

SUMMARY

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

Epidemiology and background: Sudden cardiac death occurs in approximately 100,000 people annually in the UK and is usually due to ventricular tachyarrhythmia. Increasing numbers of people are surviving a first episode of ventricular tachyarrhythmia and are at high risk of further episodes. Standard treatment for those at high risk has been anti-arrhythmic drugs, catheter ablation or surgery and increasingly vasodilating beta-blockers.

Number and quality of studies and direction of evidence: 7 randomised controlled trials on effectiveness, 8 cost-effectiveness analyses (*plus 2 cost-effectiveness models from industry*) and 2 literature reviews were found. 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 included randomised controlled trials are 0.23 to 0.8 additional years of life with ICD therapy compared with amiodarone/sotalolol.

Costs: Unit cost of ICDs ranges from £12,500 to £22,000. Total discounted costs for three years range from £20,000 to £29,000.

Cost-effectiveness: ICD therapy is associated with increased costs, with cost-effectiveness estimates in the literature ranging from £11,000 to £120,000 per life year saved (£.....
.....*taking the confidential industry figures into account*). Using UK cost data and trial survival data, this review's authors' estimate of cost-effectiveness ranges between £40,300 to £87,000 per life year saved.

Cost-utility: Cost per QALY is estimated by this review's authors' at £21,300 to £108,800 (using data from one trial and clinical opinion). Quality of life data from ongoing trials will inform future UK cost-effectiveness/utility analyses.

Implications: If implemented for indications supported by RCTs, ICDs may cost the NHS in excess of £24 M.

Future research: Future research should include the use of BPEG registries to assess the use of different types of ICD and current service provision.

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ABBREVIATIONS and DEFINITIONS OF TERMS

Cardiological

Arrhythmia	An abnormality in the rate or rhythm of the heart, caused by a defect in the generation or conduction of electrical impulses.
Cardioversion	A carefully timed direct current shock applied to the heart to treat an arrhythmia.
Catheter ablation	Application of energy (radio frequency) to site generating arrhythmia, thereby destroying it.
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.
LVEF	Left ventricular ejection fraction
PES	Programmed electrical stimulation.
PTX	Pneumothorax.
SCD	Sudden cardiac death.
SWORD	Survival with oral sotalol.
Supraventricular Tachycardia SVT	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 is the rapid and chaotic activity of the lower chambers of the heart.
VT	Ventricular tachycardia is the abnormally rapid heart rate caused by ventricular activity.

Epidemiological

ARR	Absolute Risk Reduction. The subtracted difference between event rates.
BPEG	British Pacing and Electrophysiological Group
CI	Confidence intervals. The 95% CI is the range of values in which it is 95% certain that the true value lies for the whole population.
NNT	Number needed to treat. The number of patients who need to be treated to achieve one additional favourable outcome.
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.
QALY	Quality adjusted life year
QALYE	Quality adjusted life expectancy

1. 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 compared with conventional therapy, in patients at risk of sudden cardiac death from arrhythmias.

2. BACKGROUND

Evidence is accumulating on the use of implantable cardioverter defibrillators (ICDs) in the management of sudden cardiac death (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 last 20 years has offered a new alternative. Recent editorials in peer reviewed press^{2,3} have recommended that patients at high risk of sustained ventricular tachycardia or successful resuscitation from ventricular fibrillation 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.

2.1 Description of underlying health problem

Sudden cardiac death 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} (see 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 one hour of onset of symptoms.⁶ SCD is often due to ventricular tachyarrhythmia⁷ 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. 50% will be re-hospitalised within 1 year^{8,9}, and 40 % will die within 2 years.¹⁰ In the UK, fewer than 5% of people survive the initial cardiac arrest (personal communication, J Morgan, January 2000).

Subgroups of patients with the highest relative risk for SCD (survivors of cardiac arrest, low left ventricular ejection fraction) are a small proportion of the total population burden of SCD, making identification of those patients that could potentially most benefit from ICD difficult.^{11;12} The risk of SCD in the general population is 2 per 1000 persons per year¹³, making population screening for risk factors a current challenge. Risk stratification using techniques such as ambulatory electrophysiological study (EPS), signal averaged ECG's,

heart rate variability have been used, although the evidence base for these is often not strong.^{14;15} Research is ongoing into the effectiveness of these techniques.

Aetiological determinants of SCD are those risk factors associated with coronary heart disease (80% of SCD) e.g. 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 imbalance, and ischaemia.^{1;15}

Table 1: Deaths in England and Wales, 1997

	Males	Females	Total
Coronary heart disease ¹⁶	78,500	73,500	152,000
Sudden cardiac death ^{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

2.2 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, catheter ablation therapy, surgery or ICD. The latter two options apply to a very small patient group with specific pathology that is amenable to these treatments. Drugs will treat by far the majority of patients. Class I antiarrhythmic drugs increase SCD¹⁷, and there are inconsistent results using *d*-sotalol as seen in the SWORD and ESVEM trials.^{18;19} Beta blockers may improve survival in patients with chronic heart failure²⁰. Of antiarrhythmic agents Class III drugs such as amiodarone have been shown to have the best efficacy profile and are very commonly used. A meta-analysis of the effects of amiodarone showed that it reduced total mortality by 10%-19% (95% CI: 6%, 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%, 22%, $p = 0.3$) and a 29% reduction in arrhythmic deaths (95% CI: 15%, 41%, $p = 0.0003$).²² However, typically around 25% of patients have needed to withdraw from treatment because of side effects. Most of these are not fatal, but an excess risk of potentially fatal pulmonary toxicity of 1% has been reported.²²

2.3 Description of new intervention

ICDs are similar in size to a pacemaker (30-40cc in capacity), weigh <80 grams, and are placed under the skin in the pectoral region. The latest devices offer graded responses to a sensed ventricular arrhythmia (see Appendix 1). Anti-tachycardia 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 $\leq 1\%$.²³ Electrocardiogram 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 PES (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 1980²⁴, 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 USA.²

There have been no agreed UK guidelines for use of ICD. 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 10 per million population (for a typical Health Authority of 500,000 this represents approximately 4 annually). This practice is lower than other European countries and North America (See Table 2).

In addition, it has been suggested that there is a ratio of 1:1,200,000 of electrophysiologists to population size in the UK, compared to 1:274,410 in USA.²⁵ It has been suggested by some authors that a service, in order to maintain high quality, needs to be implanting around 10 ICD per year with additional need for full back up resources.²⁵

Table 2: Frequency and number of ICD implanted
(1998 data, J. Morgan personal communication)

Region/country	Estimated number of ICD inserted	Approximate ratio of ICD inserted to population
USA	16,900	169 per million
Germany	4,890	60 per million
Quebec Canada	175	48 per million
Denmark	140	27 per million
Sweden	180	23 per million
Australia	525	20 per million
Italy	1,010	20 per million
Netherlands	230	15 per million
Spain	645	15 per million
UK	645	10 per million
France	565	9 per million

3. EFFECTIVENESS

3.1 Methods for reviewing effectiveness

The methods of the rapid review are outlined in the research protocol (see Appendix 2). Sources of information, including databases searched and key search terms, can be found in Appendix 3.

Studies identified by the search strategy were assessed for inclusion through three stages (Appendix 3, 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. One reviewer extracted data from the included studies and assessed their quality; these steps were checked by a second reviewer. Any differences in opinion were resolved through discussion. Randomised controlled trials were quality assessed using the Jadad scale²⁶ and systematic reviews were assessed for quality using the criteria developed by NHS CRD²⁷ (see Appendix 4).

3.2 Quantity and quality of research available on effectiveness

One systematic review (see Table 3 and Appendix 5) and seven RCTs (see Table 3 and Appendix 6) met the inclusion criteria for the review.

In the systematic review of the outcomes from the use of ICDs¹⁵ 34 studies are cited, 3 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.

Table 3: Summary of review of the effectiveness of ICDs to reduce SCD.

Author, Year and Study Details	Results	Disbenefits
Hider (1997)¹⁵ Intervention: ICD v 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 less than 1%, lead displacement 1%-10%, infection less than 4%, wound problems 0%-16%, thrombosis 1%-16%, perforation less than 1%.

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.^{28;29}

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

Table 4: Summary of RCTs of the effectiveness of ICD vs medication to reduce SCD.

