Is prophylaxis the best use of the ICD?

Introduction

When Michel Mirowski initially conceived of the implantable defibrillator the aim was to protect the patient at risk of sudden arrhythmic death[1]. In the late 1960s, when Mirowski and co-workers projected the development of an automatic implantable defibrillator, out-of hospital resuscitation was a rare event. However, the out-of-hospital resuscitation initiatives led by investigators from Seattle and Miami[2,3] started providing large groups of patients, thereby facilitating the clinical evaluation and acceptance of implantable cardioverter defibrillator (ICD) therapy, in the 1980s[4]. The fact that patients resuscitated from cardiac arrest frequently develop recurrent potentially lethal arrhythmic episodes, combined with the development and increasing use of programmed ventricular stimulation, created the basis for their identification. Thus, during the first two decades, the ICD was used almost exclusively for secondary prevention of sudden death in patients who had already developed clinically documented sustained ventricular tachyarrhythmias.

At the end of the first decade of ICD therapy — and in the spirit of ‘evidence-based medicine’ — four prospective randomized trials were begun, to evaluate the effectiveness of the ICD for secondary prevention, and three others for primary prevention[5,6]. These studies were concluded within the 1990s, and demonstrated that patients enjoyed better survival with ICD therapy compared to conventional pharmacological alternatives. Furthermore, this benefit was evident both in patients with previous sustained ventricular tachyarrhythmias and without. The time has come to assess which patients benefit most from ICD therapy. The aforementioned trials provide strong and possibly surprising insights into this question, and are the focus of this article.

Brief overview of the ICD trials

To date, seven studies — four for secondary prevention and three for primary prevention — have been completed[7–13]. All of these studies have now been published. Table 1 provides the acronyms, and a description of the enrolled patients. The overall results, in terms of all-cause mortality, are shown in Fig. 1. The four trials shown on the left side of the figure were in patients who had been resuscitated from ventricular fibrillation or ventricular tachycardia; whereas the three trials on the right hand side were conducted in patients who had had no previous history of sustained ventricular tachycardia/ventricular fibrillation. The figure shows that in six of the seven studies, patients randomized to ICD had a better survival than their controls. The exception is CAGB-Patch, which had a neutral outcome. In AVID, the Dutch study, MADIT and MUSTT the beneficial effect of the ICD on total mortality reached statistical significance. The CASH and CIDS studies only showed strong trends in favour of the ICD (see Discussion below). In spite of the lack of homogeneity in the populations recruited by AVID, CIDS and CASH, Conolly et al. have conducted a meta-analysis pooling the data from the three trials. The meta-analysis corrects the power issues that affect CIDS and CASH and concludes that ‘... results from the three trials are consistent with each other. There is a 28% reduction in the relative risk of death with the ICD that is due almost entirely to a 50% reduction in arrhythmic death’[14].

As to the primary prevention studies, it is noteworthy that MADIT and MUSTT enrolled nearly identical patient populations, as seen in Table 2, where the only real difference is the mean length of NSVT runs — nine in MADIT and five in MUSTT. This difference and the slightly poorer left ventricular function for the MADIT cohort (mean LVEF 0·26 vs 0·30 for MUSTT) may account for the somewhat higher control group mortality in MADIT (32% at 2 years, compared to 28% for MUSTT). Thus, the fact that the two studies had such remarkably similar outcomes (Fig. 2)[15] provides highly convincing evidence that patients selected for the MADIT/MUSTT cascade are at very high risk, and that their mortality risk is substantially reduced by ICD therapy. MUSTT has responded soundly to the criticisms of MADIT, and in particular to the concern about ‘beta-blocker imbalance’ and lack of a no-therapy limb[16]. These two studies have now reinforced the
idea that patients with previous myocardial infarction, depressed left ventricular ejection fraction, documented runs of non-sustained ventricular tachycardia, and inducibility into sustained ventricular tachycardia with programmed stimulation, have a very substantial risk for death (around 30% at 2 years), and that treatment with an ICD reduces that risk by over 50%.[11,13]

Comparing outcomes of the primary and secondary prevention trials

In AVID, MADIT and MUSTT the hazard ratios in favour of ICD therapy are 0.62, 0.46, and 0.49, respectively. In each trial the beneficial effect of the ICD on mortality was statistically significant, with two-sided \( P \)-values <0.02, <0.009, and <0.001,

