CARDIOVASCULAR MEDICINE

Implantable cardioverter-defibrillators in arrhythmias: a rapid and systematic review of effectiveness

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Objective: To review the effectiveness of implantable cardioverter-defibrillators (ICDs) in the management of risk factors for sudden cardiac death.
Design: Systematic review of randomised controlled trials identified from searching eight electronic databases, bibliographies of relevant studies, and consulting experts.
Main outcome measures: Absolute and relative reduction in mortality.
Results: Seven trials met the inclusion criteria. These showed changes in absolute risk of total mortality ranging from +1.7% to –22.8% (relative risk reductions –7% to +54%). Estimated benefits from ICD treatment compared with conventional drug treatment at three years were 0.23 to 0.80 additional years of life.
Conclusions: Evidence suggests that ICDs reduce total mortality in particular subgroups of patients at high risk of ventricular arrhythmias. The optimal strategy for identifying the patients who could benefit most is not clearly established. Ongoing trials into the treatment of cardiac failure with ICDs may provide further evidence about subgroups in whom ICDs are most cost effective.

Sudden cardiac death—most commonly caused by ventricular arrhythmias—is a significant public health issue, occurring in approximately 70 000 to 100 000 people annually in the UK.[1 2] Standard treatment for ventricular arrhythmias is usually with antiarrhythmic drugs (for example, amiodarone or sotalol), but around 25% of patients withdraw from treatment because of side effects. Implantable cardioverter-defibrillators (ICDs) offer an alternative for both the primary and secondary prevention of sustained ventricular arrhythmias (preventing them happening or recurring, respectively). These devices, introduced in 1980, are now used extensively in the USA and mainland Europe, but much less in the UK, where it has been estimated that the implantation rate is half that for western Europe and less than 10% of that in the USA.[3]

However, demand for ICD treatment is increasing in the UK, and we were commissioned by the National Health Service (NHS) Health Technology Assessment Programme to undertake a rapid review of the evidence on the clinical and cost effectiveness of ICDs in patients at risk of sudden cardiac death from arrhythmias. This paper summarises the clinical effectiveness issues identified by the review.[4]

METHODS

Electronic databases (Medline, PubMed, Embase, Cochrane systematic reviews database, Cochrane controlled trials register, Database of abstracts of reviews of effectiveness, and the National Research Register) were searched from January 1980 to December 1999 (search strategies are available on request). Additional studies were identified through searching bibliographies of related publications and through contact with experts.

We sought English language randomised controlled trials that compared ICD treatment with conventional treatment; included people at risk of sudden cardiac death from arrhythmia; and used patient based outcomes such as mortality, cardiac arrest/ventricular tachycardia, and quality of life measures.

We assessed the quality of systematic reviews and randomised controlled trials using criteria developed by the Centre for Reviews and Dissemination[5] and Jadad and colleagues,[6] respectively. Decisions about inclusion criteria, quality criteria, and data extraction were made by one reviewer and checked by a second, with disagreements resolved through discussion.

Studies were combined through narrative synthesis with full tabulation of included studies. Meta-analysis was not appropriate because of pronounced heterogeneity in patient characteristics and comparative interventions.

RESULTS

Seven randomised controlled trials, published between 1993 and 2000, met the inclusion criteria (table 1).[7–14] There were three primary prevention and four secondary prevention trials.

Most participants were men, with ages ranging from 57 to 67 years. Earlier trials used predominantly transthoracic devices whereas later trials used transvenous devices. The patients studied varied but in five trials they had a left ventricular ejection fraction of less than 40%. All the secondary prevention trials included cardiac arrest survivors and this was the sole entry criterion in two trials. The trials were large, ranging from 60 to over 1000 participants, and average follow up was 32 months. The trials were generally well conducted, although insertion of an ICD is practically impossible to double blind.

