs detailed • Direct costs from national published data on hospital costs and outpatient visits • Authors state that costs per life-year gained seem impressive and comparable to other procedures performed by the NHS (e.g. CABG one-vessel disease £12,000 per QALY drug treatment of raised cholesterol £19,000 per QALY) • Cost–utility analysis not performed for ICD, no prospective data on quality of life published			

continued

TABLE 14 contd

Study	Intervention	Subjects	Outcome measures/ sensitivity analysis
Kupersmith & Holmes-Rovner, 1995[55] USA Markov model	Cost-effectiveness of ICD compared with EP-guided drug therapy Resource use Transthoracic implantation mostly	High-risk patients with VT/VF direct costs	Sensitivity analysis: Perioperative mortality Battery life Effectiveness no pre-implant EP Consideration of only ICD or drugs
Results • Device hardware is expensive ($22,000) • Mean increase in life expectancy with ICD 2.03 years and cost-effectiveness $31,000 per life-year saved • Sensitivity analysis without the assumption that time of first shock would have been the time of death showed that cost increased only when < 38% of first shocks equalled death • Patients with LVEF > 0.25 had cost-effectiveness $27,000 per life-year gained compared with $44,000 per life-year gained with LVEF < 0.25 • Cost-effectiveness without EP studies $18,000 per life-year gained • If ICD were used in lower-risk/prophylactic indications, cost-effectiveness would be less favourable • 5% discount rate			
Comments • Data sources included Medicare for charges and the literature • Assumes that time to first shock equates with mortality without the ICD, which is erroneous • Does not compare directly drugs and ICD, which is major alternative therapy • No cost–utility analysis • US costs and data limit generalisability			
Wever *et al.*, 1996[56] The Netherlands Clinical trial	ICD compared with drug therapy Transthoracic approach	Survivors of cardiac arrest caused by VF/VT	Outcome measures: Total mortality Factors reflecting quality-of-life exercise tolerance Major non-fatal events Sensitivity analysis: Hospitalisation charges EPS cost
Results • Cost-effectiveness ratio $11,315 per patient per life-year saved by early ICD implantation • Costs in ICD group only higher in first 3 months, but were superseded by EP-guided therapy thereafter • Costs in drug-alone group were lowest but had highest mortality resulting in a less favourable cost-effectiveness ratio • ICD device and hospitalisation were major contributors to total costs • ICD more cost-effective as first-line therapy than when used after drug therapy has failed • Quality-of-life measures taken into account seem to make cost-effectiveness more favourable, though quantitative analysis was not performed			
Comments • Clear question, with description of alternatives, and costs collected alongside RCT • No indirect costs • Not discounted • Sensitivity analysis performed • European data • Small study • No cost–utility analysis • Relatively short duration of study did not allow inclusion of replacement devices • Use of ICD as second-line therapy may allow a greater number of patients to die who would have survived if they had received ICD initially • Authors anticipated further improvement of cost-effectiveness of ICD with tranvenous approach and refinement of technology			