Author, Year and Study Details	Results	Disbenefits
Primary prevention of VT/VF		
<p>Moss (1996)³⁰ MADIT Multicenter Automatic Defibrillator Implantation Trial Intervention: Prophylactic ICD vs conventional tiered therapy (anti-arrhythmic drugs). 27 months follow-up. 47% transthoracic, 53% transvenous Subjects: MI three weeks or more before entry, with documented asymptomatic unsustained VT unrelated to MI, LVEF\leq0.35, with inducible VT not suppressed by procainamide, New York Heart Association 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</p>	<p>Absolute mortality: ICD: 15.8% Conventional therapy: 38.6%</p> <p>ARR: 22.8%. RR ICD arm: 0.46 (95% CI: 0.26, 0.82; P=0.009) RRR: 54%</p> <p>NNT= 5 (3 to 10)</p>	<p>Drug: 12/101 patients with adverse events, 5 unexplained syncope, 7 VT/VF, amiodarone discontinued in 46% patients</p> <p>ICD: 19 /95 patients with adverse events, 2 pneumothorax, 2 infection, 7 lead problems, 7 rhythm problems</p>
<p>Buxton(1999)^{31;32} MUSTT Multicenter UnSustained Tachycardia Trial Intervention: Conservative (ACE inhibitor and/or beta-blocker) or EPS guided treatment sotalol/propafenone, ICD/drugs, sequential therapy until VT no longer inducible. Transvenous. Median follow-up 39 months. Subjects: Coronary heart disease, nonsustained VT. LVEF<40% and EP diagnosed inducible sustained VT N=704</p>	<p>Absolute all cause mortality Control 48% EPG 42%</p> <p>ARR 6% RRR 13% NNT 17</p> <p>Total mortality in EPG arm (non-randomised comparison) ICD 24% Drug therapy 55% ARR 31%, RRR 56% NNT = 3</p>	<p>Complications occurred in 5 patients with inducible sustained VT (0.7%) non-fatal.</p>
<p>Bigger (1997)³³ CABG Patch Coronary Artery Bypass patch Trial Intervention: ICD vs usual treatment. Transvenous. Average 32 months \pm16 (SD). Subjects: Patients having CABG with LVEF <0.36 and abnormalities of signal averaged ECG N=900</p>	<p>Absolute mortality: ICD: 22.6% at 32 mths Amiodarone: 20.9% at 32 mths</p> <p>ARR in amiodarone group: 1.7% RR in ICD arm: 1.07 (P=0.64) NNH = 58 (14 to infinity)</p>	<p>Significantly different complications in ICD: 12.3% infection, 8.5% pneumonia, deep sternal wound infection 2.7% Control: 4.2% MI</p>
Secondary prevention (recurrent VT/VF)	Results	Disbenefits

<p>Zipes (1997)³⁴ AVID Antiarrhythmic Versus Implantable Defibrillator</p> <p>Intervention: Amiodarone or sotalol (n=509) vs ICD (n=507). Transvenous. 45 months, mean 27 months followup</p> <p>Subjects: Cardiac arrest survivors and/or symptomatic tachyarrhythmia N=1016</p>	<p>Absolute mortality: ICD: 10.7% (1yr), 18.4% (2yr), 24.6% (3yr) Amiodarone/sotalol: 17.7% (1yr), 25.3% (2yr), 35.9% (3yr). ARR: 7% (1yr) 6.9% (2yr), 11.3% (3yr).</p> <p>Relative reduction in total mortality (adjusted) in ICD arm: 37%±22% (1 yr), 24%±22% (2 yr), 29%±23% (3 yr). P value =<0.02 NNT = 9 (95% CI: 6 to 18)</p>	<p>Drug: 5% pulmonary toxic, 16% req thyroid replacement medication ICD: 19/507, 6 bleeding, 13 haematoma, 10 infection, 8 pneumothorax, 1 cardiac perforation.</p>
<p>Siebels (1993)²⁹ CASH Cardiac Arrest Study Hamburg (“preliminary results” only published) Intervention: (i) ICD (ii) Amiodarone (iii) metoprolol (iv) Propafenone Transthoracic pre 1990 Transvenous post 1990 11 months (propafenone arm deleted) and 24 months follow-up Subjects: Survivors of cardiac arrest N=230</p>	<p>Total mortality: ICD 11.5% Propafenone 29.3% Trial stopped.</p> <p>Absolute total mortality: ICD: 19.6% at 2 years Amiodarone/ metoprolol: 12.1% at 2 years ARR: 7.5% (P = 0.047). RRR: 37% NNT = 14 (6 to infinity)</p>	<p>Propafenone: 12/56 side effects, drug stopped</p>
<p>Connolly (2000)^{35;36} CIDS Canadian Implantable Defibrillator Study Intervention: ICD vs amiodarone First 33 transthoracic remaining 277 transvenous. 36-60 months follow-up. Subjects: Survivors of cardiac arrest, tachyarrhythmias with symptoms, with LVEF less than 35%. N=600</p>	<p>Absolute mortality: ICD: 23% at 5 yrs Amiodarone: 27% at 5 yrs</p> <p>ARR: 3.7% at 5 yrs RRR: 19.7% at 5 yrs with ICD (P=0.142)</p> <p>NNT= 24 (10 to infinity)</p>	<p>At 3 years: Amiodarone: 22% stopped, 19.6% pulmonary toxic, 5.1% hepatic, 8.8% thyroid, CNS 26% ICD: 5.1% infection, lead fracture 2.6%, 11.9% pulmonary toxic, 0.9% hepatic, 1.8% thyroid, 8.5% CNS.</p>
<p>Wever et al (1995)³⁷ Intervention: ICD vs tiered drug therapy. Transthoracic apart from 3 transvenous. 27 months follow-up. Subjects: Survivors of cardiac arrest N=60.</p>	<p>Absolute mortality: Early ICD: 14% at 2 years Conventional group: 35% at 2 years. ARR: 21% at 2 years</p> <p>RR of death in ICD arm: 0.27 (0.09 to 0.85; P=0.02) NNT = 5 (3 to infinity)</p>	<p>ICD: Migration of lead in 1 patient, infection in 1 patient Drug: 16/31 late ICD (15 pre-discharge)</p>

3.3 a) Assessment of effectiveness

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

Do ICD reduce total mortality?

Do ICD stop tachyarrhythmias?

Do ICD improve quality of additional life?

Evidence from secondary research

Hider's systematic review (CRD Quality Score 4/6)¹⁵ assessed 4000 abstracts and retrieved assessed and summarised 500 relevant articles. The review concluded that:

- 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 was 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 amongst 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.
- 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 to 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 (NNT 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.

Evidence from primary studies

Six studies found a favourable survival advantage for patients treated with ICD.

Randomisation reduced the effects of confounding and bias. General concern has been raised about the problems of evaluating ICD effectiveness by comparison to drug therapy rather than placebo. This is because many studies have found that between 40% to 70% of patients with ICD require anti-arrhythmic medication to suppress SVTs, 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, by raising defibrillator thresholds or interfering with the ability to detect VT or VF. As a placebo-controlled trial would be considered to be unethical, these limitations are probably unavoidable.

Primary prevention studies

- **MADIT**³⁰ (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 6 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 MI population and fewer than 10% of all cardiac related deaths.
- **MUSTT**^{31;32} (Jadad Quality Score 1/5). Conclusions drawn are that the population of patients in the trial (LVEF 40% or less, 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. The comparison between outcomes of those patients receiving ICD therapy compared to 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. Most patients discharged receiving anti-arrhythmic drugs were treated with class I agents. Greater use of class III agents may have improved outcomes amongst patients treated with anti-arrhythmic drug therapy thereby overestimating 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**³³ (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 LVEF <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 to AVID and MADIT. CABG may reduce the risk of SCD which may influence the results.

Secondary prevention studies

- **AVID study**³⁸ (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 criteria³⁹. This sub-study 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 crossover rate in the trial (33.7% ICD group receiving amiodarone and 24.3% amiodarone group receiving ICD at three years), which may have reduced the power of the study, and compromised the intention to treat (ITT) analysis. Comparison of a drug (subject to compliance issues) and a device (whose interaction is involuntary and requires removal, which is more difficult and measurable) may also make ITT analysis less appropriate. Although subgroup analyses showed that these treatment imbalances had no statistically significant effect on the outcome, some

concern remains that some of the survival benefit from ICD may have been due to beta-blocker therapy (or poorer outcomes in drug arm due to their more severe cardiac failure). Beta-blockers have been shown to be an effective treatment in patients post myocardial infarction, producing a 20% reduction in total mortality and a 30% reduction in arrhythmic deaths.⁴⁰

There are eight substudies based on AVID data at the time of writing, (7 published and one unpublished). The results of these that are not mentioned elsewhere in the text are summarised in Appendix 7.

Initial cost data have been communicated via personal communication and will be presented in the economic evaluation section (section 4.3).

- **CASH**^{29 28} This has only recently finished and the final results are not published at the time of writing although they were presented at the 1999 meeting of North American Society of Pacing and Electrophysiology. The 5-year results showed a continuing trend toward benefit from ICD compared to drug therapy. Comparison between metoprolol and amiodarone showed no difference in mortality, although this arm was underpowered. The role of a baseline EP study showed that those patients who had a cardiac arrest but no inducible VT/VF had a better outcome than those with inducible VT. 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 peri-operative risks may have led to an underestimate of true effect.
- **CIDS**^{35;36} (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 crossover plus the rate of beta-blocker treatment, (30% of ICD patients receiving beta-blockers at 5 years compared with 22% of patients receiving amiodarone), 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 confidence intervals on effect size may indicate that these differences in relative risk reductions between the trials are due to chance. Authors state that the true benefit probably lies between the two values (20% and 29% RRR). Quality of life data and cost data have not yet been published.
- **Wever et al**³⁷ (Jadad Quality score 2/5, see Appendix 3). In this small study, the randomisation method is not reported, reducing the overall quality of the trial. The use of Class I antiarrhythmics 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 over estimate 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 is present in the public domain only as a conference proceeding.⁴¹ It showed a strongly significant benefit of ICDs, with a RRR 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 a LVEF of less than 35% had a marked benefit from ICD and patients with LVEF \geq 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.

b) 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.¹⁵

Peri-insertion complications

- **Mortality.** This is now reported to be less than 1% with transvenous compared to 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 dislodgment** This is related to the experience of the operator implanting the ICD, and is the most common of the peri-operative 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 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 to 16% in 9 studies) assessed in his review. This may be due to differences in definitions between studies. The use of concurrent anticoagulation, 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%). Consensus from the literature is that whilst 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 to 40), and has led to considerable variation in reported frequency (0% to 43%).¹⁵ 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 later. Hider found that literature suggests that 10 to 30% of recipients receive inappropriate shocks per year. 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 (OR 7.3). Hyperthyroidism is statistically more common in patients receiving amiodarone than those receiving placebo in controlled trials (OR 2.5). Thyroid dysfunction along with peripheral neuropathy (OR 2.8), bradycardia (2.6), liver dysfunction (OR 2.7) and lung infiltrative disease (OR 3.1) are major adverse experiences associated with early permanent drug discontinuation in placebo controlled trials.²²

c) Effects on quality of life

There are few quality of life studies, and those from recent RCTs are not all published.

