Lessons learned from neutral ICD trials

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Multiple prospective randomized trials with implantable cardioverter defibrillators (ICDs) over the past decade have convincingly established the efficacy of ICD therapy in reducing all-cause mortality, by significantly reducing sudden cardiac death. Nevertheless, four trials have failed to show improved survival. Analysing these, in comparison with the positive trials, provides important information concerning the type of patients not likely to receive benefit from ICDs: (i) those with relatively low mortality (<18% within 2 years of follow-up); (ii) those whose mechanism of death is predominantly non-arrhythmic; (iii) patients early (within 6 weeks) after infarction.

KEYWORDS
Implantable cardioverter defibrillator; Sudden death; ICD trials

Introduction

Following the introduction of the implantable cardioverter defibrillator (ICD) into clinical practice in 1980 by Mirowski et al., numerous clinical trials were performed during the decade of the 1990s to ascertain the efficacy of this therapy. Randomized clinical trials (RCTs) have been carried out both in patients with a previous history of life-threatening ventricular tachyarrhythmias, so-called secondary prevention trials, and in patients without previous out-of-hospital cardiac arrest or sustained ventricular tachycardia, referred to as primary prevention trials. Some of these RCTs have been carried out in patients with previous myocardial infarction, others only in patients with non-ischaemic cardiomyopathy (NICM), and the remaining ones have studied heterogeneous populations. The vast majority of these studies have turned out positive for ICD therapy, demonstrating its superiority in terms of reduction in all-cause mortality, compared with conventional medical therapy, often amiodarone (Figure 1). Understandably, these results have subsequently been incorporated into guidelines indicating appropriate patient cohorts for this therapy and, importantly, those who stand little chance of benefit.

Four neutral (non-positive) studies

The study populations, study designs, and the results of the positive ICD studies have been previously reported. Therefore, we will comment only on those aspects of these positive trials which relate to the comparison with the four neutral (non-positive) trials, which is our primary focus. The four trials which concluded with neutral, neither positive nor negative, results were Coronary Artery Bypass Graft (CABG)-Patch trial, Cardiomyopathy Trial (CAT), Amiodarone versus Implantable Cardioverter Defibrillator Randomized Trial (AMIOVIRT), and Defibrillator in Acute Myocardial Infarction Trial (DINAMIT). The University of Münster (G.B. and co-workers) was involved in all but the AMIOVIRT. Table 1 provides the patient inclusion criteria, the groups randomized, and the duration of follow-up. Of the four trials, only AMIOVIRT compared ICD with a specific antiarrhythmic agent (amiodarone). Two of these trials (CAT and AMIOVIRT) included only patients afflicted by NICM (see Table 1 footnotes for precise definition), whereas the other two enrolled patients with ischaemic cardiomyopathy: in one shortly post-MI (DINAMIT), and in the second, patients requiring revascularization (CABG-Patch). Table 2 summarizes the patient characteristics for the subjects studied in the four trials. Most patients in these four neutral RCTs were middle-aged, mean age between 52 and 64 years. About two-thirds presented with NYHA classes II–III heart failure, with depressed ventricular function and a left ventricular ejection fraction (LVEF) of 0.27 (weighted mean value). The patients in three
of these trials where data were available tended to have slightly elevated heart rates at rest.

