Who needs an implantable defibrillator?

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Ventricular arrhythmias account for 80% of sudden cardiac deaths. The implantable defibrillator (ICD) is an effective means of preventing these deaths. This article discusses which patients may benefit from ICD implantation and addresses the cost-effectiveness of their use.

Sudden cardiac death (SCD) kills 90 000 adults per annum in the UK. Observational data suggest that survivors from arrhythmic death suffer a recurrence rate of 30–50% within 2 years. Recent studies suggest that the best way of preventing such patients from subsequently dying of a recurrence may be the use of an implantable defibrillator (ICD). In spite of this, many patients in the UK receive no specific treatment or antiarrhythmic drug (AAD) treatment alone.

THE ROLE OF AAD THERAPY

Because most sudden death episodes occur in patients who have ischaemic heart disease and have suffered a previous myocardial infarction (MI), drug trials aimed at reducing arrhythmic death in this group are relevant in considering the role of ICD therapy.

Randomized placebo-controlled trials of class 1 AADs, such as flecainide, which were designed to show a reduction in subsequent arrhythmic death, unfortunately showed an excess of deaths in patients after MI (Echt et al, 1991). It is widely believed that all class 1 agents have a similar deleterious effect. Indirect evidence for this comes from the ESVEM study (Mason and the ESVEM Investigators, 1993), where a number of class 1 agents were used to treat ventricular arrhythmias, and all performed very poorly in comparison with sotalol. Unfortunately, in the SWORD (Survival with oral d-sotalol) study (Waldo et al, 1996), sotalol was also shown to increase mortality over placebo when prescribed post-MI, and is no longer licensed in the UK for use in such patients.

As a result of these drug failures, amiodarone is currently considered the most effective AAD. However, the benefits after MI are not clear. Small non-randomized, non-controlled trials comparing amiodarone with 'conventional medical therapy' (usually involving the use of class 1 agents) as a primary preventative agent, after MI, have suggested a benefit from amiodarone. However, in larger randomized, placebo-controlled studies such as EMIAT (European myocardial infarct amiodarone trial) (Julian et al, 1997), the benefit almost disappears (*Figure 1*; Sim et al, 1997). In EMIAT amiodarone did reduce arrhythmic death in patients with impaired left ventricular function after MI, but all-cause mortality was not significantly different from placebo.

Use of amiodarone in secondary prevention is more promising but remains limited. In the CASCADE (Cardiac arrest in Seattle: Conventional *vs* Amiodarone drug evaluation) study (Greene and the CASCADE Investigators, 1993) patients who had survived out of hospital ventricular fibrillation (VF) were randomized to receive either empirical amiodarone (n=113) or class 1 AADs guided by electrophysiological (EP) study (n=115). Nearly half (105) also received an ICD. Most had suffered a previous MI and half had a history of congestive cardiac failure with an overall mean left ventricular ejection fraction (LVEF) of 35%.

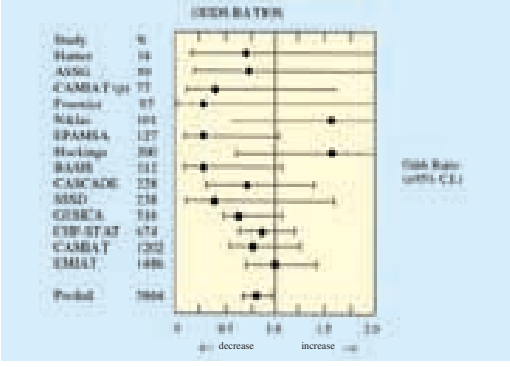

Figure 1. Odds ratios for total mortality in randomized trials of amiodarone vs control (Sim et al, 1997).

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Survival free of cardiac death, resuscitated VF or syncopal defibrillation at 2, 4 and 6 years was 82%, 66% and 53% with amiodarone and 69%, 52% and 40% with conventional drug therapy respectively (P=0.007). Although the amiodarone-treated group had a significantly better outcome, their overall mortality remained high and discontinuation of treatment in this group was substantial because of serious side-effects such as thyroid disease and pulmonary toxicity. This trial further underlines the poor outcome to be expected with class 1 AADs, which now have no place as the sole management of patients with a risk of SCD.