Quality of life data from three of the effectiveness RCTs are in the public domain, one published⁴² and two unpublished (AVID, MADIT). The CABG Patch Trial showed that patients in the ICD group at six months had lower levels of psychological well-being, reported feeling less healthy and had reduced physical and emotional role functioning compared to 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.⁴³ 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.⁴⁴

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.⁴⁵

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 8 for details of relevant ongoing studies).

A literature review which includes qualitative studies, examined the psychosocial impact of ICD found 5 studies with pre and post assessment of psychosocial adjustment in recipients of ICD and 18 studies of post implantation assessment.⁴⁶ 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 for example, 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 over one year.⁴⁷ Anxiety about the ICD firing was closely linked to occurrence of depression, as was avoidance of activities.⁴⁷ Psychosocial adjustment risk profiles indicate that younger ICD recipients (< 50 years) and those with high discharge rates may experience the most adjustment difficulties.⁴⁸

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

In one study 62% 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 ICD and a similar group with coronary artery disease found that the quality of life did not differ between the groups, patients with ICD being less anxious. However with increasing number of shocks the percentage of psychologically distressed patients rose from 10% to >50%, with patients having lower quality of life scores.⁴⁹

4. ECONOMIC ANALYSIS

4.1 Methods for reviewing 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.⁵⁰

4.2 Quantity and quality of research available on cost-effectiveness

Ten cost-effectiveness studies were identified. Details are shown Appendix 9 and Table 5.

Table 5: Summary of cost-effectiveness studies of ICD

Author, Year and Study Details	Method of evaluation	Marginal effectiveness of ICD (years of life saved)	Marginal cost-effectiveness per year of life saved
Kuppermann (1990) ⁵¹ USA Intervention: ICD vs antiarrhythmics. Transthoracic implantation. Subjects: Cardiac arrest survivors, inducible VT/VF.	Markov model	+1.9 years	\$17,100
Larsen (1992) ⁵² USA Intervention: ICDs vs amiodarone vs conventional antiarrhythmics. Transthoracic. Subjects: High risk patients from past history of recurring arrhythmia	Modeling	+2.2 years	\$39,400
O'Brien (1992) ⁵³ UK Intervention: ICD vs amiodarone. Transthoracic. Subjects: Cardiac arrest survivors.	Markov model	+1.7 years	£15,400
Kupersmith (1995) ⁵⁴ USA Intervention: ICD vs antiarrhythmics. Transthoracic. Subjects: Cardiac arrest survivors, patients with VT/VF.	Markov model	+1.72 years	\$25,700
Wever (1996) ⁵⁵ Netherlands Intervention: ICD vs antiarrhythmics transthoracic. Subjects: cardiac arrest survivors.	Markov model		\$11,315
Owens (1997) ⁵⁶ USA Intervention: ICD vs amiodarone vs amiodarone to ICD. Transvenous. Subjects: 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) ⁵⁷ Intervention: ICD vs antiarrhythmics. Transvenous and transthoracic. Subjects: 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 (2000) ⁵⁸ Canada unpublished data from conference abstract Intervention: ICD vs amiodarone. Subjects: Survivors of cardiac arrest, tachyarrhythmias with symptoms, with LVEF less than 35%.	Clinical trial (CIDS)	0.23 years	CA\$213,543 (US\$ 146,180, UK £93,000) sensitive to longer follow-up with suggested improved cost-effectiveness of ICD
<i>Guidant Ltd 2000 Unpublished commercial in confidence</i>			
<i>Medtronic (2000) Unpublished, commercial in confidence</i>			

Secondary Research

Stanton. A literature review of cost-effectiveness of implantable cardioverter defibrillator therapy in the management of ventricular fibrillation and tachycardia has been published⁵⁹ (CRD Quality Score 2/6). Secondary synthesis of data has been performed (see Table 6). 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 antiarrhythmic 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.

Table 6: Summary of secondary cost-effectiveness analysis (Stanton)⁵⁹

Economic analysis	Break even (year)	ICD follow-up /Life Expectancy (years)	Savings \$*	Incremental cost per LYS \$ base case
Wever	1.0	2.4 follow-up	33,733	
Mushlin **	2.9	3.7 follow-up	8928	28,751
Kupermann**	2.9	5.1 life expectancy	54,426	32,910
Kupersmith **	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.

*If the average patient on antiarrhythmic drugs survived as long as the average patient implanted with ICD

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

4.3 Assessment of cost-effectiveness

- 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, although Owens⁶⁰ 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 and Mushlin^{55;57}) data were collected retrospectively and so the two populations used may not be comparable.
- In the MADIT cost-effectiveness analysis⁵⁷ 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 tacharrhythmias 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 shorter battery life, higher insertion costs and higher incidence of complications.

- Owens⁶¹ and O'Brien⁵³ have attempted a cost-utility analysis, deriving a cost for ICD per quality adjusted life year.
- The generalisability of these studies is limited. This is because most used USA cost data and USA 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 lower cost-effectiveness ratio. Kupersmith⁵⁴ found it more cost effective to implant ICDs in patients with a better LVEF because more people would die in the poorer LVEF fraction regardless of the intervention. Owens⁶¹ 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.⁶¹ (See Table 7). 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, whilst 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.⁶²

**Table 7: Marginal cost-effectiveness of ICD - sensitivity analysis⁶¹
ICD only regimen compared with amiodarone only regimen**

	RRR 40%	RRR 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 lifetime costs are expressed in 1995 USA dollars
RRR - is the reduction in total mortality from ICD relative to amiodarone therapy

- A cost analysis model using UK cost and observational study data published in 1993⁶³, 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 p.a. 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 technical 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/year of life saved (out to 3 years) was estimated at approximately \$125000/yr. (Personal communication, Hallstrom, 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 over estimate as the trial was terminated early at three years.
- *In the new UK [Guidant model commercial in confidence]*
- *The Medtronic model [commercial in confidence]*

4.4 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 one year; 81.6% compared with 74.7% at two years; and 75.4% compared with 64.1% at three years. Using survival curve analysis, this equates to 20 additional years of life for every 100 patients treated for three years with ICD (see Appendix 11, Table 11a).

Quality of life data from the AVID trial await publication but quality of life has been estimated. Expert clinical opinion 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 11, Table 11c). 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 antiarrhythmic drug therapy and ICD therapy cohorts.⁵¹

4.5 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 BNF (1999) and are shown in Table 9. Total costs are calculated for treatment with amiodarone and with ICD over a 3 year period, with and without discounting at 6%.

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*	22000	14688	12500
Hospital stay	2135	1220	2205
Hospital overheads	62	65 (included)	
Cost per Case	24596	16372	15155
Ongoing Costs per year			
5 outpatient visits annually	300	300	1035
Readmissions 0.5 per patient per year @ 3 days	1065	1065	440
Adjunctive therapy	190	190	190
Total ongoing costs per year	1555	1555	1665
Total Cost first year	26151	17927	16820
Total Cost for 3 years	29261	21037	20150
Discounted @ 6% over 3 years	29,000	20,800	19,700

*Range of costs due to variation in sophistication of ICD and hospital contracts.

Table 9: Amiodarone-associated costs

Amiodarone 400mg od	190
8 outpatient visits annually	480
Readmission 7 days 6 times annually	2562
1 emergency resuscitation	850
Total Cost first year	4082
Total cost for 3 years	12246
Discounted @ 6% over 3 years	11600

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

4.6 Estimated costs to NHS

Table 10 compares the estimated cost to the NHS if various criteria for the use of ICD were to be followed, and ranges from £12 million to £100 million.

The American College of Cardiology and American Heart Association guidelines^{64;65} for the Implantation of ICD are shown in Appendix 10. This illustrates the basis for the hundreds of millions of dollars that are expended annually on ICD in USA.

Table 10: Estimated cost to the NHS of ICD use in different patient groups

Patient group / trial	Approximate number of patients in the UK per annum	Approximate cost if device available to all eligible patients	Approximate number of patients reduced by 25% (50%)**	Approximate cost if device available to 25% (50%) fewer patients
All survivors of cardiac arrest	4000*	£100 million	3000 (2000)	£75 million (£50 million)
AVID trial ³⁴	1000	£24.1 million	750 (500)	£18 million (£12 million)
MUSTT trial ³²	1400	£50 million	1050 (700)	£37.5 million (£25 million)

Adapted from Anderson and Camm 1993⁶³ (using 1998 average costs).