continued

TABLE 14 contd

Study	Intervention	Subjects	Outcome measures/ sensitivity analysis
Owens *et al*., 1997[57] USA Markov model	ICD compared with amiodarone Transvenous approach	Survivors of cardiac arrest, cost-effectiveness of patients at intermediate risk for SCD receiving ICD alone, amiodarone alone and amiodarone crossing to ICD	Sensitivity analysis: Effectiveness of ICD replacement interval
Results • Cost of replacement devices is an important component of the cost of ICD (50% to 65% of initial implantation costs) • ICD most expensive of regimens • In high-risk patients, quality-adjusted life expectancy with ICD = 4.18 years ($88,400), amiodarone alone = 3.68 years ($51,000), that is reported as 6 months extra of quality life for $37,500 • If ICD use reduced overall mortality by 40%, high-risk patients will live an extra 1.17 years longer than amiodarone alone for an additional $43,700, and intermediate-risk patients with ICD live 1.28 QALYs longer than in amiodarone group at a cost $46,300 • For high-risk patients marginal cost-effectiveness ranges from $37,000 to $74,000 per QALY (ICD reduces mortality by 20% or 40%) • For intermediate-risk patients using an RRR of 20%, cost–utility is calculated to be $76,800 per QALY with ICD compared with amiodarone; using an RRR of 40%, cost–utility is calculated to be $36,300 per QALY • Estimates of cost-effectiveness are substantially influenced by RRR used, ICD frequency of device replacement, quality of life with therapy and cost of initial implantation			
Comments • Evidence of effectiveness comes from RCT and patient registries; assumed that ICD use would reduce total mortality by 20% to 40%; sensitivity analysis varied this effect • Comparison is with amiodarone, which is the alternative therapy of choice in most patients • Analyses use transvenous approach only, which has superseded transthoracic • Cost–utility analyses were performed • Crossover strategies were examined • Calculation of cost utilities used RRR of total mortality of 20% and 40% • Authors conclude that early implantation with ICD is more cost-effective than delayed • Authors conclude that cost-effectiveness changes only modestly when intermediate-risk patients are implanted; this may be an underestimate if the quality of life of those patients at intermediate risk of SCD have a higher quality of life than those at high risk • US data limit generalisability			
Mushlin, 1998[58] MADIT Germany and USA Clinical trial with simultaneous costs	ICD compared with conventional medical therapy	VT, prior MI, LVEF < 0.35 and inducible ventricular tachyarrthymia on EPS not suppressed by procainamide *n* = 181 Average follow-up 27 months	Outcome measures: Total mortality Sensitivity analysis: Cost of device Crossover
Results • Cost of device is largest contributor to cost and cost-effectiveness may be expected to improve with reduction in price of device • Incremental cost-effectiveness ratio $27,000 per life-year saved ($22,800 for transvenous device) • Using present 16,000 patients in USA meeting MADIT criteria and each offered ICD steady state annual extra cost approximately $320 million for 32,000 years of life saved • Extrapolation of results to 8 years with use of transvenous devices and anticipated reduction in device price estimated incremental cost-effectiveness ratio would be $10,000 per life-year saved with average saving of 2 years of life and life-time cost increase of $20,000 per patient • Patients with ICD could expect to live 3.46 out of 4 years and conventional therapy 2.66 out of 4 years (discounted) • Discount at 3%			
Comments • US data limit generalisability • Some cost data derived from self reports from patients, no indirect costs assessed • No cost–utility analysis attempted • Conversion methods for charges to costs imperfect • Trial powered to detect difference in mortality not to obtain estimates of cost-effectiveness ratio resulting in very wide CIs around estimations • Both transvenous and transthoracic devices used			

continued

TABLE 14 contd

Study	Intervention	Subjects	Outcome measures/ sensitivity analysis
O'Brien *et al.*, 2000[59] Canada CIDS trial (unpublished abstract only)	ICD compared with amiodarone transvenous approach	Survivors of cardiac arrest, cost-effectiveness of patients at intermediate risk for SCD receiving ICD alone, amiodarone alone and amiodarone crossing to ICD	Sensitivity analysis: Discount rate Device costs Follow-up period for analysis
Results • Cost of ICD higher than cost for non-ICD (Can$87,715 vs Can$38,600) • Incremental cost-effectiveness ratio of the ICD group compared with non-ICD group was Can$213,543 per life-year gained • Results not sensitive to discount rate, or alternative assumptions for device costs • Results sensitive to extension of follow-up period for analysis using modelling projections beyond the trial suggesting improved cost-effectiveness of ICD therapy			
Comments • Comparison is with amiodarone, which is the alternative therapy of choice in most patients • Analyses use RCT data • Data on 65% of total sample (430 patients); no detail on how representative this sampling was, and whether this could have had any effect on the economic analysis • No cost–utility analyses have been reported • Authors conclude that ICD is both more effective and more costly than non-ICD therapy • Authors conclude that cost-effectiveness of ICD is more costly than most accepted therapies • Canadian data limit generalisability			

continued

TABLE 14 contd

Study	Research question	Inclusion criteria	Search strategy
Stanton & Bell, 2000[62] Literature review	To summarise current literature on comparative economics of ICD and conventional therapies	RCT, prospective and retrospective studies and economic models, published in English	MEDLINE was searched from 1990–97 using the terms implantable cardioverter defibrillator, or cardioverter defibrillator, and cost, economics or cost-effectiveness Conference proceedings from US scientific meetings were searched

Results

- Of initial 24 studies, seven were identified to be included in the review; six of these are the same studies cited in this report, along with the AVID cost data that have been presented in abstract form only. (O'Brien economic analysis was not included)
- The authors did not perform meta-analysis due to lack of data provided in the studies
- Incremental cost per life-year saved varied between cost savings of US$13,975 per life-year saved to incremental cost US$114,917
- The break-even times using updated cost and sensitivity data, vary between not breaking even (Owens, 1997[57]) (Larsen, 1992[53]) to break-even times between 1 year (Kupersmith & Holmes-Rovner, 1995[55]), (Wever, 1996[58]) and 3 years (Kuppermann, 1990[52])
- The cost of ICD therapy is sensitive to battery life (which in turn depends on type of battery and patient requirement for pacing and therapeutic shocks), use of a pre-implant EPS and RRR in mortality associated with ICD therapy compared with anti-arrhythmic drug therapy
- Advances in ICD technology, such as transvenous insertion, pectoral implant, extended battery life, endocardial ICD systems, along with clinical practice shifts, such as elimination of pre-implant EP and pre-discharge device tests, use of conscious sedation rather than general anaesthesia, have allowed ICD to become more cost-effective
- Influences on the cost-effectiveness of ICD include: inappropriate hospital admissions following device discharge by inexperienced physicians and poorly educated patients; use of ICD in lower-risk groups, which do not fall into those subgroups of patients demonstrated by the published studies to have a reduction in total mortality from ICD therapy
- The shortened follow-up times in AVID and MADIT studies may affect the cost-effectiveness results for ICD therapy, both underestimating it by not taking into account battery replacement costs and overestimating it by not having longer-term survival data with which to estimate longer-term incremental costs
- Future research areas delineated are implications of truncated follow-up periods by economic modelling, addition of social and patient costs to analyses, and implications on economic analysis of patient-derived quality-of-life parameters for ICD and drug therapies
- Conclusions are that the ICD is a cost-effective therapy for management of life-threatening ventricular tachyarrhythmias as judged by the Kupersmith[54] cost-effectiveness guidelines (highly cost-effective US$0–20,000; cost-effective US$20,000–40,000; borderline US$40,000–60,000; expensive US$60,000–100,000; very expensive US$100,000–120,000)