Two of the three primary prevention and all four secondary prevention studies found a survival advantage for patients treated with ICD (table 2). The secondary prevention trials showed absolute risk reductions (ARR) for ICD treatment ranging from 3.7% to 21.0%, and relative risk reductions

Abbreviations: AVID, antiarrhythmics versus implantable defribrillators trial; CABG patch, coronary artery bypass graft patch trial; CASH, cardiac arrest study Hamburg; CIDS, Canadian implantable defibrillator study; ESVEM, electrophysiologic study versus electrocardiographic monitoring trial; ICD, implantable cardioverter-defibrillators; MADIT, multicenter automatic defibrillator implantation trial; MUSTT, multicenter unsustained tachycardia trial

Table 1 Summary of randomised controlled trials of implantable cardioverter-defibrillators versus drug treatment to reduce sudden cardiac death: trial characteristics

Study and year of publication	n	Patients; inclusion criteria	Age (years)*	Sex (% male)	Intervention and type of ICD insertion	Comparitor	Duration of follow up
Primary prevention of VT/VF (prevent SCD from first incident of VT/VF)							
Moss (1996)[7]: MADIT (multicenter automatic defibrillator implantation trial)	196	MI three weeks or more before entry, with documented asymptomatic unsustained VT unrelated to MI, LVEF 0.35, with inducible VT not suppressed by procainamide, NYHA functional class I, II or III; and no indications for CABG/angioplasty within 3 months	63 (9)	92	Prophylactic ICD; 47% transthoracic devices, 53% transvenous devices	Conventional tiered treatment	27 months
Buxton (1999)[9 31]: MUSTT (multicenter unsustained tachycardia trial)	704	Coronary heart disease, non-sustained VT; LVEF <40% and EP diagnosed inducible sustained VT	†66.5 (58 to 72)	90	EP guided treatment (ACE inhibitor and/or β blocker, and sequential antiarrhythmic drug treatment supplemented with ICD if drugs failed to make VT no longer inducible); transvenous devices	Conservative (ACE inhibitor and/or β blocker when tolerated and no antiarrhythmic drug treatment)	39 months
Bigger (1997)[8]: CABG patch (coronary artery bypass patch trial)	900	Patients having CABG with LVEF <0.36 and abnormalities of signal averaged ECG	63.5 (9)	85.5	ICD; transvenous devices	Control (usual treatment)	Average 32 (16) months
Secondary prevention (prevent recurrence of cardiac arrest caused by VT/VF)							
Zipes (1997)[10]: AVID (antiarrhythmic versus implantable defibrillator)	1016	Cardiac arrest survivors (45%) or sustained VT with syncope, or symptomatic sustained VT (55%) with LVEF ⩽40%	65 (11)	79.5	ICD; transvenous devices	Amiodarone or sotalol	45 months, mean 27 months
Kuck (2000)[11]: CASH (cardiac arrest study Hamburg)	288	Survivors of cardiac arrest	58 (11)	80	ICD; transthoracic devices pre-1991 (55%); transvenous devices post-1991 (44%)	Amiodarone or metoprolol (propefenone arm deleted in 1992 owing to high mortality)	Mean 57 (34) months; minimum 2 year follow up
Connolly (2000)[14 32] CIDS (Canadian implantable defibrillator study)	600	Survivors of cardiac arrest, tachyarrhythmias with symptoms, with LVEF less than 35%	63.5 (9.0)	84	ICD; first 33 transthoracic devices; remaining 277 transvenous	Amiodarone	36–60 months
Wever (1995)[13]	60	Survivors of cardiac arrest	57 (10)	90	ICD, apart from three transvenous devices	Tiered drug treatment	27 months

*Mean (SD); †median.
ACE, angiotensin converting enzyme; CABG, coronary artery bypass graft; EP, electrophysiology; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.

(RRR) of 19.7% to 37.0%. In two of the primary prevention trials, the ARR with ICDs ranged from 22.8–24% (non-random evidence) and RRR from 54–56%. The reduction in total mortality was mainly because of fewer arrhythmic deaths.