* Based on 8.3 survivors of cardiac arrest per 100,000 people.

** 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).

4.7 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 three 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 £8,400 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 11.

5. 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 trial⁶⁶, 52% of patients presenting to CCU with sustained ventricular arrhythmia not related to MI 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 CCU 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 NNT of 9 is taken (that is for every nine people treated with ICD one life is saved) and current costs of ICD are between £20,000 and £29,000 (excluding replacement costs), then an investment per typical Health Authority would be between £180,000 and £261,000 per life saved (or an additional £75,600 to £156,600 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 amongst the medical services who may not have sufficient knowledge of ICD and its indications, may lead to eligible patients not receiving ICD. The very long waiting times to see cardiac electrophysiologists/specialist cardiologists also result in reduced uptake of ICD therapy. 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 in order to implement any increased rate of implantation of ICD.

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. Also the recent national initiative to provide external defibrillators for resuscitation within the community, increasing paramedic ambulances and trained members of the public, may contribute to an increase.

6. CONCLUSION

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

By addressing the objectives stated in the protocol (see Appendix 2) we have addressed the following policy-relevant questions:

a) 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 as compared to 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 ranges from 0.23 to 2.2 years of life saved.
- Cost per life year saved may vary from £32,400 to £69,600 per year of life saved. (From the literature from a saving of \$11,315 to CA\$213,543 per year of life saved.)
- Cost per QALY is calculated 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 appears to be no advantage of one make of ICD over another.
- The recent advances in dual chamber devices offer advantages to a possible 50% of patients eligible for ICD therapy.

b) 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 sudden cardiac death due to ventricular tachyarrhythmias. The evidence for this is derived from RCT which have compared first line use of ICD therapy vs first line use of drug therapy.

c) 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 RCT (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 $\leq 40\%$.
- The subgroups of patients that may benefit from ICD therapy identified by 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 VT on EPS,
 - patients post MI with unsustained VT, LVEF $\leq 35\%$ with inducible VT not suppressed by procainamide with no indications for coronary artery surgery within 3 months.
- The optimal strategy for the identification of subgroup of patients who could benefit from ICD is not clearly established. LVEF $< 35\%$ 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 which may have implications for those sub-groups of patients in whom ICD are effective.
- Patients with rarer conditions such as long QT syndrome, Brugada syndrome and hypertrophic cardiomyopathy have been shown to benefit from ICD.

7. COMMENT

7.1 Statement of Principal Findings and Implications

The main findings of the rapid review of ICDs are:

Sudden cardiac death 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 RRR 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 consistently clinically relevant effectiveness in those patients that 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 NHS. In 1998 the American College of Cardiology issued guidelines for implantation of ICD, which considerably widened the indications for ICD treatment.⁶⁵ 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 1999 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 numbers 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.^{14;67} Similarly, signal activated ECG has not been found to be helpful. Modelling work by Owens team^{60;68} 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 sub-studies cited in section 3.3 have explored 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 utilitarian approach (greatest good for greatest number) and 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.

7.2 Strengths and Limitations of the review

The rapid review has certain strengths including:

- i) 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.
- ii) 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.
- iii) 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, specifically:

- i) 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.
- ii) The quality of the RCTs was assessed using the Jadad scale. Although the Jadad scale includes key elements by which to assess the quality of RCTs, including randomisation, blinding and withdrawals/dropouts, it could be criticised for excluding other elements that may cause bias (eg. not including the level of

withdrawal/dropout). It has also been pointed out that the Jadad scale “gives more weight to the quality of reporting than to actual methodological quality”.^{26;27}

- iii) 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.

7.3 Implications for Research

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

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 randomised controlled trial 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 (BPEG) registries to monitor the diffusion and effectiveness of different types of ICD and current service use. BPEG registries could be used to supply epidemiological data and data to inform natural history of underlying conditions in the UK.

The Health Technology Assessment programme has prioritised a systematic review of the literature to assess the cost-effectiveness of ICD v 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 to 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.

8. ACKNOWLEDGEMENTS

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The report remains the responsibility of The Rapid Reviews Team, National Coordinating Centre for Health Technology Assessment, University of Southampton.

9. AUTHORSHIP

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10. APPENDICES

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 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.⁶⁹ 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 nonthoracotomy leads in the pectoralis region. Continued developments are likely to produce lower-output and smaller devices. However, there is concern that with smaller devices, there may be less efficient capacitor charging.

One randomised controlled trial which compared two transvenous defibrillator models found no statistically significant difference in the ventricular fibrillation detection times between a dual chamber type and control device.⁷⁰ The study concluded that the dual chamber model had a similar effectiveness to sense, detect and treat ventricular fibrillation 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 study⁷¹ 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 randomised controlled trials which compare ICD 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 sudden cardiac death, although potential indications for dual chamber are still controversial. A retrospective study⁷² on the potential usage of dual chamber pacing has been conducted which analysed all patients who received a nonthoracotomy ICD at the Mayo clinic from March 1991 to October 1996 in order to determine the proportion of patients in whom a dual chamber pacing ICD may be indicated. Definitions used were: i) definitely indicated = pacemaker present at ICD implant or NASPE Class I pacing indication; ii) probably indicated = NASPE Class II pacing indication, NYHA Functional Class III or IV, or history of systolic congestive heart failure; iii) possibly indicated = history of paroxysmal atrial fibrillation or ejection fraction $\leq 20\%$. 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: Rapid review methods from the research protocol

Full Title of Research Question

- The clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators in people with arrhythmias.

Objectives/Purpose of review

- The aim of the review is to provide a rapid review of the clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators v conventional therapy in patients at risk of sudden cardiac death from arrhythmias. All types of implantable cardioverter defibrillators will be considered.
- Evidence of clinical and cost-effectiveness which distinguishes between types of implantable cardioverter defibrillator will be reviewed.
- By addressing these objectives we hope to provide answers to the following policy-relevant questions:
 - d) are ICDs effective (or cost-effective) in reducing mortality, preventing tachyarrhythmia and improving quality of life?
 - e) are ICDs more effective (or cost-effective) as first line therapy or in patients for whom drugs do not work?
 - f) can a subset of patients be identified for whom ICDs are more effective (or cost-effective)?

Report Methods

- The review will be undertaken as systematically as time allows, following the general principles outlined in NHS CRD Report 4.
- It should be noted that the research protocol will be updated as the research programme progresses. Any changes in the protocol will be notified to the NCCHTA.

Search Strategy

- Electronic databases that will be searched include: Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, NHS CRD (University of York) DARE and NHS EED, Medline (Silverplatter), PubMed, Embase and National Research Register. These will be searched for the period 1980 to 1999 and will be limited to English language studies and studies with an English language abstract. The Internet will also be used.
- Bibliographies of related papers will be assessed for relevant studies.
- Experts in the field will be contacted to identify additional published and unpublished references.
- Industry submissions to NICE. (Submissions have been requested from ELA UK, Medtronic, St Jude Medical, Biotronik and Guidant.)

Inclusion Criteria

Interventions

- Implantable cardiac defibrillators compared with conventional therapy (such as anti-arrhythmic drugs, catheter ablation or surgery).

Participants

- People at high risk of sudden cardiac death usually due to ventricular tachyarrhythmia.

Study Designs

- Systematic reviews, meta-analyses and randomised controlled trials comparing ICDs with conventional therapy. These will include published evaluations of cost-effectiveness.

Types of Outcome Measure

- Three main patient outcomes to be assessed are reduction in mortality, prevention of tachyarrhythmias and improved quality of life.

Data Extraction Strategy

- Data extraction will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Quality Assessment Strategy

- Included studies will be assessed using the critical appraisal criteria and standard checklists such as those developed by the Critical Appraisal Skills programme (CASP) and CRD.
- Primary studies will be scored using the Jadad et al (1996) scale and secondary studies will be scored using the CRD Review Score scale.
- Quality assessment will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Methods of analysis/synthesis

- Narrative review with full tabulation of results of all included studies. Formal meta-analysis will not be undertaken because of lack of time.

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

- Quality of life information to estimate Quality Adjusted Life Years (QALYs) will be obtained from the literature and consultation with experts.
- Costs will be sought from Southampton General Hospital (a Regional Centre) and at least two other centres in England.
- Cost/QALY will be estimated by combining effectiveness information from the trials and QALYs. Sensitivity analysis will be performed to determine how robust estimates are to the assumptions made.

Appendix 3: 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

Cochrane Library 1999 no 3
Medline 1980-1999

Embase 1980-1999

BIDS Science Citation index

National Research Register

Gears

International Network of Agencies for Health technology Assessment

NHS Electronic Economic Database

Mesh terms used

implantable cardiac defibrillator, implant* defib* (ft)
implant* defib* (ft), ventricul* Arrhythm*(ft), cardi*
arrest*(ft) defibrillators implantable(mh), ventricular
fibrillation(mh), heart arrest(mh), quality of life (mh),
clinical trial (pt), english (lg).

as Medline

as Cochrane

implant* and defibrill*, sudden cardiac death, vent*
arrhy*

To identify randomised-controlled trials, the Lefebvre strategy was used.