In the aforementioned studies, amiodarone was prescribed empirically. Waller et al (1987) investigated the role of EP study assessment of AAD therapy efficacy in predicting future arrhythmic events and mortality. Two hundred and fifty eight patients with inducible ventricular arrhythmias underwent serial EP studies after loading with AAD treatment. The majority received amiodarone. They were placed into 3 groups according to whether the AAD rendered the arrhythmia non-inducible (group 1), beneficially modified it (group 2) or had no beneficial effect (group 3).

Total mortality and SCD over a follow-up of 0.1–57.4 months were reduced in groups 1 and 2 at 13% and 12% respectively compared with group 3 at 39%. Arrhythmia recurrence was more frequent in group 2 compared with group 1 (39% *vs* 7%), but mortality did not differ (*Figure 2*).

This suggests an important role for EP assessment of AAD efficacy in patients with symptomatic ventricular arrhythmias, identifying those who remain inducible (who do badly), and those who are not inducible and do well. Waller's study also shows that patients who remain inducible fall into two groups. Some patients have an apparent benefit from treatment, with slowing and better toleration of induced ventricular tachycardia (VT). Others have no benefit. These two groups unfortunately comprise the vast majority of amiodarone-treated patients undergoing EP study after loading with the drug. Outcome studies show that both groups have a high rate of recurrence of VT, although this is much less often fatal in the group who have some apparent benefit from the drug.

Beta-blockers have an established role in reducing SCD when prescribed empirically after MI (Norwegian Multicenter Study Group, 1981), but their role in secondary prevention in patients with previous ventricular arrhythmias has not been formally investigated.

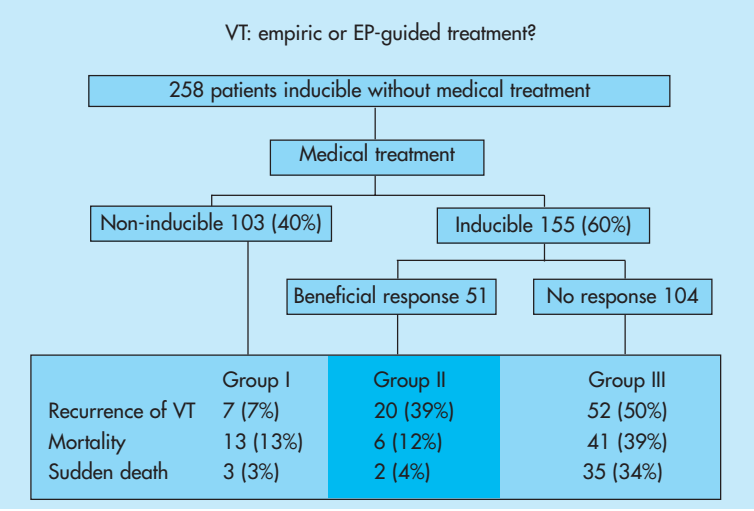

Figure 2. Prognosis with electrophysiologically(EP)-guided antiarrhythmic drug therapy. VT = ventricular tachycardia. From Waller et al (1987).

EVOLUTION OF THE ICD

Clearly, AADs have severe limitations and may have harmful effects in patients at high risk of SCD. Long before this was fully appreciated, however, work had begun in Israel, and subsequently the USA, on a fully implantable, automatic, internal defibrillator. Pioneering work was done by Mirowski and colleagues (1970), leading to approval for human use in the USA in 1985. At this time devices were crude, had few programmable features, no ability to store and retrieve episodes, and had to be implanted via a thoracotomy using large shocking leads sutured directly to the epicardial surface of the heart. Reductions in generator size (*Figure 3*) and use of transvenous lead systems currently allow implantation in the infraclavicular region either subcutaneously or submuscularly below the pectoralis major.

Catheter laboratory implants by cardiologists were first described by Fitzpatrick et al (1994). Patients are often anaesthetized but a series of successful implants under local anaesthetic and conscious sedation have been reported (Lipscomb et al, 1998).