Comparing the patients in the positive and neutral ICD trials

The patients included in all these ICD studies presented with quite different aetiologies. Therefore, it is not very helpful to compare the patient profiles in the four neutral studies (Table 2) with the ones in the positive studies. Nevertheless, a few points are worth noting. Two of the neutral RCTs, CAT and AMIOVIRT, studied exclusively non-ischaemic patients, whereas the patients in nearly all the other trials enrolled either exclusively patients with previous myocardial infarction or ~80% of the enrolled patients had an ischaemic aetiology. The major exception was DEFINITE, which like CAT and AMIOVIRT enrolled patients with NICM. In the other two neutral studies, CABG-Patch and DINAMIT, the underlying substrate may be considered as ‘unstable’: in CABG-Patch, patients enrolled required CABG surgery to correct their documented ischaemia; this should have led to improvement in regional ventricular function. In DINAMIT, patients were enrolled at a mean of 18 days post-MI,\(^1\) hence well before remodelling of the infarcted myocardium had reached a stable phase in most of them. In both trials, LV dysfunction was required as an inclusion criterion. In DINAMIT, patients showed a slight improvement in left ventricular function, from 0.28 at baseline to 0.30 by 6–8 weeks following their acute infarction, showing that LV dysfunction may be potentially reversible in some of the patients, in the early period following infarction.\(^1\) In contrast to CABG-PATCH and DINAMIT, in all the positive studies, patients were enrolled well after their most recent MI or coronary revascularization. In fact, patients in studies such as MUSTT, MADIT, and MADIT II were enrolled, on an average, 3 years or more following their most recent infarction (although in MUSTT, a small minority, 17%, were enrolled within the first month). In summary, two of the neutral RCTs involved NICM patients; the other two enrolled patients with a potentially unstable, evolving substrate related to prior ischaemia that may have been improved by revascularization (CABG-Patch) or spontaneously (DINAMIT).

Comparing outcomes between the positive and neutral ICD trials

All trials had all-cause mortality as the primary endpoint. This identical endpoint allows for a direct comparison of mortality outcomes observed in the four neutral ICD trials, on which we will focus. The first important observation is that the control group mortality at 2 years in each of these four RCTs was relatively low and far lower than that in the positive ICD trials. For example, the patients in the control group of AVVID, CASH, CIDS, Dutch,\(^3\) MADIT, MUSTT, MADIT II, and COMPANION (COMPANION was not strictly an

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Randomization</th>
<th>Mean F/u</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT</td>
<td>LVEF ≤0.30, symptomatic, dilated NICM(^a) ≤9 months, NYHA Classes II–III</td>
<td>ICD vs. conventional</td>
<td>66 months</td>
</tr>
<tr>
<td>AMIOVIRT</td>
<td>NICM(^b), LVEF ≤0.35, NSVT</td>
<td>ICD vs. amiodarone</td>
<td>24 months</td>
</tr>
<tr>
<td>CABG-Patch</td>
<td>Scheduled for CABG with LVEF ≤0.35, SAECG positive</td>
<td>ICD vs. no ICD</td>
<td>32 months</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>Recent MI (6–40 days), LVEF ≤0.35, depressed HRV (SDNN ≤70 ms), or mean heart rate ≥80 bpm</td>
<td>ICD vs. conventional</td>
<td>30 months</td>
</tr>
</tbody>
</table>

\(^a\)NICM—the absence of coronary artery disease confirmed by coronary angiography.

\(^b\)NICM defined as LV dysfunction in the absence of CAD or disproportionate to the severity of CAD.

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Table 2 Overview of patients enrolled in the neutral (non-positive) ICD trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>NYHA class I (%)</th>
<th>NYHA class II (%)</th>
<th>NYHA class III (%)</th>
<th>LVEF (mean)</th>
<th>Per cent of patients</th>
<th>Per cent of patients</th>
<th>Per cent of patients</th>
<th>Hx of hypertension (%)</th>
<th>LBBB (%)</th>
<th>Mean heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT</td>
<td>52</td>
<td>15.5</td>
<td>65.3</td>
<td>34.6</td>
<td>24.0</td>
<td>3.8</td>
<td>96.2</td>
<td>96.2</td>
<td>29.9</td>
<td>29.9</td>
<td>72.5</td>
</tr>
<tr>
<td>AMIOVIRT</td>
<td>59</td>
<td>15.5</td>
<td>63.5</td>
<td>34.6</td>
<td>22.5</td>
<td>51.5</td>
<td>85.5</td>
<td>85.5</td>
<td>62.5</td>
<td>47.5</td>
<td>79</td>
</tr>
<tr>
<td>CABG-P</td>
<td>63.5</td>
<td>65.3</td>
<td>34.6</td>
<td>75.2</td>
<td>27.0</td>
<td>17.9</td>
<td>66</td>
<td>66</td>
<td>53</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>61.8</td>
<td>58.8</td>
<td>27.5</td>
<td>27.5</td>
<td>28</td>
<td>87</td>
<td>94</td>
<td>94</td>
<td>46</td>
<td>30</td>
<td>80</td>
</tr>
</tbody>
</table>