To identify economic evaluation the CRD high sensitivity strategy was used⁷³.

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.

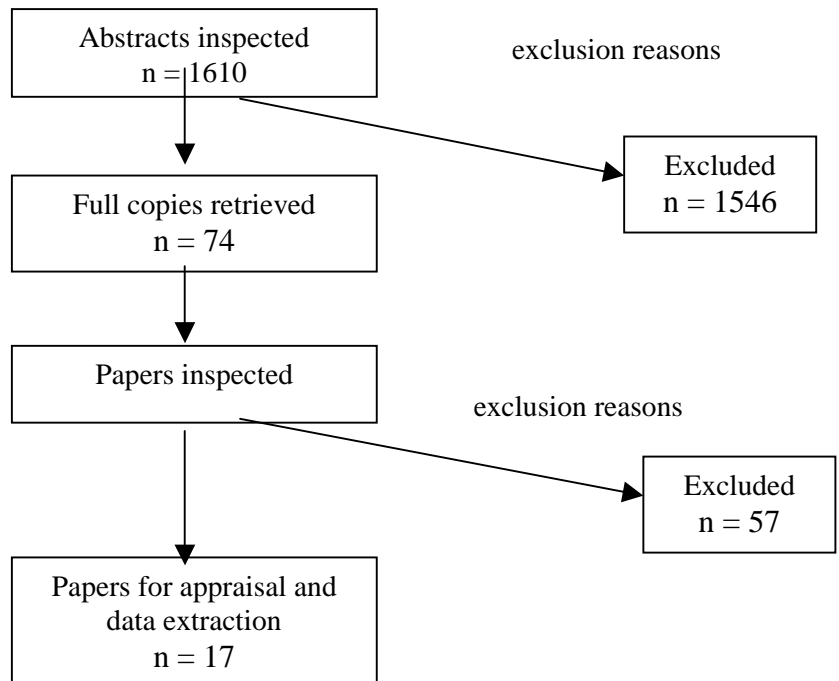
Studies were graded according to the level of evidence. Due to limitations of time, only those studies of higher level of evidence, systematic review, meta-analysis and randomised controlled trial, were located and appraised. Economic evaluations have been located and appraised.

Authors of two retrieved RCT (Zipes, Hallstrom, and Connolly) and one ongoing trial (Hlatky) were contacted to answer queries or to seek further information/data.

Critical appraisal of retrieved studies was performed using checklists developed by the Critical Appraisal Skills programme (CASP) and NHS CRD.

Inclusion criteria for studies were that they were in English, and the methodology conformed to higher levels of evidence.

Figure 1: Flowchart of Identification and Inclusion of Studies for ICD Review



Appendix 4: Methods for assessing the quality of systematic reviews and RCTs.

(a) Criteria for assessing good quality systematic reviews²⁷

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, health care 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

(b) Instrument to Measure the Likelihood of Bias in RCTs²⁶

1. QUESTIONS TO ASSESS THE LIKELIHOOD OF BIAS

1. Was the study described as randomised (this includes the use of the words such as randomly, random and randomisation)?

2. Was the study described as double blind?

3. Was there a description of withdrawals and dropouts?

Scoring the items:

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

Give 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 (eg. comparison of tablet vs. injection with no double dummy).

2. GUIDELINES FOR ASSESSMENT

1. 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.

2. Double blinding*

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

3. Withdrawals and dropouts

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

* 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.

Appendix 5: Systematic review of effectiveness of ICD

Reference	Research Question	Inclusion Criteria	Search Strategy
<p>Hider¹⁵ 1997 NZ HTA</p> <p>NHS CRD Quality Score: 4/6</p>	<p>To determine health outcomes from the use of implantable cardiac defibrillators, including effectiveness, comparison to other therapies, identification of patients who would most benefit, and cost-effectiveness.</p>	<p>Descriptive, observational, and RCT reviewing the efficacy, cost-effectiveness, indications or complications related to the use of ICD.</p> <p>Sample size ≥ 50</p> <p>Follow-up period ≥ 3 months</p> <p>Trial gave explicit description of study design, results and analysis.</p> <p>Intention to treat analysis in RCT was performed.</p> <p>English language.</p> <p>All articles examining the indications or prioritisation for ICD were reviewed.</p>	<p>Medline and Embase were searched from 1993 using an explicit strategy. Cochrane Library and INAHTA database were searched using an explicit strategy.</p> <p>Relevant sites on the Internet were searched using the same terms.</p>
<p>Results</p> <p>ICD consistently shown to be effective at terminating ventricular arrhythmias and therefore reducing the incidence of SCD in recipients.</p> <p>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 endpoint further limit the results of these studies.</p> <p>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 amongst 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.</p> <p>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.</p> <p>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 to alternatives. In addition some authors suggest the cost-effectiveness of the ICD compares favourably with many other established treatments for other conditions.</p> <p>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.</p> <p>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 tacharrhythmias on basis of spontaneous or inducible arrhythmia, without an arrest, who are not eligible or failed other medical or surgical treatments and who usually have underlying ischaemic heart disease and/or a low LVEF.</p>			
<p>Comments</p> <p>The review contains a methods section identifying the finding of relevant trials and assessment of validity.</p> <p>Explicit methods were used to determine which articles to include.</p> <p>Selection and assessment of primary studies is reproducible and free from bias.</p> <p>Quality of studies was appraised using valid, explicit schedules.</p> <p>Differences in individual studies were adequately explained.</p> <p>Reviewers conclusions were supported by the data cited.</p> <p>Results were not combined.</p> <p>Generalisability limited by the predominance of North American studies especially in cost-effectiveness studies.</p> <p>The review has not been widely peer reviewed.</p> <p>Unpublished research was not searched for.</p>			

Appendix 6: Randomised controlled trials of ICDs – primary prevention trials

Reference and Design	Intervention	Subjects	Outcome measures
<p>Moss³⁰ 1996 Multicentre Automatic Defibrillator Implantation Trial (MADIT) prospective RCT randomisation stratified according to interval between most recent MI and enrolment (≤ 6 months or ≥ 6 months) and according to centre.</p>	<p>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.</p>	<p>Patients with MI three weeks or more before entry, with documented asymptomatic unsustained VT unrelated to MI, with a left ventricular ejection fraction ≤ 0.35, with inducible VT on electrophysiological study not suppressed by procainamide, and were in New York Heart Association functional class 1,1,1,1 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).</p>	<p>All cause mortality 5 year follow-up average length of follow-up 27 months.</p>
<p>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 were 12% vs 27% in ICD group and conventional medical therapy group respectively RRR =0.57 ARR = 15%. Regression analyses revealed no evidence that antiarrhythmic medication or other cardiac medication being given one 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. 5 of the ICD group did not receive ICD and two were inactivated. Therapy related adverse events reported- 12 with conventional therapy 19 with ICD.</p>			
<p>Comments Randomisation method not reported. Intention to treat analysis performed and all patients accounted for. There were a higher number of beta-blockers in the ICD group: 30% compared to 8.6% at one month and 31% versus 6% at last contact. Similarly a higher number of patients on digoxin in ICD group: 62% versus 41% at one month and 66% versus 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 antiarrhythmic drugs for underlying SVT or cardiac problems and these may interfere with the proper functioning of the ICD.</p>			
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 dropouts?	1		
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	3 patients lost to follow-up (2 conventional, 1 ICD)		

Appendix 6: Summary of randomised controlled trials of ICD – Primary prevention trials (contd)

Reference and Design	Intervention	Subjects	Outcome measures
Buxton ^{31,32} 1999 MUSTT (Multicentre un Sustained T achycardia T rial)	Randomised to conservative treatment (ACE inhibitor and/or beta-blocker) or EP guided therapy tiered and sequential drug /drug/ICD/drug	Coronary heart disease, LVEF less than 40%, nonsustained VT, inducible sustained VT on EPS	Primary cardiac arrest or arrhythmic death Secondary total mortality
Results			
<p>The enrolled patients with nonsustained 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 (ACE inhibitor and or beta-blocker), 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.</p> <p>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.</p> <p>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 and RRR 23%. ARR 7% at 5 years.</p> <p>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.</p> <p>The cardiac death rate at 60 months was 34% vs 40% in intervention and control respectively. RRR 15% ARR 6%</p> <p>Spontaneous sustained VT at 60 months was 20% vs 21% in intervention and control respectively p=0.9 RRR 5% ARR 1%.</p> <p>Death from cardiac arrest/ arrhythmia in intervention arm was 9% vs 37% in patients with ICD therapy compared to those not receiving an ICD p=< 0.001 RRR76% ARR 28%.</p> <p>All cause death at 60 months in intervention arm was 24% vs 55% in those patients receiving ICD therapy compared to those who did not RRR 56% ARR 31%.</p> <p>Adjusted relative risk of arrhythmic events in patients in intervention arm receiving ICD compared to those who did not is 0.24 (95% CI 0.13 to 0.45), and an adjusted relative risk of overall mortality of 0.40 (95% CI 0.27 to 0.59).</p> <p>The secondary outcome of total mortality did not reach statistical significance although the trend was toward better performance in the intervention group.</p> <p>Subgroup analysis patients receiving ICD performed better than any other group-92% alive at 60 months, and when this group removed from the antiarrhythmic group, no significant difference between conservative group and anti-arrhythmic drug group.</p>			
Comments			
<p>This was a trial of electrophysiological guided therapy versus no anti-arrhythmic therapy (apart from beta blockers). The comparison between outcomes of those patients receiving ICD therapy compared to 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.</p> <p>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.</p> <p>The study supports the conclusion it draws that the population of patients in the trial (LVEF 40% or less, 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.</p> <p>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.</p> <p>The guided therapy patients frequently ended up with an ICD when EPS testing did not reveal an anti-arrhythmic drug that suppressed the inducible VT.</p>			
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 dropouts?	nk		
What proportion of sample (intervention and control groups separately) withdrew or dropped out?			