Table 1 Overview of completed ICD trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Randomization</th>
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<tbody>
<tr>
<td>Dutch CES (Dutch Cost-Effectiveness Study)</td>
<td>Resuscitated cardiac arrest with coronary artery disease</td>
<td>ICD vs ‘Conventional’</td>
</tr>
<tr>
<td>AVID (Antiarrhythmics vs Implantable Defibrillator)</td>
<td>Resuscitated cardiac arrest or symptomatic VT</td>
<td>ICD vs amiodarone or sotalol (96% amio)</td>
</tr>
<tr>
<td>CASH (Cardiac Arrest Study Hamburg)</td>
<td>Cardiac arrest (any etiology)</td>
<td>Metoprol/amiodarone/propafenone/ICD ICD vs amiodarone</td>
</tr>
<tr>
<td>CIDS (Canadian Implantable Defibrillator Study)</td>
<td>Resuscitated cardiac arrest or VT</td>
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<tr>
<td>MADIT (Multicenter Automatic Defibrillator Implantation Trial)</td>
<td>Late post-MI, LVEF ( \leq 0.35 ), NSVT, inducible/non-suppressible VT</td>
<td>ICD vs ‘Conventional’ (75% amiodarone)</td>
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<tr>
<td>CABG-Patch (Coronary Artery Bypass Graft Patch Trial)</td>
<td>CABG patients with LVEF ( \leq 0.35 ), SAECG+</td>
<td>ICD vs no ICD</td>
</tr>
<tr>
<td>MUSTT (Multicenter UnSustained Tachycardia Trial)</td>
<td>Late post-MI, LVEF ( \leq 0.40 ), NSVT, inducible VT</td>
<td>EP-guided therapy vs no antiarrhythmic therapy</td>
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MI=myocardial infarction; LVEF=left ventricular ejection fraction; NSVT=non-sustained ventricular tachycardia; VT=ventricular tachycardia; SAECG=signal average electrocardiogram; VF=ventricular fibrillation; EP=electrophysiological.

Figure 1 ICD studies — reduction in mortality compared to conventional medical therapy. Shown here are the all-cause mortality, at 2 years follow-up, for each study for both the ICD-randomized patients (solid bars) and the control group (open bars). Shown above each study histogram are the percentage reductions in mortality and corresponding \( P \)-values for the secondary prevention studies — AVID, Dutch, CASH and CIDS — and the primary prevention studies — MADIT, MUSTT, and CABG-Patch. For each of these prospective, randomized studies, the reductions were calculated for total mortality, comparing patients randomized to ICD therapy vs control (see text for further details).
respectively. The meta-analysis of AVID, CIDS and CASH indicated a 28% reduction in all-cause mortality (\(P<0.001, 95\%\) confidence limits 0·60–0·87) for patients treated with ICDs\[14\]. By contrast, the all-cause mortality reductions in favour of patients receiving ICDs were 54% in MADIT and 51% in MUSTT (95% confidence limits 0·26–0·82 and 0·35–0·69, respectively). By comparing the AVID/CIDS/CASH results to the average of MADIT/MUSTT (Fig. 3), we can appreciate that patients using the ICD ‘prophylactically’ profit more from such a therapeutic device than the ‘classic’ ventricular tachycardia/ventricular fibrillation survivors. The difference in mortality reduction between these two groups of patients (53% vs 28% in primary versus secondary prevention indications) is noticeable enough to warrant some reflection.

**Table 2** MADIT and MUSTT patient demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>MADIT (n=196)</th>
<th>MUSTT (n=704)</th>
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</thead>
<tbody>
<tr>
<td>Mean time MI to enrolment (months)</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Previous CABG/PTCA (%)</td>
<td>71</td>
<td>66</td>
</tr>
<tr>
<td>Mean age</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>% Males</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>LVEF (mean)</td>
<td>0·26</td>
<td>0·30</td>
</tr>
<tr>
<td>NSVT (mean beats)</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>CHF II–III (% patients)</td>
<td>65%</td>
<td>64%</td>
</tr>
</tbody>
</table>

MI=myocardial infarction; CABG=coronary artery bypass grafting; PTCA=angioplasty; LVEF=left ventricular ejection fraction; NSVT=non-sustained ventricular tachycardia; NYHA=New York Heart functional class of heart failure.

Figure 2 Kaplan–Meier freedom from all-cause mortality curves for MADIT and MUSTT. The upper curves show survival outcomes for patients treated with ICDs in each study. The three lower curves represent electrophysiologically guided antiarrhythmic drug therapy or no antiarrhythmic for MUSTT, and conventional therapy in MADIT. Also shown are the risk ratios (with 95% confidence limits) for reduction in all-cause mortality for the ICD treated patients compared to controls in the two studies. (Reprinted, with permission, from Ref. \[15\].)

