EDITORIAL

Sudden cardiac death: opportunities for prevention

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The evidence base for implantable cardioverter-defibrillator (ICD) therapy requires expansion of guidance/indications to allow UK physicians to treat a broader range of patients. The ICD clinical consultees to the National Institute for Health and Clinical Excellence (NICE) review current guidance/guidelines, explain the evidence base, and suggest a UK ICD implantation strategy

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Sudden cardiac death (SCD) is responsible for 100 000 deaths annually in the UK, most of which are caused by coronary heart disease.¹ SCD is effectively prevented by the implantable cardioverter-defibrillator (ICD), both in patients surviving SCD, sustained ventricular tachycardia (VT) or fibrillation (VF) (secondary prevention), and those without previous SCD or VT/VF, identified by screening techniques to be at high risk (primary prevention). The National Institute for Health and Clinical Excellence (NICE) published guidance on ICD use in management of patients with serious ventricular arrhythmias in 2000.² More recent evidence supports extension of ICD use in primary prevention of SCD to post-myocardial infarction (MI) patients selected by ejection fraction (EF) alone, an indication now adopted broadly in Europe and North America but not the UK, where the limited resources of the National Health Service (NHS) have led NICE to suggest restricting endorsement of this indication to a limited post-MI population identified by electrophysiologic study (EPS).³ We suggest an alternative approach: non-invasive risk stratification targeting ICD therapy for the primary prevention of SCD to those at greatest risk.

ICD USE IN THE UK

The ICD implantation rate has risen in the UK since publication of NICE guidance, but remains low compared with western Europe. Despite NICE's recommendation² that post-MI patients with EF $\leq$ 35%, non-sustained VT, and inducibility at EPS be identified for ICD therapy, this guidance has not been followed,⁴ probably because EPS, only available in larger cardiac departments, is perceived as a block.

EXPANSION OF INDICATIONS FOR ICD IMPLANTATION: THE EVIDENCE BASE

Further evidence on primary prevention ICD use has been published recently.^{5–6} MADIT II,⁵ selecting post-MI patients on EF ($\leq$ 0.30) alone for randomisation to ICD therapy or not, demonstrated an absolute mortality reduction of 5.6% after 20 months (hazard ratio (HR) 0.69,

95% confidence interval (CI) 0.51 to 0.93, $p = 0.0016$, in ICD patients). SCD-HeFT⁷ recruited patients with New York Heart Association (NYHA) class II/III heart failure and EF $\leq$ 0.35 to receive placebo, amiodarone, or an ICD and demonstrated an absolute mortality reduction of 7.2% after five years in patients who received an ICD (HR 0.77, 95% CI 0.62 to 0.92, $p = 0.007$). Both trials showed an ICD mortality benefit in patients selected on the basis of left ventricular EF alone. Meta-analysis demonstrates an absolute mortality reduction of 7.9% for primary prevention. Excluding patient groups known not to benefit from ICD implantation for primary prophylaxis (patients $\leq$ 40 days of MI, EF $\leq$ 0.35 and impaired autonomic function, and those undergoing revascularisation) the reduction in absolute mortality is 6.6%.

Despite this evidence, and North American^{7–8} and European acceptance of it^{9–10} in guidelines, the NICE appraisal committee that reviewed UK ICD guidance was not persuaded that such an extension (to post-MI patients selected by EF alone) would be a cost effective use of NHS resources.³ It considered that neither the baseline risks (7–12%) of these patients, nor specifically the patient's capacity to benefit as indicated by the relative risk reduction in SCD (approximately 25–30%), were sufficient evidence.

RISK STRATIFICATION OF THE PRIMARY PREVENTION POST-MI POPULATION

A principal difference in MADIT I and II was selection of patients using EPS. MADIT I is flawed by the absence of a registry and inadequate information about outcome in those screened but not entered into the trial.¹¹ MUSTT demonstrated that an EPS guided strategy with antiarrhythmic drugs was deleterious compared to no antiarrhythmic therapy,