Appendix 6: Summary of randomised controlled trials of ICD – Primary prevention trials (contd)

Reference and Design	Intervention	Subjects	Outcome measures
Bigger ³³ 1997 Coronary artery bypass patch trial CABG PATCH 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 less than 80 years, left ventricular ejection fraction of less than 0.36, and had abnormalities on signal averaged ECG. Patients excluded if sustained VT or VF, poorly controlled diabetes, life expectancy of less than 2 years. n=900, 446 to ICD group and 454 to control	Overall mortality Average follow-up 32 ± 16 months(SD)
<p>Results</p> <p>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).</p> <p>Regression model stratified according to LVEF and clinical centre yielded hazard ratio of 1.02 (0.76 to 1.35).</p> <p>Separate Cox regression analyses with each of 10 prospectively identified covariates showed no significant interaction with ICD.</p> <p>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.</p> <p>After 4 years of follow-up actuarial mortality in ICD 27% and 24% in control (p=0.64)</p> <p>57% of patients with ICD received a shock within the first two years after implantation.</p> <p>Significantly more post-operative infections were reported in ICD group and more MI in long term follow-up in control group.</p> <p>At 42 months cumulative rate of crossover to the control group was 10%, and the cumulative rate of crossover to the ICD group was less than 5%.</p> <p>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.</p>			
<p>Comments</p> <p>Randomisation method reported</p> <p>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.</p> <p>Intention to treat analysis was performed and all patients randomised accounted for.</p> <p>Groups treated equally apart from the intervention.</p> <p>Groups appear to be similar at baseline especially in beta blockade which is less for the ICD group than the control.</p> <p>Patients recruited into trial represent a high risk group but compared to AVID trial (actuarial mortality at 24 months 24%) and MADIT (32%) and CABG Patch (18%) sample was lower risk.</p> <p>Inclusion criteria for CABG Patch was ECG abnormalities and not 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.</p> <p>It may be that CABG decreases the risk of sudden death.</p> <p>The use of German and USA hospitals limits the applicability of the results to the UK.</p>			
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 dropouts?		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 less than 5%.	

Appendix 6: Summary of randomised controlled trials of ICD – Secondary prevention trials

Reference and Design	Intervention	Subjects	Outcome measures
AVID³⁴ The Anti-arrhythmic Versus Implantable Defibrillators Investigators 1997 multicentre prospective RCT	ICD or class III drugs (further randomisation to sotalolol or amiodarone in the drug arm if no contra-indications to sotalolol)	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 left ventricular ejection fraction of 0.40 or less. N = 1017 (507 ICD) 153 of drug arm further randomly assigned-79 to amiodarone and 74 to sotalolol.	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)
<p>Results</p> <p>Reductions in mortality (unadjusted) with ICD 39 (95%CI: 19, 59) at 1 year, 27 (95%CI: 6, 48) at 2 years and 31 (95%CI: 10, 52) at three years.</p> <p>Absolute mortality: ICD 10.7% (1 yr), 18.4% (2 yr), 24.6% (3 yr); drugs 17.7% (1 yr), 25.3% (2 yr), 35.9% (3 yr). Overall survival (unadjusted) 89.3 % in ICD versus 82.3 % in drug arm at one year, 81.6% versus 74.7% at two years, 75.4% versus 64.1% at three years (P= ≤ 0.02)</p> <p>Average adjusted length of additional life associated with ICD was 2.7 months at three years Nine people would need to be treated for three 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 one year 59.5% of ICD and 55.6% of drugs rehospitalised At three years 83.3% of ICD and 75.5% of drugs rehospitalised. 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 two years. Bleeding requiring transfusion or reoperation in 6 patients in ICD group and serious haematomas in 13. 9 patients had insertion problems (pneumothorax, cardiac perforation) 10 patients had infections. Quality of life results (unpublished conference abstract data): ≥1 vs 0 shocks Short Form-36 Mental Score -1.96 (95% CI -3.81, -0.12; p<0.05), Patient concerns quality of life 1.47 (95% CI 0.39, 2.54; p<0.05). ≥3 vs <3 shocks SF-36 Mental Score -4.91 (95% CI -8.06, -1.76; p<0.001), Patient concerns quality of life 2.16 (95% CI 0.15, 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.</p>			
<p>Comments</p> <p>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</p>			
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 dropouts?	1		
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	3 patients dropped out		

Appendix 6: Summary of randomised controlled trials of ICD – Secondary prevention trials (contd)

Reference and Design	Intervention	Subjects	Outcome measures
Siebels ²⁹ 1993 Cardiac Arrest Study Hamburg CASH Prospective multicentre RCT	Randomised to receive amiodarone (loading dose 1000mg/day for 7 days and 400-600mg/day after day 8), metoprolol (initial dose 12.5-25 mg /day up to 200mg/day as tolerated), propafenone (450mg/day initially to 900mg /day as tolerated) or trans thoracic 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 of 2 years follow-up
<p>Results</p> <p>No significant difference at 11 months in total mortality among those patients on amiodarone, metoprolol and ICD. Significant higher mortality in propafenone arm compared to ICD (12% SCD and 23% SCD or cardiac arrest on propafenone versus 0% in ICD. P=0.05).</p> <p>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 when compared to the ICD arm (29.3% versus 11.5%, respectively, P = 0.0121, relative risk 2.61, 95% confidence interval, 1.1-7.6). Enrollment into the propafenone arm was discontinued at that time.</p> <p>Final results were analyzed 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 (CAD). There was a 7.5% reduction in overall mortality among those assigned to the ICD treatment arm (12.1% versus 19.6%) when compared to those receiving amiodarone or metoprolol (P = 0.047). The mortality data comparing amiodarone and metoprolol were similar.</p> <p>There was a significant decrease in SCD in patients treated with ICD when compared to medical management (2% versus 11%, P < 0.001).</p> <p>Patients receiving the transvenous ICD systems had an overall better survival rate compared to those receiving epicardial systems (P = 0.037), because mortality-related transvenous placement was significantly lower than that associated with open thoracotomy.</p>			
<p>Comments</p> <p>The propafenone arm of this trial was discontinued due to the excessive number of sudden deaths.</p> <p>No randomisation method mentioned, but groups appear similar at baseline.</p> <p>Recruitment duration was very long 1987-1996. 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.</p> <p>Patients assigned to ICD received a transthoracic device if enrolled before July 1990 and transvenous lead system if enrolled after July 1990.</p> <p>Preliminary data only is published although a 2-year 39% reduction of all cause mortality in the ICD arm compared with the drug arm recently presented at 1999 Annual Scientific Sessions of North American Society of Pacing and Electrophysiology.</p> <p>Use of a one tailed test to compare two treatment strategies prevents the testing of the potential deleterious effects of ICD.</p>			
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 dropouts?		nk	
What proportion of sample (intervention and control groups separately) withdrew or dropped out?			

Appendix 6: Summary of randomised controlled trials of ICD – Secondary prevention trials (contd)

Reference and Design	Intervention	Subjects	Outcome measures
Connolly ^{35,74} 1999 Canadian Implantable Defibrillator Study (CIDS) multicentre RCT	Randomisation to insertion of ICD (the first 33 via transthoracic route, remaining 277 via transvenous) or to treatment with amiodarone (1200mg/day for first week in hospital, followed by greater than or equal to 400mg/day for at least 10 weeks, followed by greater than or equal to 300mg/day for long term treatment.	Patients with documented VF, out-of-hospital cardiac arrest, presentation of VT at a rate greater than or equal to 150beats/minute causing presyncope or angina in the patient with left ventricular ejection fraction less than or equal to 35% or unmonitored syncope with subsequent documentation of either spontaneous or inducible VT. Patients excluded if MI less than 3 days prior to randomisation, intolerant of amiodarone or having received amiodarone of 6 weeks or more in the past. n=600 In ICD arm =310	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
<p>Results</p> <p>28% of patients receiving ICD were also receiving amiodarone. Of those in amiodarone group 22% had received subsequent ICD insertion.</p> <p>Beta blocker treatment was four times greater in patients randomised to ICD group compared to those in the amiodarone group.</p> <p>After 5 years of follow-up the patients randomised to ICD group had a 19.7% relative risk reduction in all cause mortality compared to those in amiodarone group (not statistically significant p=0.142). NNT 24. Relative risk reduction in arrhythmic death was 32.8% (not significant p=0.094). 23.3% mortality in ICD group compared to 27% in amiodarone group after 3 years of follow-up.</p> <p>Mortality difference was not affected significantly by subgroup analysis of age, entry criteria or LVEF.</p> <p>Complications of ICD therapy were infrequent. Infection 4.6%, lead fracture 2.4%. Transvenous approach improved peri operative mortality (0.3% 30-day mortality compared to 3.3% when using the thoracotomy approach).</p> <p>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 versus 19.6% in amiodarone group), thyroid (1.5% versus 8.8%), hepatic (0.9% versus 5.1%) and CNS (8.5% versus 26.0%) toxicity.</p>			
<p>Comments</p> <p>The primary outcome was changed in 1995 to all cause mortality.</p> <p>Cost analyses are not published and quality of life results not yet in public domain.</p>			
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 dropouts?		0	
What proportion of sample (intervention and control groups separately) withdrew or dropped out?		30% crossover to amiodarone, 22% crossover to ICD.	