There are some specific points to note in relation to the results in table 2.

- The ICD effectiveness results from MUSTT (randomised multicenter unsustained tachycardia trial) are based on non-randomised comparisons and so may be open to confounding.
- The CABG patch (coronary artery bypass graft patch) trial showed a non-significant increase (1.7%) in the risk of death in the ICD group. The risk of sudden cardiac death in this study was low and surgery in the control group may also have reduced the risk of death.
- Some of the ICDs used in the MADIT (multicenter automatic defibrillator implantation trial) and CASH (cardiac arrest study Hamburg) trials and in the trial by Wever and colleagues [13] were older transthoracic devices, which are associated with a greater morbidity and mortality. These earlier trials are also the smallest, the Wever trial having 6% of the study population included in the AVID (antiarrhythmics versus implantable defibrillators) trial.
- In CASH, the benefits of ICDs were more evident in the first five years after the index event and gradually declined, reaching an ARR of 10.6% at year 8.
- From non-randomised AVID evidence, there appears to be no advantage of one make of ICD over another.

Two other outcomes of ICD use need considering. Firstly, they can have unwanted effects, especially peri-implantation (for example, infection, bleeding, pneumothorax) (table 3). Secondly, patients' quality of life can be impaired as well as improved by ICDs. Three randomised controlled trials reported changes in quality of life. The CABG patch trial showed that patients with ICDs had lower levels of psychological wellbeing and reduced physical and emotional role functioning than controls at six months.[15] Unpublished AVID data show that sporadic defibrillator shocks are associated with a significant reduction in mental wellbeing and an increase in patient concerns.[16] Unpublished data from MADIT showed no difference in quality of life between ICD and controls, and found quality of life scores inversely correlating with number of shocks received. [17]

DISCUSSION

In this review, guided by an advisory panel of experts, we have considered systematically the best evidence on the effectiveness of ICD treatment. Although we searched hard for all randomised controlled trials we may have missed some, leaving the review open to possible publication bias. Given this caveat, we found seven randomised controlled trials. Six of these showed that ICDs reduced total mortality in patients at high risk of sudden cardiac death from ventricular arrhythmias not occurring in association with reversible pathology.

Table 2 Summary of randomised controlled trials of implantable cardioverter-defibrillators versus drug treatment to reduce sudden cardiac death: main results