Abbreviations: ATP, antitachycardia pacing; AVID, antiarrhythmics versus implantable defibrillators study; CABG Patch, coronary artery bypass graft patch trial; CARE-HF, cardiac resynchronization-heart failure study; CASH, cardiac arrest study Hamburg; CIDS, Canadian implantable defibrillator study; CRT, cardiac resynchronisation therapy; DAVID, dual chamber and VVI implantable defibrillator trial; DINAMIT, defibrillator in acute myocardial infarction trial; EF, ejection fraction; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; MADIT I, multicenter automatic defibrillator implantation trial; MADIT II, multicenter automatic defibrillator implantation trial II; MI, myocardial infarction; MUSTT, multicenter unsustained tachycardia trial; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; NYHA, New York Heart Association; QoL, quality of life; SCD, sudden cardiac death; SCD HeFT, sudden cardiac death in heart failure trial; VF, ventricular fibrillation; VT, ventricular tachycardia

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whereas an EPS guided strategy with an ICD was advantageous.¹² The MUSTT registry allows comparison of non-inducible (at EPS) patients with those in the trial; 24% registry patients (non-inducible at EPS) suffering cardiac arrest/SCD at five years compared with 32% in the untreated (inducible) trial control group. The ICD treated group had a 9% five year cardiac arrest/SCD rate. Therefore, although EPS identified a slightly higher risk group, ICDs might have prevented many of the SCDs in registry patients, who were clearly *not* a low risk group.

Most receiving an ICD in MADIT II underwent EPS; 36% were inducible. Inducibility was associated with greater chance of ICD therapy for VT, but less for VF, suggesting that the EPS was unhelpful in predicting SCD. Similarly, EPS was not useful in predicting SCD (and, by inference, ICD benefit) in either CASH¹³ or AVID.¹⁴

Clearly, the value of EPS for risk stratification is controversial.¹⁵ While Buxton¹⁵ argues for its use, emphasising the high mortality in the control group of MADIT II (where there were many other risk factors), his analysis of the MUSTT database¹⁵ demonstrates that patients with the only additional risk factor (after selection into MUSTT) of EF < 0.30 had a predicted two year mortality of 6.2%, and predicted cardiac arrest/SCD risk of 3.5%. In contrast, additional risk factors, including use of digoxin, non-sustained VT detected ≥ 10 days after revascularisation, age ≥ 65 years, intraventricular conduction defect or left bundle branch block, inducible sustained VT (not VF) at the enrollment EPS, and non-sustained VT as an inpatient, predict a two year mortality risk of > 40%, and SCD/cardiac arrest risk of 36%. These risk factors therefore could be used to select patients for ICDs. Moss¹⁵ argues against an EPS strategy, and describes a retrospective analysis of outcome in MADIT II in which age ≥ 72 years, EF ≤ 0.25 , atrial fibrillation, NYHA III/IV, creatinine ≥ 1.4 mg/dl, and QRS ≥ 130 ms were all independent predictors of death. Low risk patients (with none of the above; 20% of the MADIT population) did not receive any benefit from the ICD and may even have been harmed. Those with 1–2 additional risk factors had a two year mortality of 20% and a relative risk reduction with the ICD of 0.54 ($p < 0.001$); those with ≥ 3 additional risk factors had a two year mortality of 41%, with a relative risk reduction with the ICD of 0.55 ($p < 0.001$).¹⁵

Various risk factors among the MADIT I population, including EF < 0.26, QRS > 120 ms, and a history of treated heart failure, identified patients at substantially higher risk, but who also gained more from the ICD. The hazard ratio for the ICD group fell progressively from 0.69 in patients with no additional risk factors to 0.20 for patients with all three. It is also clear in secondary prevention (AVID¹⁶ and CIDS¹⁷) that patients with lower EFs benefit most from the ICD.

Primary and secondary prevention trials are consistent: sickest patients with highest mortality risk can be identified by various additional risk factors, and gain most from ICD therapy.

The annual absolute mortality reduction attributed to the ICD is 10.0% in MADIT I and 6.2% in MUSTT, which NICE accepts justifies ICD implantation. The annual absolute mortality reduction attributed to the ICD in MADIT II is lower at 3.0% but for patients selected by the additional risk factors considered above, annual absolute mortality reduction attributable to the ICD is 5.4% in those with 1–2 risk factors, and 11.3% in those with ≥ 3 . It is logical that these higher risk MADIT II patients should receive ICDs.

In summary, age, symptomatic status, other clinical factors (more severely impaired ventricular function, QRS width, treated heart failure, advancing age, and microvolt QT alternans) may identify patients likely to benefit from an

ICD. The sensitivity and specificity of invasive EPS in risk stratification are insufficient to make it a useful clinical tool.

DO ICDs CAUSE HARM?