Appendix 6: Summary of randomised controlled trials of ICD – Secondary prevention trials (contd)

Reference and Design	Intervention	Subjects	Outcome measures
Wever³⁷ 1995 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 or more 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 Left ventricular ejection fraction Duration of hospitalisation Changes in antiarrhythmic drug
<p>Results</p> <p>35% died in conventional therapy arm and 14% in ICD. 42% total number of main outcome events in conventional arm compared to 13.8% in ICD. All cause mortality relative risk 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.</p>			
<p>Comments</p> <p>Small number of patients in trial. Randomisation method not reported. Intention to treat 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 if effect of ICD. Generalisability may be limited.</p>			
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 dropouts?		1	
What proportion of sample (intervention and control groups separately) withdrew or dropped out?		4 patients died in ICD group, 11 patients died in conventional group.	

Appendix 7: 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 antiarrhythmic therapy, but a protective effect was not prominent in patients already receiving amiodarone or a defibrillator.⁷⁵ (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.)^{76 77}

Based on proportional hazards modeling, 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 a LVEF more than 27%, or a history of revascularisation.⁷⁸

When the LVEF was <35%, the benefit of ICD therapy compared with anti-arrhythmic drug therapy was considerably greater than if the LVEF was >35%. In patients with LVEF >35% there was no difference in survival between drug therapy and ICD therapy. The same size of benefit was seen in sub-groups LVEF <20% and the 20-34%. This difference in benefit was not statistically significant between the two groups. Further sub-dividing 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 who 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 which 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 whilst 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 8: 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
<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 electrophysiologically guided treatment which may be one or a combination of antiarrhythmic drugs or coronary revascularisation or ICD. QOL 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. 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 MI 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 are being presented at the NASPE conference on May 20th 2000. (personal communication Dr M Griffith, 10 May 2000).
- Sudden Cardiac Death in Heart Failure (SCD-HeFT) Trial. 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 antiarrhythmic 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 three to six months.
- MUSTT II
- 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 9: Summary of economic evaluations of ICD

Reference and Design	Intervention	Subjects	Outcome measures <i>Sensitivity Analysis</i>
<p>Kuppermann 1990⁵¹ Markov model data from literature (non RCT) expert opinion</p>	<p>ICD compared with drug therapy.</p>	<p>Survivors of cardiac arrest, not associated with MI and inducible VT/VF.</p>	<p>Effectiveness, initial hospitalisation cost, rehospitalisation, concurrent drug treatment with ICD.</p>
<p>Results 1.9 years of life saved in ICD group (5.1 compared to 3.2). \$17100 per life year saved (\$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.</p>			
<p>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. USA data limits generalisability.</p>			

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference and Design	Intervention	Subjects	Outcome measures <i>Sensitivity analyses</i>
Larsen⁵² 1992 Markov model Based on literature historical controls	ICD versus amiodarone versus conventional therapy (patients on anti arrhythmic drugs who still have inducible arrhythmia). Transthoracic implantation.	VT/VF patients aged 55 years n=64	<i>Life of device, QALY, efficiency of amiodarone</i>
<p>Results</p> <p>ICD most expensive alternative. Marginal effectiveness of ICD = 2.2 years of life saved. Cost-effectiveness ICD versus amiodarone \$39,400 per life year saved. Cost-effectiveness amiodarone vs conventional therapy \$8,900 per life year saved. Cost-effectiveness ICD vs conventional therapy £26,600 per life year saved. In sensitivity analyses 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 less than 65% of amiodarone, in order for amiodarone to be preferred over ICD therapy. Cost per YLS saved of amiodarone therapy to overstep that of ICD it would have to decrease in efficacy from 69% to 15%. 5% discount rate used.</p>			
<p>Comments</p> <p>USA data limiting generalisability. Old devices with transthoracic approach. Assumed no crossovers. Assumed each group identical apart from therapy.</p>			

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference and Design	Intervention	Subjects and model used	Outcome measures <i>Sensitivity analyses</i>
O'Brien ⁵³ 1992 Markov model	Incremental cost- effectiveness of ICD compared to amiodarone	Patients at high risk of SCD Model constructed from published data and other secondary sources. Differences in patient survival from two US studies	Cost-effectiveness of ICD over 20 years discounted at 6% Sensitivity analysis on alternate estimates of patient survival, initial cost of ICD implantation, alternative treatment assumptions e.g. Amiodarone costs, life span of ICD
<p>Results</p> <p>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 survive i.e. the size of the mortality benefit attributable to ICD.</p>			
<p>Comments</p> <p>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 LYG 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.</p>			

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference and Design	Intervention	Subjects and ICD technique used	Outcome measures and <i>sensitivity analyses</i>
Kupersmith ⁵ 4 1995 Markov model	Cost-effectiveness of ICD compared with EP guided drug therapy	High risk patients with VT/VF direct costs Mostly transthoracic	<i>Sensitivity analysis on perioperative mortality, battery life, resource use, effectiveness no pre-implant EP Consideration of only ICD or drugs</i>
Results			
<p>Device hardware is expensive (\$22,000). Mean increase in life expectancy with ICD 2.03 years and cost-effectiveness \$ 31,000 per YLS. Sensitivity analysis without the assumption that time of first shock would have been the time of death showed that cost increased only when less than 38% of first shocks equalled death. Patients with LVEF more than 0.25 had cost-effectiveness \$27 000 per LYG compared to \$44,000 per LYG with LVEF less than 0.25. Cost-effectiveness without EP studies \$18,000 per LYG. If ICD were used in lower risk/prophylactic indications, cost-effectiveness would be less favourable. 5% discount rate.</p>			
Comments			
<p>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. USA costs and data limiting generalisability.</p>			

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference and Design	Intervention	Subjects	Outcome measures and sensitivity analyses
Wever⁵⁵ 1996 Clinical trial	ICD compared with drug therapy Transthoracic approach	Survivors of cardiac arrest caused by VF/VT	Total mortality Factors reflecting QOL-exercise tolerance, major non-fatal events Sensitivity analysis on hospitalisation charges, EP study cost,
<p>Results</p> <p>Cost-effectiveness ratio \$11,315 per patient per life year saved by early ICD implantation. Costs in ICD group only higher in first three 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. QOL measures taken into account seem to make cost-effectiveness more favourable although quantitative analysis was not performed.</p>			
<p>Comments</p> <p>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, smaller devices reduced rehospitalisations, of stay initially.</p>			

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference and Design	Intervention	Subjects	Outcome measures	Sensitivity analyses
Owens⁵⁶ 1997 Markov model	ICD compared to 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		<i>Sensitivity analyses effectiveness of ICD, replacement interval,</i>
<p>Results</p> <p>Cost of replacement devices is an important component of the cost of ICD (50% to 65% of initial implantation costs).</p> <p>ICD most expensive of regimens.</p> <p>In high risk patients, quality adjusted life expectancy with ICD = 4.18 yrs (\$88400), amiodarone alone =3.68 yrs (\$51000), that is reported as 6 months extra of quality life for \$37500.</p> <p>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 \$43700, and intermediate risk patients with ICD live 1.28 quality adjusted years longer than in amiodarone group at a cost \$46 300.</p> <p>For high risk patients marginal cost-effectiveness ranges from \$37000 to \$74000 per QALY (ICD reduces mortality by 20% or 40%).</p> <p>For intermediate risk patients using a RRR=20%, cost utility is calculated to be \$76 800 per QALY with ICD compared to amiodarone. Using a RRR=40%, cost utility is calculated to be \$36 300 per QALY.</p> <p>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.</p>				
<p>Comments</p> <p>Evidence of effectiveness comes from RCT and patient registries; assumed that ICD use would reduce total mortality by 20% to 40%. Sensitivity analyses varied this effect.</p> <p>Comparison is with amiodarone which is the alternative therapy of choice in most patients.</p> <p>Analyses use transvenous approach only, which has superseded transthoracic.</p> <p>Cost-utility analyses were performed.</p> <p>Crossover strategies were examined.</p> <p>Calculation of cost utilities used RRR of total mortality of 20% and 40%.</p> <p>Authors conclude that early implantation with ICD is more cost effective than delayed.</p> <p>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.</p> <p>USA data limits generalisability.</p>				