Author, year	Relative reduction in risk	Absolute results	NNT (95% CI)*
Primary prevention of VT/VF			
Moss (1996)[7]: MADIT (multicenter automatic defibrillator implantation trial)	RR, ICD arm: 0.46 (95% CI, 0.26 to 0.82; p=0.009); RRR, 54%	Absolute mortality: ICD, 15.8%; conventional treatment, 38.6%; ARR, 22.8%	NNT=5 (3 to 10)
Buxton (1999)[9 31]: MUSTT (multicenter unsustained tachycardia trial)	Absolute all cause mortality in randomised comparison: conservative *v* EP guided; RRR, 13%	Absolute all cause mortality in randomised comparison: conservative, 48%; EP guided, 42%; ARR 6%	NNT=17
	In EPG arm (non-randomised comparison) ICD compared with drug treatment; RRR 56%	In EPG arm (non-randomised comparison) ICD compared with drug treatment: total mortality ICD 24%; drug treatment 55%; ARR 31%	NNT=3
Bigger (1997)[8]: CABG patch (coronary artery bypass patch trial)	RR in ICD arm, 1.07 (95% CI, 0.81 to 1.42); p=0.64. Adjusted RR, 1.03 (95% CI, 0.75 to 1.41)	Absolute mortality: ICD, 22.6% at 32 months; control, 20.9% at 32 months. ARR in usual treatment group, 1.7%	NNH=58 (14 to infinity)
Secondary prevention (recurrent VT/VF)			
Zipes (1997)[10]: AVID (antiarrhythmic versus implantable defibrillator)	Relative reduction in total mortality (adjusted) in ICD arm†: 37 (22)% at 1 y; 24 (22)% at 2 y; 29 (23)% at 3 y; p<0.02	Absolute mortality: ICD, 10.7% at 1y; 18.4% at 2 y; 24.6% at 3 y; amiodarone/sotalol, 17.7% at 1 y; 25.3% at 2 y; 35.9% at 3 y; ARR, 7% at 1 y; 6.9% at 2 y; 11.3% at 3 y	NNT=9 (95% CI, 6 to 18)
Kuck (2000)[11]; Siebels (1993)[12]: CASH (cardiac arrest study Hamburg)	At 2 years: RR, 0.766 (upper 97.5% CI 1.112); RRR, 23.4%; p=0.081	Total mortality: ICD, 13.6%; propefenone, 29.3%. Trial stopped Absolute total mortality at 2 years: ICD, 36.4% (95% CI 26.9% to 46.6%); amiodarone/metoprolol, 44.4% (95% CI 37.2% to 51.8%); ARR, 8.0% % Reduction in mortality, year 1 to 9: 41.9, 39.3, 28.4, 27.7, 22.8, 11.4, 9.1, 10.6, 24.7	NNT=13 (6 to infinity)
Connolly (2000)[14 32]: CIDS (Canadian implantable defibrillator study)	RRR at 5 years: 19.7% with ICD (p=0.142)	Absolute mortality at 5 years: ICD, 23%; amiodarone, 27%; ARR, 3.7%	NNT=24 (10 to infinity)
Wever (1995)[13]	RR of death in ICD arm: 0.27 (0.09 to 0.85); p=0.02	Absolute mortality: early ICD, 14% at 2 years; conventional group, 35% at 2 years; ARR, 21% at 2 years	NNT=5 (3 to infinity)

*Calculated by the authors using Arcus software.
†Mean (SD).
ARR, absolute risk reduction; CI, confidence interval; ICD, implantable cardioverter-defibrillator; NNT, number needed to treat; RR, relative risk; RRR, relative risk reduction.

The randomised controlled trials were generally well conducted but some methodological issues should be highlighted. Randomised controlled trials of ICDs pose special problems: comparing drugs and devices raises issues of blinding and compliance; the differential use of β blockers in ICD groups seen in two of the three trials for which data are available may have contributed to the apparent effectiveness of ICD (although there is evidence that they did not convey a survival advantage[18 19]); and the evolution of devices over time makes the applicability of results from trials of older, transthoracic devices (which carry greater risks than transvenous devices) problematic. Two of the trials (CIDS and CASH) were underpowered to detect significant differences in outcomes, though this was partly addressed by the meta-analysis of three secondary prevention trials.[18] Finally, the clinical characteristics of the patients included need to be considered carefully. For example, patients in CASH had a greater left ventricular ejection fraction and were relatively more healthy, so they would be expected to derive less benefit from ICDs than those in the AVID trial.[20]

The patient groups that benefited in the trials included are listed in table 4. In addition there is widespread clinical consensus that patients with certain rare conditions also benefit from ICD treatment.[10 21–26] However, the optimal strategy for identifying those patients who could most benefit from ICDs is not clearly established. Techniques such as electrophysiological study, signal averaged ECGs, and heart rate variability have been used, although the evidence base for these is often weak.[27–29] Ongoing trials including those into treatment of cardiac failure with ICD, and elaboration of quality of life outcomes in patients with ICDs, will provide evidence that may have implications for those subgroups of patients in whom ICD are maximally effective.