A typical device consists of a single lead inserted through the cephalic or subclavian vein into the right ventricular apex with a high voltage circuit between a right ventricular coil (cathode) and the generator can (anode) (*Figure 4*). Modern devices allow a variety of treatments to be programmed into the device and subsequently deliv-

Figure 3. Typical implantable defibrillator generator.

ered automatically from bradycardia pacing, antitachycardia pacing of VT to DC cardioversion/defibrillation of VT and VF as necessary. The latest generation of ICDs incorporate dual chamber lead systems that facilitate greater accuracy in arrhythmia detection and diagnosis plus atrioventricular sequential pacing when needed.

However, ICDs are very costly, and debate continues as to which patient groups will benefit from ICD implantation, how they may be selected and how the cost implications should be addressed.

THE ICD IN SECONDARY PREVENTION

Three randomized prospective trials have compared the ICD with AAD therapy in subjects with previous life-threatening ventricular arrhythmias. These have reported within the last 2 years and have showed a significant survival advantage in the ICD-treated groups.

The most important of these trials was the National Institutes of Health-sponsored AVID (Antiarrhythmics *vs* implantable defibrillators) trial (AVID Investigators, 1997) which compared ICD (n=507) with either empirical amiodarone (n=496) or 'guided' sotalol (n=13). Patients randomized had survived an episode of VF, suffered an unexplained syncopal episode and then exhibited inducible VT during EP study, or presented with VT resulting in haemodynamic compromise in the presence of LVEF of ≤40%. A response to sotalol was guided by Holter monitoring or EP study. Sotalol was prescribed to few patients either because of its failure to suppress ventricular arrhythmias or because of concerns over its use in the presence of impaired ventricular function.

Follow-up took place over 3 years (mean 18.2±12.2 months), and showed a significant reduction over this period in the primary end-point of mortality in the ICD-treated group of 31% (absolute 24.6% *vs* 35.9%). Significant mortality benefits (38% reduction) were seen within 12 months *(Figure 5)*. A criticism of the AVID trial is the increased use of β-blockers in the ICD group compared with the amiodarone-treated patients (45% *vs* 13%,) but, following a sub-study to correct for this bias, a significant benefit remained.

The CIDS (Canadian implantable defibrillator study) trial (Dorian et al, 1994) used similar patient inclusion criteria as AVID. Patients were randomized to ICD (n=328) or amiodarone (n=331) and followed up for 3 years. Mortality was reduced by 20% (absolute 25% *vs* 30%) in the ICD-treated group.

The CASH Study (Cardiac arrest study of Hamburg) (Siebels and Kuck, 1994) studied survivors from VF alone and randomized them to ICD (n=99) or AAD with amiodarone (n=92), metoprolol (n=97) or propafenone (n=58). The propafenone arm was stopped early because of an increased mortality rate. Follow-up over 2 years showed a 37% (absolute 12.1% *vs* 19.6%) reduction in mortality in the ICD group compared with the amiodarone or metoprolol groups.

These trials make the case for the use of ICDs rather than best available medical therapy in patients who have had an episode of life-threatening ventricular arrhythmia. However, they do not evaluate the role of treatment with amiodarone guided by EP study *vs* ICD. They also do not directly address issues of cost-effectiveness.

THE ICD IN PRIMARY PREVENTION

Two randomized trials have investigated prophylactic use of ICDs, based on the rationale that patients with impaired left ventricular function are at increased risk of SCD in the absence of prior documented sustained VT or VF.

The MADIT trial (Multicenter Automatic Defibrillator Implantation Trial) (Moss et al, 1996) enrolled patients who had sustained a

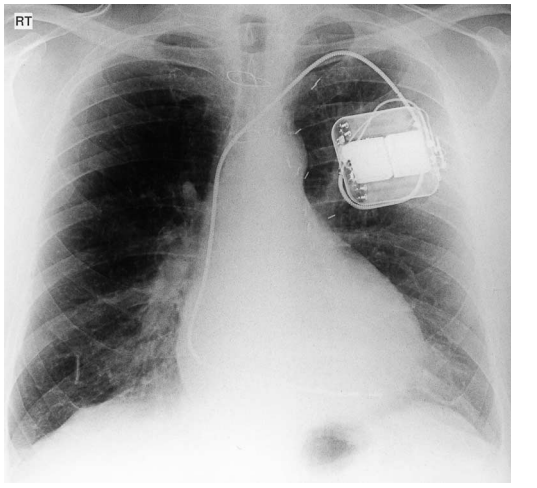

Figure 4. Chest X-ray showing sub-pectorally placed single chamber implantable defibrillator and lead to right ventricular apex. Note arterial clips and sternal wires of previous coronary bypass surgery.

