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

J Parkes, J Bryant, R Milne

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. 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.

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.

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 and Jadad and colleagues, 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). 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 defibrillators trial; CABG, coronary artery bypass graft; CASH, cardiac arrest study Hamburg; CIDS, Canadian implantable defibrillator study; ESVM, electrophysiologic study versus electrocardiographic monitoring trial; ICD, implantable cardioverter-defibrillator; MADDIT, multicenter automatic defibrillator implantation trial; MUSTT, multicenter sustained tachycardia 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 an increase in patient concerns. Unpublished AVID data show that sporadic defibrillator shocks are associated with a significant reduction in mental wellbeing and an increase in patient concerns.

### 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.
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 blindness and compliance; the differential use of drugs and devices (which carry greater risks than transvenous devices) may have implications for those subgroups of patients in whom ICDs are maximally effective. Future research could help to inform evidence based decisions about the use of ICDs. In the first place, what is known 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.

ICDs from 17 per million to 50 per million. 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 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.

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. 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 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.

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 blindness 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); 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. 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.

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. 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. 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 ICDs are maximally effective.
Implantable cardioverter-defibrillators in arrhythmias

Table 3  Unwanted effects of interventions in the trials included

<table>
<thead>
<tr>
<th>Study</th>
<th>ICD treatment</th>
<th>Anti-arrhythmic drug</th>
</tr>
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<tbody>
<tr>
<td>Primary prevention of VT/VF</td>
<td>19/95 patients with adverse events: 2 pneumothorax, 2 infection, 7 lead problems, 7 rhythm problems</td>
<td>12/101 patients with adverse events: 5 unexplained syncopes, 7 VT/VF, amiodarone discontinued in 46%</td>
</tr>
<tr>
<td>MADIT (multicenter automatic defibrillator implantation trial)</td>
<td>EP-guided arm: complications occurred in 5 patients with inducible sustained VT (0.7%), non-fatal</td>
<td></td>
</tr>
<tr>
<td>MUSTT (multicenter unsustained tachycardia trial)</td>
<td></td>
<td>5% pulmonary toxic, 16% needed thyroid replacement treatment</td>
</tr>
<tr>
<td>CASH (cardiac arrest study</td>
<td>Significant differences in complications in ICD: 12.3% infection, 8.5% pneumonia, deep sternal wound infection 2.7%</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention (recurrent VT/VF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CASH (cardiac arrest study</td>
<td>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%</td>
<td></td>
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<tr>
<td>CIDS (Canadian implantable defibrillator study)</td>
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</tr>
<tr>
<td>AVEF</td>
<td>Migration of lead in 1 patient, infection in 1 patient</td>
<td>16/31 late ICD (15 pre-discharge)</td>
</tr>
</tbody>
</table>

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*

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients surviving cardiac arrest</th>
<th>Patients having symptomatic sustained</th>
<th>Patients with underlying coronary heart disease with unsustained VT and inducible</th>
<th>Patients post MI with unsustained VT, LVEF ≤35% with inducible VT not suppressed by propranolol</th>
<th>Long QT syndrome</th>
<th>Brugada syndrome</th>
<th>Hypertrophic obstructive cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td>Patients having symptomatic sustained ventricular tachyarrhythmias</td>
<td>Patients with symptomatic sustained</td>
<td>Patients having underlying coronary heart disease with unsustained VT and inducible VT on EPS</td>
<td>Patients post MI with unsustained VT, LVEF ≤35% with inducible VT not suppressed by propranolol</td>
<td>Propranolol</td>
<td>Metoprolol</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td></td>
<td>Ventricular tachyarrhythmias and LVEF ≤40%</td>
<td>VT on EPS</td>
<td>With no indication for coronary artery surgery within 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Long QT syndrome</td>
<td>Brugada syndrome</td>
<td>Hypertrophic obstructive cardiomyopathy</td>
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*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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REFERENCES
5 NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD guidelines for those carrying out or commissioning reviews. CRD Report No 4, 1999.
IMAGES IN CARDIOLOGY

Glycoprotein Ilb/IIia induced coronary thrombolysis

A 35 year old female patient with symptoms of unstable angina and a positive troponin T 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 Ilb/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 Ilb/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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