The policy implications for ICD treatment are huge, with demand rising in most European countries. Recent NHS guidance, if implemented, will lead to an estimated increase in ICDs from 17 per million to 50 per million.[30] This is likely to be costly and to present policy makers with challenging decisions about value for money. For instance, speculative estimates of cost utility from a recent report[4] show a cost per QALY (quality adjusted life years) of £21 300 to £108 800. But there is a tension between the utilitarian approach and the right to rescue for the individual. Eligible patients and their families may expect this treatment to be offered, perceiving it as a life saving benefit, but cost effectiveness remains a barrier.

Future research could help to inform evidence based decisions about the use of ICDs. In the first place, what is needed is information about the benefits and costs of ICDs over the longer term. As most costs occur early in treatment, cost effectiveness may become more favourable as patients survive longer, battery life of ICD extends beyond six to seven years, patient acceptability increases, cost of device is reduced, and improvements to efficacy occur. Secondly, we need to know more about current patterns of service use, equity of provision between different social groups, and the diffusion and effectiveness of different devices. Finally, we need to know more about the changes in patients' quality of life that ICDs bring.

Table 3 Unwanted effects of interventions in the trials included

Study	ICD treatment	Anti-arrhythmic drug
Primary prevention of VT/VF		
MADIT (multicenter automatic defibrillator implantation trial)	19/95 patients with adverse events: 2 pneumothorax, 2 infection, 7 lead problems, 7 rhythm problems	12/101 patients with adverse events: 5 unexplained syncope, 7 VT/VF; amiodarone discontinued in 46%
MUSTT (multicenter unsustained tachycardia trial)	EP guided arm: complications occurred in 5 patients with inducible sustained VT (0.7%), non-fatal	
CABG patch (coronary artery bypass patch trial)	Significantly different complications in ICD: 12.3% infection, 8.5% pneumonia, deep sternal wound infection 2.7%	
Secondary prevention (recurrent VT/VF)		
AVID (antiarrhythmic versus implantable defibrillator)	19/507: 6 bleeding, 13 haematoma, 10 infection, 8 pneumothorax, 1 cardiac perforation	5% pulmonary toxic, 16% needed thyroid replacement treatment
CASH (cardiac arrest study Hamburg)	5.1% died perioperatively (5); 3/5 epicardial devices; infection (3), explantation (2), haematoma (6), pericardial effusion (1), pleural effusion (3), pneumothorax (1), dislodgement/migration of leads (3), device dysfunction (5). Overall complication, 23%; explantation rate, 2.1%	Propefenone: 12/56 side effects, 61% higher total mortality; drug stopped Amiodarone: hyperthyroidism in 3% (3); drug stopped in 9% (9) Metoprolol: drug stopped in 10% (10)
CIDS (Canadian implantable defibrillator study)	At 3 years: infection 5.1%, lead fracture 2.6%, pulmonary toxicity 11.9%, hepatic toxicity 0.9%, thyroid problems 1.8%, CNS problems 8.5%	Amiodarone at 3 years: 22% stopped; pulmonary toxicity 19.6%, hepatic toxicity 5.1%, thyroid 8.8%, CNS 26%
Wever *et al*	Migration of lead in 1 patient, infection in 1 patient	16/31 late ICD (15 pre-discharge)

Numbers of patients in brackets.
CNS, central nervous system; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 4 Characteristics of patients who would benefit from implanted cardioverter-defibrillator treatment*

Primary prevention	Patients surviving cardiac arrest
	Patients having symptomatic sustained ventricular tachyarrhythmias
	Patients with symptomatic sustained ventricular tachyarrythmias and LVEF ⩽40%
Secondary prevention	Patients having underlying coronary heart disease with unsustained VT and inducible VT on EPS
	Patients post MI with unsustained VT, LVEF ⩽35% with inducible VT not suppressed by procaineamide with no indications for coronary artery surgery within 3 months
Other	Long QT syndrome
	Brugada syndrome
	Hypertropic obstructive cardiomyopathy

*Derived from trial data and clinical evidence.[10 21–26]
EPS, electrophysiological study; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VT, ventricular tachycardia.