Comments

- The review contains a methods section identifying the finding of relevant trials
- The search method is confined to one electronic database, plus a limited, focused search for unpublished research presented at North American conferences
- There is no reported assessment of the validity of the included studies
- Explicit methods were used to determine which articles to include
- Selection and assessment of primary studies are reproducible, though exclusion of the UK O'Brien economic analysis is not adequately explained
- Quality of studies was not explicitly appraised using valid, explicit schedules
- Evidence for the methodology of the secondary analysis was not reported
- Differences in individual studies were explained by differences in the determination and measurement of costs and benefits of treatment, and the time period over which costs are tracked
- Reviewers' conclusions are based on a scale of cost-effectiveness that is not 'standard' in the UK
- Conclusions about impact of new technology based on two of the included economic analyses and other studies that were not part of the formal literature review; this could lead to bias
- Results were not combined
- Generalisabilty limited by majority of studies having a North American setting
- The review has been peer-reviewed
- Authors are funded by, and parent organisation is cited as, Medtronic, which manufacturers ICDs

Appendix 9

QALY estimations and sensitivity analysis

Life-years saved from ICD therapy

The additional years of life saved by ICD therapy can be calculated using the AVID data and survival curve analysis, and are shown in *Table 16*. This has not been extrapolated beyond trial results and may be an underestimate of benefits over a longer period of time. This may in turn lead to an overestimate of the incremental cost-effectiveness ratio or cost per QALY.

Utility gain from ICD therapy

Experts were asked for their clinical judgement on possible utility associated with ICD therapy using the Index of Health-related Quality of Life Scale, and results are shown in *Table 17*. It is assumed that pre-ICD therapy utility is equivalent to that associated with drug therapy, as most patients will be on drug therapy before receiving an ICD.

This range in utility gain seems to be plausible because there are at least two categories of secondary prevention patients. First, those with haemodynamically unstable VT/VF who require shock therapy from ICD which can be excruciatingly painful and who may have no gain in quality of life. Second, those with haemodynamically stable VT/VF who require painless pacing therapy from ICD and who may experience large quality of life gains.

QALY calculation

Using results of the survival curve analysis for each year, multiplied by each utility estimate, a range of QALYs gained from ICD therapy can be calculated, and are shown in *Table 18*.

Sensitivity analysis

In calculating incremental cost per life-year saved and incremental cost per QALY in the sensitivity analysis, various assumptions are made and these are shown in *Table 19*.

The incremental cost per life-year saved and the incremental cost per QALY over 3 years, using the above assumptions are shown in *Table 20*. This is based on current best available data but remains speculative.

TABLE 16 *Survival after ICD therapy*

	Proportion alive with ICD therapy from AVID	Proportion alive with drug therapy from AVID	Life-years lived with ICD therapy from SCA	Life-years lived with drug therapy from SCA
At start of study	1	1		
At end of year 1	0.893	0.823	0.95	0.91
At end of year 2	0.816	0.747	0.85	0.79
At end of year 3	0.754	0.641	0.79	0.69
Total life-years saved			2.59	2.39
Incremental life-years saved by ICD			**0.20**	

SCA, survival curve analysis

TABLE 17 *Estimated utility gain from ICD therapy*

	Pre-ICD/drug therapy alone	Post-ICD therapy	Utility gain from ICD therapy
Expert 1	0.86	0.94	0.08
Expert 2	0.81	0.81	0.0

TABLE 18 *QALYs gained from ICD therapy*

	Life-years lived		QALYs (Expert 1)		QALYs (Expert 2)	
	ICD	**Drug**	**ICD**	**Drug**	**ICD**	**Drug**
Utility	–	–	0.94	0.86	0.81	0.81
Total	2.59	2.39	2.43	2.06	2.09	1.94
QALY gain			**0.38**		**0.16**	