One of the early reactions to the MADIT trial echoed the sentiment, ‘... we have to take care of the patients with a history of ventricular tachycardia/ventricular fibrillation before we can consider the ICD prophylactically’. This reaction was certainly based on the obviously valid medical obligation to protect the already hospitalized patient from the consequences of probable ventricular tachycardia/ventricular fibrillation recurrence. For others, this reasoning was founded more on economic grounds, i.e. using the available budgets for the ‘proven’ patients before expending monies trying to protect patients, whose risk was considered only theoretical. There is little counter argument to the first point, indeed the official published guidelines everywhere prescribe the ICD as a class I indication for patients resuscitated from life-threatening ventricular tachyarrhythmias\[17–19\]. However, with regard to the economic argument, ironically, it might well be that the best financial use of available funds might be in indicating ICDs prophylactically. We hesitate to compare ICD cost-effectiveness studies, simply as only one—the MADIT cost-effectiveness study—was carried out prospectively and with nearly 100% collection of cost data\[20\]. Two recent publications have pointed to the problems of using incomplete cost-effectiveness studies, and in particular in ‘truncating’ the period of follow-up, allowing insufficient...
time to realize the full (ICD) investment\textsuperscript{21,22}. The MADIT study showed that the cost-effectiveness of the ICD was approximately $23,000 per life year saved (for a 4-year life device, implanted transvenously)\textsuperscript{20}. The major reason for this excellent cost-effectiveness came from the fact that patients randomized to ICDs had their lives extended by nearly one year more than those receiving medical therapy. In contrast, AVID reported an extension of life of 2.7 months at 3 years follow-up\textsuperscript{20}. Clearly, one of the interpretations from this data and from Fig. 3 is that implanting ICDs in MADIT or MUSTT type patients appears highly cost-effective.

Are there possible explanations for the difference seen in Fig. 3? First of all, it is now evident that the MADIT/MUSTT screening is extremely effective in identifying not only a high-risk patient, but in particular a high potentially fatal arrhythmia-risk patient. These patients have a 2-year mortality, of about 30\%, in the absence of ICDs, which is somewhat higher than that found in AVID (25\%-3\%). Might it be that surviving ventricular tachycardia/ventricular fibrillation identifies patients with a certain likelihood of surviving subsequent episodes of the same or a similar arrhythmia, so that the actual risk of sudden death in this patient population is lower than in other clinical subsets, as represented by the MADIT/MUSTT patient profile? Interestingly, the sudden death risk reduction achieved with ICDs was around 50\% in the AVID/CIDS/CASH analysis, as compared to 76\% in MUSTT\textsuperscript{13,14}. In practical terms, these results indicate that the MADIT/MUSTT patient population now represent ideal candidates for ICD therapy, despite receiving the device before having developed a sustained episode of ventricular tachycardia/ventricular fibrillation. This statement does not negate the value of the ICD in the ‘AVID’ type of patient, since the reductions in sudden death and all-cause mortality achieved in that study are manifestly significant, not only statistically speaking but also from the clinical point of view.

Analysis of AVID, CIDS, CASH

The publication of CIDS and CASH, where the ICD did not show a statistically significant mortality reduction in survivors of potentially lethal ventricular tachyarrhythmias, might be taken as an argument to raise doubts about the validity of the conclusions of the AVID study. The reasons why CIDS has not duplicated, from the statistical point of view, the results of AVID have been reviewed elsewhere\textsuperscript{23}. A detailed scrutiny of the AVID and CIDS trials suggests that the latter study failed to reach statistical significance principally due to: (a) insufficient power and (b) the inclusion of an undetermined number of relatively lower-risk patients as compared with those recruited in AVID\textsuperscript{23,24}. We have pointed out previously that a possible contributing factor to the lower impact of ICDs in CIDS might have been due to the larger proportion of patients allocated to the ICD arm, who were not implanted (5-5\% in CIDS vs 2\% in AVID), and we emphasized the importance of this difference, when considering that 2\%-1\% of ICD-randomized patients died while awaiting implantation\textsuperscript{23}. However, although it has been stated that cross-over rates might also account for the observed differences between AVID and CIDS\textsuperscript{24}, the lower CIDS mortality in the amiodarone group as compared to AVID is not explained by cross-over. In fact, the cross-over rate was higher in AVID as compared to CIDS. At 3 years, 33\%-7\% of the patients allocated to amiodarone in AVID received an ICD, compared with only 21\%-7\% in CIDS. In spite of this, mortality at 3 years was 35\%-9\% in the drug arm of AVID as compared with 27\%-0\% in the amiodarone group of CIDS. This point reinforces the impression that the CIDS population simply represented a lower-risk cohort compared to the AVID population.