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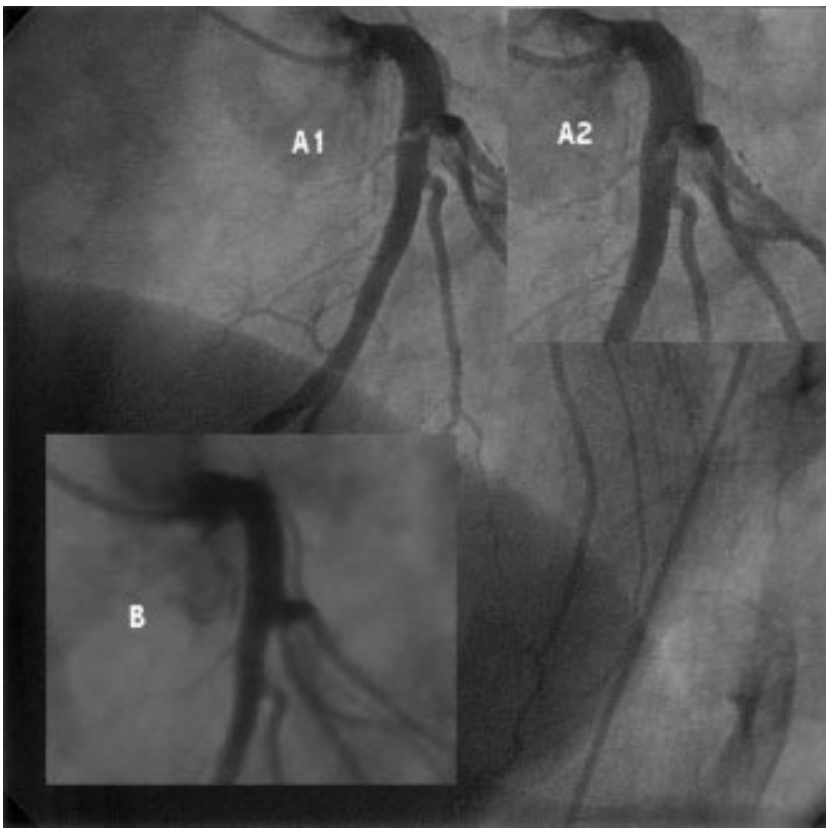
IMAGES IN CARDIOLOGY

Glycoprotein IIb/IIIa induced coronary thrombolysis

A 35 year old female patient with symptoms of unstable angina and a positive troponin I test was admitted to our hospital three days after coloscopic biopsy was performed elsewhere. Immediate coronary angiography revealed a coronary thrombus in the bifurcation of the main stem of the left coronary artery with involvement of the origin of the circumflex artery as well as the proximal segments of the marginal and intermediate branches. A flap of the thrombus extended into the LAD, giving rise to systolic/diastolic oscillations (A1 and A2). In order to spare the young patient with severe symptoms an aortocoronary bypass operation, we decided to administer the glycoprotein IIb/IIIa receptor blocker tirofiban. In view of the recent coloscopic biopsy and the increased risk of bleeding, only half the normal initial bolus (0.2 μg/kg/min for 30 minutes) and half the normal maintenance dose (0.05 μg/kg/min) were given. As no intestinal bleeding occurred, the dose was increased after 24 hours to the normal maintenance dose (0.1 μg/kg/min) so as to achieve the maximum effect of the drug. Following three days' tirofiban administration and initiation of antiplatelet treatment with 75 mg clopidogrel and 300 mg aspirin daily, plus low molecular weight heparin twice daily, control coronary angiography showed complete regression with no coronary thrombi present (B).

Aggressive antiplatelet treatment with tirofiban, a potent inhibitor of glycoprotein IIb/IIIa receptors on the surface of platelets, in combination with low molecular weight heparin, led to complete thrombolysis in the affected coronary vessels of this patient with unstable angina.



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