TABLE 19 *Assumptions used in the sensitivity analysis (and justification)*

Parameter	Low value	Base-case	High value
Incremental costs (and justification)	£8100 (lowest hospital cost)	£11,600 (average of three hospital costs)	£17,400 (highest hospital cost)
Life-years saved (and justification)	0	0.20 (from SCA)	0.4 (arbitrary high value, double base-case)
QALY gain (and justification)	0	0 (from clinical judgement)	0.16, 0.38 (from two clinical judgements)

TABLE 20 *Incremental cost per life-year saved and incremental cost per QALY gained*

Incremental cost over 3 years	Life-years saved over 3 years	QALY gain over 3 years	Cost/per life-year saved	Cost per QALY
£8100	0.2	–	£40,500	–
£8100	0.4	–	£20,250	–
£8100	–	0.16	–	£50,600
£8100	–	0.38	–	£21,300
£11,600	**0.2**	–	**£58,000**	–
£11,600	0.4	–	£29,000	–
£11,600	–	0.16	–	£72,500
£11,600	–	0.38	–	£30,500
£17,400	0.2	–	£87,000	–
£17,400	0.4	–	£43,500	–
£17,400	–	0.16	–	£108,800
£17,400	–	0.38	–	£45,800

Appendix 10

American College of Cardiology and American Heart Association Guidelines – Implantation of ICDs[64]

TABLE 21

Indications	Level of evidence	Class
Cardiac arrest due to VT/VF not due to a transient or reversible cause	Multiple RCT with large number of patients	I (conditions for which there is evidence and/or general agreement that a procedure or treatment is beneficial, useful, and effective)
Spontaneous sustained VT	Limited number of trials involving comparatively fewer patients or well-designed observational or data analyses	I
Syncope of undetermined origin with clinically relevant haemodynamically significant sustained VT/VF inducible at EPS when drug therapy is ineffective, not tolerated, or not preferred	Limited number of trials involving comparatively fewer patients or well-designed observational or data analyses	I
Non-sustained VT with coronary heart disease, prior MI, LV dysfunction and inducible VF or sustained VT at EPS not suppressed by class I anti-arrhythmic drug	Limited number of trials involving comparatively fewer patients or well-designed observational or data analyses	I
No indications for ICD		IIa (conditions for which there is conflicting evidence and/or divergence of opinion about efficacy/usefulness of a treatment – weight of evidence/opinion is in favour of usefulness/efficacy)
Cardiac arrest presumed to be due to VF when EPS is precluded by other medical conditions	Consensus opinion of experts	IIb (conditions for which there is conflicting evidence and/or divergence of opinion about efficacy/usefulness of a treatment – usefulness/efficacy less well established by evidence/opinion)
Severe symptoms attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation	Consensus opinion of experts	IIb
Inherited conditions with high-risk life-threatening VT/VF (e.g. long QT syndrome, HOCM)	Limited number of trials involving comparatively fewer patients or well-designed observational or data analyses	IIb
Non-sustained VT with coronary heart disease prior MI and LV dysfunction and inducible VT/VF on EPS	Limited number of trials involving comparatively fewer patients or well-designed observational or data analyses	IIb
Recurrent syncope of undetermined aetiology in presence of ventricular dysfunction and inducible VT/VF at EPS when all other causes have been excluded	Consensus opinion of experts	IIb
Syncope of undetermined cause in a patient without inducible ventricular tachyarrythmia	Consensus opinion of experts	III (conditions for which there is evidence and/or general agreement that procedure/ treatment is not useful/effective and in some cases may be harmful)

LV, left ventricular; HOCM, hypertrophic obstructive cardiomyopathy

continued

TABLE 21 contd

Indications	Level of evidence	Class
Incessant VT/VF	Consensus opinion of experts	III
VT/VF resulting from arrhythmias amenable to surgical or catheter ablation (e.g. atrial arrhythmias associated with Wolf Parkinson White syndrome, right ventricular outflow tract VT, idiopathic LV tachycardia or fasicular VT)	Consensus opinion of experts	III
Ventricular tachyarryhmias due to a transient or reversible disorder (e.g. acute MI, electrolyte imbalance, drugs, trauma)	Consensus opinion of experts	III
Significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up	Consensus opinion of experts	III
Terminal illnesses with projected life expectancy less than 6 months	Consensus opinion of experts	III
Patients with coronary artery disease with LV dysfunction and prolonged QRS duration in the absence of spontaneous or inducible sustained VT who are undergoing coronary bypass surgery	Limited number of trials involving comparatively fewer patients or well-designed observational or data analyses	III
NYHA Class IV drug-refractory congestive heart failure in patients who are not candidates for cardiac transplantation	Consensus opinion of experts	III

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