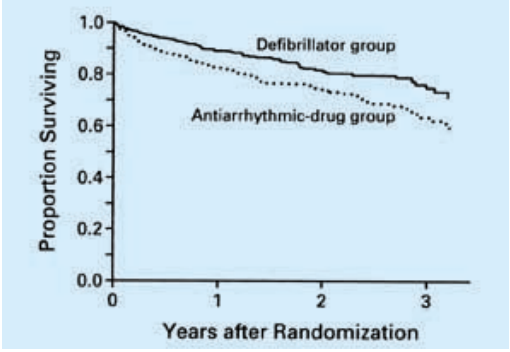

Figure 5. Antiarrhythmics vs implantable defibrillators (AVID) trial survival curves (AVID Investigators, 1997).

recent (≥3 weeks before enrolment) MI and subsequently had a LVEF ≤35%. Patients had to have non-sustained VT on Holter monitoring in order to be considered, and then had to undergo EP study testing. At EP study, in order to be randomized, patients had to exhibit inducible VT or VF that was not suppressible with intravenous procainamide. Such patients were then randomized to ICD (n=95) or 'conventional' therapy (n=101). Conventional therapy was at the physicians' discretion and resulted in prescription of amiodarone to 45% and β-blockers to 5% of these patients.

The trial was terminated prematurely at 2 years after enrolment of 75% of the planned total number of patients because of an observed 54% reduction in mortality (absolute 15.8% *vs* 38.6%). The timing of termination was dependant on a sequential monitoring statistical algorithm, designed to minimize the number of deaths required to obtain a statistically significant conclusion. This had the disadvantage of limiting the number of subjects available for sub-group analysis. Examination of cause of death suggested that ICD reduced not only arrhythmic death (13 *vs* 3) but also non-arrhythmic cardiac death (13 *vs* 7) and death of unknown causes (6 *vs* 0), a finding which may be a result of inaccurate reporting, but is not fully explained. Once again there was an excess of β-blocker use in the ICD group (27 *vs* 5) but correcting for this using Cox regression analysis did not account for their improvement in survival.

The rationale for the coronary artery bypass grafting (CABG)-patch trial (Bigger et al, 1997) was developed at a time when thoracotomy was required for ICD implantation. Patients undergoing CABG with an abnormal signal-averaged electrocardiogram and LVEF ≤35% were randomized to receive an ICD (n=446) or not (n=454) at time of surgery. There was no significant difference in mortality between the two groups after 32 months of follow-up: 22.6% in the group with an ICD and 20.9% in those not receiving an ICD. It has been suggested that the difference in results between MADIT and CABG-patch might have been because the more rigorous screening in MADIT selected out a population at higher risk of SCD, or possibly that revascularization of all patients in CABG-patch reduced this risk universally.

WEAKNESSES OF A PROGRAMME OF PRIMARY PREVENTION WITH ICDS

There are two major problems with the use of ICDs in primary prevention of death caused by life-threatening ventricular arrhythmias. The first is that all methods of risk stratification of patients for such arrhythmias are imperfect. Combining the best methods only gives a 50% positive predictive accuracy. This is no better than the toss of a coin for an individual patient. The positive predictive accuracy rises with the specificity of any screening process, but at the expense of sensitivity.

This results in patients who will have events missing out on treatment because they do not fulfil all entry criteria. Also, in spite of best efforts to secure a screening process that achieves the highest positive predictive accuracy, some asymptomatic patients would receive treatment they had not sought, and did not need, which might be harmful to them if implant or other complications arose. Such instances raise ethical concerns about ICD therapy for primary prevention.