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference and Design	Intervention	Subjects	Outcome measures and Sensitivity analyses
Mushlin ⁵⁷ 1998 (MADIT) Clinical trial with simultaneous costs	ICD compared to conventional medical therapy	VT, prior MI, LVEF less than 0.35 and inducible ventricular tacharrhythmia on EP test not suppressed by procainamide N=181 average follow-up 27 months	Total mortality <i>Cost of device</i> <i>Crossover</i>
<p>Results</p> <p>Cost of device is largest contributor to cost and cost-effectiveness may be expected to improve with reduction in price of device.</p> <p>Incremental cost-effectiveness ratio \$27 000 per life year saved (\$22,800 for transvenous device).</p> <p>Using present 16000 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.</p> <p>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.</p> <p>Patients with ICD could expect to live 3.46 out of 4 years and conventional therapy 2.66 out of 4 years (discounted).</p> <p>Discount at 3%.</p>			
<p>Comments</p> <p>USA data limiting generalisability.</p> <p>Some cost data derived from self reports from patients, no indirect costs assessed.</p> <p>No cost-utility analysis attempted.</p> <p>Conversion methods for charges to costs imperfect.</p> <p>Trial powered to detect difference in mortality not to obtain estimates of cost-effectiveness ration resulting in very wide confidence intervals around estimations.</p> <p>Both transvenous and transthoracic devices used.</p>			

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference and Design	Intervention	Subjects	Outcome measures	Sensitivity analyses
O'Brien ⁵⁸ 2000 CIDS trial (Unpublished abstract only)	ICD compared to 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		<i>Sensitivity analyses discount rate, device costs, follow-up period for analysis</i>
<p>Results</p> <p>Cost of ICD higher than cost for non-ICD (CA\$87,715 vs CA\$38,600). Incremental cost-effectiveness ratio of the ICD group compared to non-ICD group was CA\$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.</p>				
<p>Comments</p> <p>Comparison is with amiodarone which is the alternative therapy of choice in most patients. Analyses use randomised controlled trial 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 limits generalisability.</p>				

<i>Reference and Design</i>	<i>Intervention</i>	<i>Subjects</i>	<i>Outcome measures</i>	<i>Sensitivity analyses</i>
<i>Guidant Ltd 2000</i>				

<i>Reference and Design</i>	<i>Intervention</i>	<i>Subjects</i>	<i>Outcome measures analyses</i>	<i>Sensitivity</i>
<p>Results <i>Cost of ICD.</i> Primary prevention trials <i>Following 100 patients over 6 years in the Markov model:</i></p> <ul style="list-style-type: none"> • • • • • • • <p>Secondary prevention trials <i>Following 100 patients over 6 years in the Markov model:</i></p> <ul style="list-style-type: none"> • • • 				

<i>Reference and Design Comments</i>	<i>Intervention</i>	<i>Subjects</i>	<i>Outcome measures analyses</i>	<i>Sensitivity</i>

Appendix 9: Summary of economic evaluations of ICD (contd) – Unpublished, commercial in confidence

<i>Reference and Design</i>	<i>Intervention</i>	<i>Subjects</i>	<i>Outcome measures</i>
<i>Medtronic 2000</i>			
<i>Results and sensitivity analysis</i>			
<i>Comments</i>			

Appendix 9: Summary of economic evaluations of ICD (contd)

Reference	Research Question	Inclusion Criteria	Search Strategy
Stanton ⁵⁹ 2000	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 1990-1997 using implantable cardioverter-defibrillator, or cardioverter defibrillator, and cost, economics or cost-effectiveness. Conference proceedings from US scientific meetings were searched.
<p>Results</p> <p>Of initial 24 studies, 7 were identified to be included in the review. 6 of these are the same studies cited in this report, along with the AVID cost data that has been presented in abstract form only. (O'Brien economic analysis was not included).</p> <p>The authors did not perform meta-analysis due to lack of data provided in the studies.</p> <p>Incremental cost per life year saved varied between cost savings of \$13,975 per LYS to incremental cost \$114,917.</p> <p>The break-even times using updated cost and sensitivity data, vary between not breaking even {Owens1997} {Larsen 1992} to break-even times between 1.0 years {Kupersmith 1995} {Wever 1996} and 3.0 years {Kupermann 1990}.</p> <p>The cost of ICD therapy is sensitive to battery life (which in turn depends on type of battery and patients requirement for pacing and therapeutic shocks), use of a pre-implant EP study and relative risk reduction in mortality associated with ICD therapy compared to anti-arrhythmic drug therapy.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Future research areas delineated are implications of truncated follow-up periods by economic modeling, 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.</p> <p>Conclusions are that ICD are a cost effective therapy for management of life threatening ventricular tachyarrhythmias as judged by the Kupersmith cost-effectiveness guidelines (highly cost-effective \$0-\$20,000, cost effective \$20000-40000, borderline \$40000-\$60000, expensive \$60,000-\$100,000, very expensive \$100,000-\$120,000).</p>			
<p>Comments</p> <p>The review contains a methods section identifying the finding of relevant trials.</p> <p>The search methodology is confined to one electronic database, plus a limited, focused search for unpublished research presented at North American conferences.</p> <p>There is no reported assessment of the validity of the included studies.</p> <p>Explicit methods were used to determine which articles to include.</p> <p>Selection and assessment of primary studies is reproducible although exclusion of the UK O'Brien economic analysis is not adequately explained</p> <p>Quality of studies was not explicitly appraised using valid, explicit schedules.</p> <p>Evidence for the methodology of the secondary analysis was not reported.</p> <p>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.</p> <p>Reviewers' conclusions are based on a scale of cost-effectiveness that is not 'standard' in the UK.</p> <p>Conclusions about impact of new technology based on two of included economic analyses and other studies that were not part of the formal literature review. This could lead to bias.</p> <p>Results were not combined.</p> <p>Generalisability limited by majority of studies having a North American setting.</p> <p>The review has been peer reviewed.</p> <p>Authors are funded by, and parent organisation is cited as, Medtronic which manufacturers ICD.</p>			

Appendix 10: American College of Cardiology and American Heart Association guidelines - Implantation of ICD⁶⁵

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 subjects	1 (condition for which 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 subjects or well designed observational or data analyses	1
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 subjects or well designed observational or data analyses	1
Non sustained VT with coronary heart disease, prior MI, LV dysfunction and inducible VF or sustained VT at EPS not suppressed by class I antiarrhythmic drug.	Limited number of trials invoicing comparatively fewer subjects or well designed observational or data analyses	1
No indications for ICD		2a 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	2b (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 whilst awaiting cardiac transplantation.	Consensus opinion of experts	2b
Inherited conditions with high risk life-threatening VT/VF e.g. long QT syndrome, HOCM.	Limited number of trials invoicing comparatively fewer subjects or well designed observational or data analyses	2b
Non-sustained VT with coronary heart disease prior MI and LV dysfunction and inducible VT/VF on EPS	Limited number of trials invoicing comparatively fewer subjects or well designed observational or data analyses	2b
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	2b
Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmia	Consensus opinion of experts	3 (conditions for which there is evidence and/or general agreement that procedure/treatment is not useful/effective and in some cases may be harmful).
Incessant VT/VF	Consensus opinion of experts	3
VT/VF resulting from arrhythmias amenable to surgical or catheter ablation; for example, atrial arrhythmias associated with Wolf Parkinson White syndrome, right ventricular outflow tract VT, idiopathic LV tachycardia or fascicular VT	Consensus opinion of experts	3
Ventricular tacharyhmias due to a transient or reversible disorder e.g. acute myocardial infarction, electrolyte imbalance, drugs, trauma.	Consensus opinion of experts	3
Significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up.	Consensus opinion of experts	3
Terminal illnesses with projected life expectancy less than 6 months	Consensus opinion of experts	3
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 invoicing comparatively fewer subjects or well designed observational or data analyses	3
NYHA Class IV drug-refractory congestive heart failure in patients who are not candidates for cardiac transplantation	Consensus opinion of experts	3

Appendix 11: 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 (SCA), and are shown in Table 11a. 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 over-estimate of cost-effectiveness.

Table 11a: 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 LYS			2.59	2.39
Incremental LYS by ICD			0.20	

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 (IHQL), and results are shown in Table 11b. 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.

Table 11b: 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

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 QoL gain. Second, those with haemodynamically stable VT/VF who require painless pacing therapy from ICD and who may experience large QoL 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 11c.

Table 11c: QALYs gained from ICD therapy

	Life years lived	Life years lived	QALYs (Expert 1)	QALYs (Expert 1)	QALYs (Expert 2)	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	

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 11d.

Table 11d: Assumptions used in the sensitivity analysis (and justification).

Parameter	Low value	Base case	High value
Incremental Costs (and justification)	£8,100 (Lowest hospital cost)	£11,600 (Average of 3 hospital costs)	£17,400 (Highest hospital cost)
Life years saved (and justification)	0	0.20 (From survival curve analysis)	0.4 (Arbitrary high value, double base case)
QALY gain (and justification)	0	0 (From clinical judgement)	0.16, 0.38 (From clinical judgement)

The incremental cost per life year saved and the incremental cost per QALY over three years, using the above assumptions are shown in Table 11e. This is based on current best available data but remains speculative.

Table 11e: Incremental cost per LYS and incremental cost per QALY gained

Incremental cost over 3 years	LYS over 3 years	QALY gain over 3 years	Cost/LYS	Cost/QALY
£8,100	0.2	-	£40,500	-
£8,100	0.4	-	£20,250	-
£8,100	-	0.16	-	£50,600
£8,100	-	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

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