BBI, beta blockers; NA, not available; Hx, history; LBBB, left bundle branch block. For trial acronyms, see text.
ICD trial, as it compared cardiac resynchronization therapy (CRT) with and without an ICD with best medical therapy. Our reasons for including this trial in this analysis is that although CRT certainly contributed to the 36% mortality reduction observed in COMPANION, this mortality reduction only reached statistical significance in the arm which included ICD back-up.) had reached mortality rates between 20 and 35% by 24 months of follow-up (Figure 2).

In contrast, as seen in Figure 3, the 2-year mortality for the non-positive ICD trials ranged from 8% (CAT) to 18% (CABG-Patch). The low mortality in CAT may be reflected by the relatively low proportion of 30% of patients with left bundle branch block, a well-established independent risk factor for mortality.21 Also, CAT only included patients with 'newly diagnosed' dilated cardiomyopathy, and it is well-known that such patients respond well to beta-blockers and angiotensin-converting enzyme inhibitors (ACE-I), with relatively low mortality when appropriately treated. In CABG-Patch, excluding the 5.5% 30-day peri-operative mortality associated with CABG surgery (as the ICD cannot have an impact on this), the subsequent mortality over the next 24 months only reached 12.5%. Two important exceptions to the pattern described earlier occurred with the SCD-Heft and DEFINITE trials, where the control group mortality at 2 years approached 15% in each. However, in SCD-Heft, the size of the study (2521 patients) coupled with the long (median 45.5 months) follow-up permitted it to reach a positive outcome despite the somewhat lower mortality. In DEFINITE, the size of the study (2521 patients) coupled with the long (median 45.5 months) follow-up permitted it to reach a positive outcome despite the somewhat lower mortality. In DEFINITE, the treatment effect of the ICD on sudden arrhythmic deaths (80% reduction in sudden deaths) was so strong that it enabled the entire trial to show a strong trend towards reduction in all-cause mortality (hazard ratio 0.65, 95% confidence limits 0.40–1.06, \(P = 0.08\)). So, clearly, one important observation is that for ICD trials to be positive, the patients’ risk must be sufficient for the ICD to be able to have a beneficial impact.

As the ICD is designed to combat an arrhythmic mechanism of death, it can only be effective in the presence of a sufficiently high incidence of sudden death. Such a patient population was actually included in DINAMIT, i.e. patients with a low ejection fraction (35% or less) and depressed heart rate variability or 24-h mean RR-intervals of 750 ms or less. These patients were considered to have a substantial risk of sudden death, which was indeed the case as 34% of patients died from an arrhythmic cause. Nevertheless, this trial did not come up with a positive result, which suggests reasons other than an insufficient arrhythmic mortality. The mode of death undoubtedly plays a major role. This is apparent from Table 2 (right-hand columns), where the mode of death, i.e. the percentage of deaths adjudicated to be 'sudden arrhythmic' is presented. Comparing the mode of death in the neutral studies with that in the positive ICD studies, there was a clear trend for a higher percentage of sudden arrhythmic deaths in the positive ICD trials (Figure 3). Specifically, the percentage of sudden deaths varied from zero (CAT) to 34% (DINAMIT) in the neutral trials and from 35% (MADIT) to 55% (MUSTT) in the positive ICD trials. The exception to this trend among the positive trials was the DEFINITE study, where sudden arrhythmic deaths accounted for 25% of all deaths. However, as indicated earlier, the strength of the treatment effect of the ICD, which lowered sudden deaths by four-fifths, permitted this trial also to show a strong trend towards reducing all-cause mortality. [Strictly speaking, DEFINITE showed ‘neutral’ results, as the ICD benefit (hazard ratio 0.65, 95% confidence limits 0.40–1.06, \(P = 0.08\)) did not reach statistical significance. However, owing to this strong trend towards a positive result, reinforced by the recent meta-analysis by Desai et al. showing ICD benefit in patients with NICM,22 we have grouped DEFINITE among the positive trials; had it been included among the neutral trials, its percentage of sudden arrhythmic deaths would have fallen into the range indicated earlier for neutral trials.)