The CASH trial recruited patients resuscitated from cardiac arrest, a group of subjects thought to represent the paradigm of the population that could benefit from ICD implantation. Although the ICD resulted in an overall reduction in total mortality of 23\% when compared with the pool of patients treated with amiodarone or metoprolol, the differences did not reach the level of statistical significance. Despite the fact that the ICD resulted in a relative risk reduction of 40\% at 2 years, such a clinically relevant figure was not statistically significant. This by itself indicates that the study was not sufficiently powered for the patient population included in the investigation. And this leads us to comment on the ‘unique’ patient population recruited in the CASH trial. The mean left ventricular ejection fraction of the CASH patients was 46\%, more than 10 points above the ejection fraction of similar studies such as the CASCADE (35\%\textsuperscript{25}) or even the AVID and CIDS patient cohorts (32\% and 34\%, respectively).

One can speculate that many of the patients resuscitated from cardiac arrest in CASH could belong to the category in which the lethal arrhythmic episode was due to an acute coronary occlusion, as suggested by Spaulding et al\textsuperscript{26}, and that the low event rate in the CASH patients may be partially due to a high rate of coronary artery interventions. The patients from CASH also do not match the characteristics of the patients reported on by Spaulding et al. since the left ventricular ejection fraction in the latter study was
34%. Therefore, for reasons that are not completely clear to us, the CASH trial recruited an extremely low-risk patient population. A retrospective analysis of the AVID data suggests that the ICD may not be better than amiodarone for patients whose left ventricular ejection fraction is >34% and many patients in the CASH had to be above this limit. This finding — that the ICD benefit seems to be highest in patients with poor left ventricular function — has been highlighted by several authors recently. However, as has been pointed out, all these findings are retrospective, and hence should be considered as 'hypothesis-generating', possibly for future trials.

Additional problems contributing to the unexpected outcome of the CASH trial are: (1) a 5% peri-operative mortality in the ICD group (half of the ICD patients were implanted using a thoracotomy) and (2) the near absolute absence of concomitant beta-blockade in the ICD patients, despite the fact that 76% of the CASH population had an underlying coronary artery disease. Both circumstances are penalties on the ICD side that might have contributed to further minimize the benefit of the ICD.

This paper would, of course, be incomplete without mentioning the one study, CABB-Patch, which failed to show benefit for the ICD. The patients enrolled in CABB-Patch — in contrast to those in all the other trials — had never had sustained ventricular tachycardia/ventricular fibrillation (whether induced as in MADIT or MUSTT or spontaneous, as in the four other studies). Furthermore, the CABB-Patch patients underwent revascularization at entry into the study, thereby profiting from the well-established benefits of this intervention. As previously reported and shown in Fig. 1, the actual mortality for patients without an ICD was only 18% at 2 years, and only 13% (!), when excluding the 30-day mortality associated with the CABB surgery. An important contribution of the CABB-Patch study, and clearly illustrated in Fig. 1, is that patients with a 2-year mortality risk under 20% stand little chance of benefiting from ICD therapy.

Conclusions

The primary reflection of this paper is that, contrary to conventional wisdom, patients without previous sustained ventricular tachycardia/ventricular fibrillation but fitting the MADIT/MUSTT profile have even more life-saving benefit from ICD therapy than those who have been resuscitated from cardiac arrest or symptomatic ventricular tachycardia. This observation does not call into question the conventional indications for the ICD in so-called secondary prevention scenarios. It means that active steps should be undertaken to systematically screen patients with a post-myocardial infarction scar and a depressed left ventricular ejection fraction to identify those with runs of non-sustained ventricular tachycardia. This patient population (the MADIT/MUSTT profile), although possibly not very large, has been shown to be at extremely high risk of arrhythmic sudden death and of obtaining a most striking benefit from the ICD in terms of mortality reduction. Therefore, at the time of writing, the MADIT/MUSTT patient population constitutes the best indication for an ICD according to the rules of evidence-based medicine.

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References


Addendum

Subsequent to the submittal of our article, another major ICD trial—very pertinent to our thesis—has just been published (‘Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction’ by A. J. Moss et al., New Engl J Med 2002; 346: 877–83). This randomized, prospective trial on 1232 patients with a mean follow-up of 20 months showed that ICD therapy lowered the risk of all-cause mortality by 31% (P=0.016), compared to optimal medical therapy. This result is a strong reinforcement of our position concerning the prophylactic role of ICD therapy.