There is morbidity related to ICD use, including anxiety and depression. There are, however, no significant differences in psychosocial outcome between patients with ventricular arrhythmias treated either with the ICD or with drugs, or between pre- and post-implant ICD patients.¹⁸ Although patients who experience multiple shocks have reduced quality of life (QoL), it has been suggested that a poor psychosocial outcome may be associated with the underlying arrhythmia, and not the ICD itself. Assessment of ICD patients using a state-trait personality inventory showed that the majority (97%) felt that it was worth having an ICD device implanted, 53% patients returned to active life, and 98% would advise another patient to have an ICD if necessary. In general, patient acceptance of the ICD is high. The major factor reducing QoL in these patients is the occurrence of shocks. Most ($\geq 80\%$) tachyarrhythmia episodes are terminated by painless antitachycardia pacing (ATP). ATP was not employed in the major studies of ICD therapy, which focused on mortality, so shock related morbidity may have been overestimated.

An additional possible adverse effect of ICD therapy results from right ventricular apical pacing. In MADIT II³ it was observed that the morbidity in the ICD group was higher than in the control group, with an excess of hospital admissions because of heart failure, but later analysis has suggested that frequency of paced beats is related to the development of new or worsened heart failure in keeping with observations in the DAVID trial,¹⁹ which demonstrated the adverse effect of pacing the right ventricle in ICD patients without a standard indication for pacing. This deleterious effect may be avoided by pacing mode selection and programming strategies which minimise ventricular pacing.

COST EFFICACY

There are no British data on the costs of the ICD in post-MI primary prophylaxis,³ as despite NICE recommendations in 2000,² few ICDs are implanted in these patients. Modelling used by NICE in its current appraisal¹ of the 2000 guidance is based on unpublished studies of predominantly secondary prevention. It is not clear whether extrapolations from secondary prevention are valid. This paucity of accurate and contemporaneous real life data on which to base modelling is a hindrance. Furthermore, data and extrapolations from the evidence base have been used. Several of these trials were terminated early, and there is evidence that the benefit of the ICD may have therefore been underestimated.²⁰ Longer term analysis of a single centre contribution to CIDS has suggested increasing benefit with time, with the trial time horizon underestimating benefit.²¹ Despite these hurdles, cost efficacy figures which approach levels acceptable to NHS resources have been reached.³ Cost efficacy analysis of the “MADIT II” population yields figures of \$51 000 per QALY gained. Both health economists and clinicians believe that targeting of ICD therapy to higher risk patients will enhance cost efficacy in the NHS context and offer access of life saving ICD therapy to a needy patient population.

However, although the expense of providing the ICD for all those “MADIT II” patients who might benefit is large, the cost effectiveness falls within currently accepted ranges and is “economically attractive by conventional standards”.²² The MADIT-II population is large. Appropriate risk stratification may allow a more cost effective strategy to be employed as demonstrated in CIDS, where ICD therapy was much more cost effective in patients with two or more additional risk factors.²³

CONCLUSION

The profession and NICE should urgently work together to expand implant guidance to allow a broader patient population protection from SCD, a major aim of the recently published chapter 8 on arrhythmias and sudden cardiac death of the National Service Framework for coronary heart disease.

Prior to the finalising of NICE guidance for ICDs now, and cardiac resynchronisation therapy (CRT) in August 2006, we suggest, based on scientific evidence with limited extrapolation, that the indications for ICD implantation be extended to include *carefully selected* MADIT II patients. Additional selection criteria should include increasing age, increasing symptoms, decreasing left ventricular EF, and increasing QRS width (with CRT if appropriate). Microvolt QT alternans may also be useful. Care should be taken to exclude patients with co-morbidities which will significantly shorten life, and with NYHA class IV heart failure (unless in association with CRT, in which case it is likely that NYHA class will improve). If revascularisation is required, consideration of an ICD for primary prophylaxis should be delayed for six months, and EF reassessed.

This opinion is consistent with the decision made by the Centers for Medicare and Medicaid Services in the USA, who determined that the evidence is adequate to conclude that an ICD is "reasonable and necessary" for the following:

- "Patients with ischaemic dilated cardiomyopathy (IDCM), documented prior myocardial infarction (MI), New York Heart Association (NYHA) Class II and III heart failure, and measured left ventricular ejection fraction (LVEF) $\leq 35\%$."

In conclusion, risk stratification of patients for primary prophylaxis of SCD using ICD therapy can be achieved by assessment of EF and other non-invasively obtained parameters.

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