The second major problem arises from the cost of such a programme of primary preventive treatment with ICDs. Cost analysis provided for MADIT (Mushlin et al, 1998) calculated a cost-effectiveness ratio of $27 000 per life year saved compared to conventional treatment. This fell to $23 000 if transvenous defibrillators had been used in place of surgically implanted ICDs. However, this did not account for the costs of screening. MADIT succeeded in randomizing just 200 patients from 31 centres in 5 years. Centres were chosen for their high volume of work, but, in spite of this, the exhaustive evaluation process resulted in few suitable patients being found. Patients could not be screened until at least 3 weeks after their index MI. All patients therefore required outpatient echocardiography and Holter monitoring, and many required costly EP study before any could be identified for randomization.

Such issues as these provide arguments against a programme of ICD implantation for the primary prevention of death from life-threatening ventricular arrhythmias.

COST IMPLICATIONS OF SECONDARY PREVENTION WITH ICDS

The typical cost of an ICD and transvenous leads in the UK is £20 500, excluding implantation and follow-up costs. Understandably, much interest has been directed at assessing the cost-effectiveness of ICD implantation in different patient groups. The majority of this work has been performed in the USA.

Wever et al (1996) performed a cost-effectiveness analysis of the use of ICDs for secondary prevention. It assessed health-care costs in a prospective study of survivors of cardiac arrest complicating previous MI with documented VT or VF. These were randomized to early ICD (n=29) or EP-guided AAD therapy (n=31). Map-guided VT surgery was performed in 5 of the EP-guided AAD group, almost doubling the cost of treatment compared to those treated with AAD alone

($44 100 *vs* $23 500). VT surgery is not commonly performed in the UK at present as few, select patients may benefit. Almost half of the EP-guided AAD patients received an ICD by the end of the study. A net saving of $11 315 per patient per year alive saved was attributed to having an ICD as first-choice therapy. Patients discharged on AAD alone had lowest total costs but an unusually high mortality (7 out of 11), translating to a poor cost-effectiveness of $196 per day alive compared to $63 per day alive for the ICD group. Length of time spent in hospital, change of AAD medication and number of invasive procedures all improved favourably in the ICD-treated group.

Owens et al (1997) used a hypothetical cohort model to estimate cost-effectiveness of ICD implantation compared with amiodarone treatment. SCD rate at 1 year on amiodarone was estimated at 8.6% for 'high risk' patients, using published data, and it was assumed that ICD reduced these rates by 20–40% per annum. Assuming a generator battery life of 4 years, the marginal cost-effectiveness ranged from $74 400 per quality-adjusted life-year gained (if ICD reduced the SCD rate by 20%) to $37 300 per quality-adjusted life-year gained (if ICD reduced the SCD rate by 40%). At the 30% effectiveness level the marginal cost-effectiveness was $49 300 per quality-adjusted life-year gained.

An interesting finding was that if patients were treated initially with amiodarone, and then required ICD because of recurrent ventricular arrhythmia, costs were increased compared with the other two groups. Life expectancy was similar to the amiodarone-only group, resulting in a poor marginal cost-effectiveness. In keeping with other trials, it may be that if an ICD is necessary it should be implanted early. Currently, there is no consensus about acceptable levels of cost-effectiveness, but $50 000 (£31 250) per quality-adjusted life-year gained is generally regarded as significant (*Figure 6* shows cost-effectiveness comparisons for established medical treatments).

At this cost, using the data from Owen's study, ICD therapy would need to be targeted to achieve a 30% reduction in all cause mortality, without a reduction in quality of life. Advances in battery technology and increased ICD longevity should further improve cost-effectiveness. We await publication of the quality of life and economic data from the recently reported randomized prospective trials, in particular the AVID trial, which included these as secondary end-points.

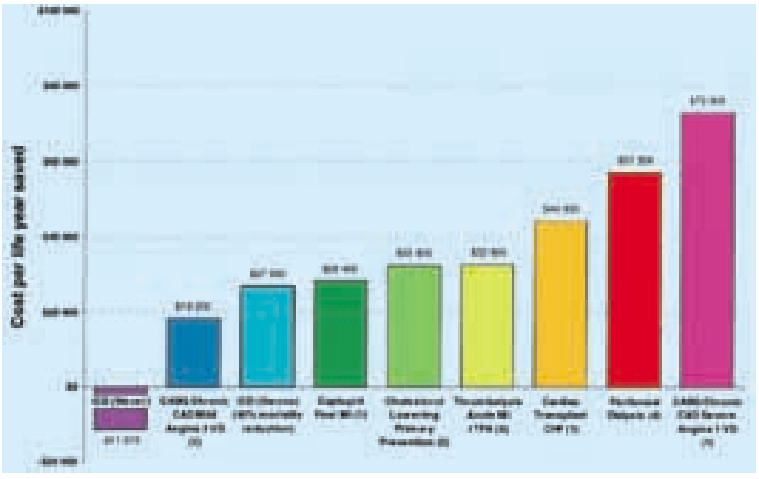

Figure 6. Cost-effectiveness comparisons of established medical treatments. Implantable defibrillator treatment highlighted. References. 1 = Kupersmith et al (1995a); 2 = Caro et al (1997); 3 = Kupersmith et al (1995b); 4 = Kupperman et al (1990); Wever = Wever et al (1996); Owens = Owens et al (1997). CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = chronic heart failure; ICD = implantable defibrillator; MI = myocardial infarction; rTPA = recombinant tissue plasminogen activator; VD = vessel disease.

INDICATIONS FOR ICD TREATMENT

In the light of the findings of recent randomized trials of ICD treatment, and the arguments above, it is possible to make some suggestions for the use of this costly and controversial technology.

Sudden cardiac death

An ICD should be recommended if a patient presents with SCD caused by VF where acute ischaemia can be excluded, cardiac failure resulting from impaired left ventricular function is not a major feature (since it confers a poor overall prognosis), and VF has not apparently degenerated from VT. Where VT was clearly the initial or index arrhythmia, the patient should undergo EP study with programmed ventricular stimulation to assess the response to amiodarone.

Life-threatening ventricular arrhythmias

Where a patient presents with life-threatening VT with syncope or severe haemodynamic compromise, EP study should be undertaken to demonstrate whether amiodarone can suppress VT or render it less hazardous. If not, an ICD should be recommended. In patients treated with amiodarone who have recurrent hospital admissions with non-fatal recurrences of sustained VT, an ICD should be considered where it is likely that antitachycardia pacing with back-up cardioversion/defibrillation would prevent further hospitalizations.

Primary prevention

Screening patients using methods of risk stratification increases positive predictive accuracy but reduces sensitivity. This ensures that patients treated are drawn from groups that convey a higher apparent risk of later life-threatening arrhythmias or SCD. However, many

patients who will have a later episode are excluded by the screening process.

Furthermore, imperfect specificity ensures that many patients without symptoms will be subjected to the risks and costs of screening and treatment, but will not go on to have a clinical episode. These considerations, coupled with uncertainty about the MADIT findings, the very small numbers of patients available using MADIT criteria, and the vast cost involved, would presently appear to make ICDs for primary prevention of SCD impractical in the UK.

Special groups

Patients who have severely impaired ventricular function and who are awaiting cardiac transplantation, but suffer from the dearth of suitable donor organs, have a high rate of SCD (approximately 30%). This can be effectively prevented by the use of ICDs, enabling many patients to survive to transplantation who would otherwise die. In this group ICDs can be used as a 'bridge to transplantation' (Sweeney et al, 1995).

Patients with primary electrical disease, such as the congenital long QT syndrome and the Brugada syndrome (Brugada and Brugada, 1992), may have a high risk of SCD. An ICD may normalize their prognosis.

Patients with a very severe family history of SCD, and yet no way of assessing risk or individual involvement in the condition should increasingly be considered for an ICD. As the risk of treatment declines to very low levels with implantation under local anaesthesia (mortality <0.5%) of devices the size of a pacemaker, it becomes harder to justify non-treatment to patients with a very high apparent risk, whose individual involvement cannot be excluded. Fortunately for healthcare systems, these patients are very rare. HM

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KEY POINTS

- The implantable defibrillator (ICD) has a defined role in secondary prevention of sudden cardiac death but its use in primary prevention remains under debate.
- Reduction in size and improved technology allow pectoral implantation with low operative risk.
- If patient groups are chosen judiciously the cost-effectiveness of ICD therapy compares favourably with other currently accepted treatments.
- Comprehensive quality of life data are awaited.