Discussion

The main findings derived from comparing the populations and results of the four neutral ICD trials with those of the large number of positive trials is that (i) there were definitely differences in the patient cohorts, (ii) the level of mortality risk was generally much higher in the positive

Figure 2  Control group mortality (%) at 2 years follow-up in all the ICD RCTs. The positive ICD trials are grouped on the left, and the four neutral ICD trials shown grouped together on the right.

Figure 3  Arrhythmic mortality (% of total mortality) in ICD trials. The positive ICD trials are grouped together on the left, and the four neutral trials grouped together on the right. (Data not available for AVID, Dutch, SCD-Heft, and COMPANION.)
ICD trials than in the neutral trials, (iii) the positive ICD trials seemed to have patients whose risk of arrhythmic death was relatively higher than in the neutral ICD trials, and (iv) ICD therapy did not improve survival in patients enrolled early after infarction (within 6 weeks). In retrospect, these findings should not surprise us; an intervention stands little chance of improving outcome if the risk of events (in the case of ICD trials, deaths from all causes) is not high enough. The reason for the generally higher overall mortality in the positive trials cannot be explained by inadequate medical therapy, as four of the largest and most recent of the positive trials (MADIT II, COMPANION, DEFINITE, and SCD-Heft) maintained excellent compliance with beta-blockers, ACE-Is, and other appropriate medications.**Furthermore, as the ICD can only have an impact on sudden deaths due to arrhythmias, it is not surprising that in patient cohorts where the arrhythmic risk was not high enough, the ICD was unable to have an impact on all-cause mortality, despite reducing the arrhythmic mortality. The DINAMIT result that ICDs did not benefit patients early after infarction is also reinforced by the MADIT II substudy by Wilber et al.,** which showed that ICDs were much more effective late after infarction. These observations and analyses are not meant in any way to criticize the studies, which yielded neutral results. In CAGB-Patch, for example, the hypothesis that patients with left ventricular dysfunction and abnormal signal-averaged ECGs (which, at the time that the trial began, were considered to be an indicator of arrhythmic risk) were at high risk for sudden death, and therefore potentially benefiting from ICDs, was very plausible. As it turned out, surgical revascularization removed much of the arrhythmia risk, so the patients post-CABG only had a 22% risk of dying from arrhythmias, too low for the ICD to be able to have an impact on all-cause mortality, as four-fifths of the deaths were due to non-arrhythmic causes, as also pointed out by Veenhuyzen et al. The only other ischaemic population with a neutral study result was DINAMIT. Here, again the relatively low mortality (17.7% at 3 years) compared with that hypothesized (30%), based on earlier publications, is most probably the main reason for this trial ending with a neutral result.

Does this analysis help understand the role and limitations of ICD therapy for patients with NICM? CAT and AMIOVIRT were two of the neutral trials and the main lesson from them is that the mortality risk for patients meeting the inclusion criteria was too low for the ICD to be able to have an impact. The only 'fault' in the design of these two trials was not having foreseen that the evolution in medical management of such patients would turn out to vastly improve their prognosis, vis-à-vis the outcomes that had been reported for such patients in earlier years. It should be added that CAT was in fact only a 'pilot trial' with just 100 patients (main trial was hypothesized to require 1348 patients), and the low observed mortality precluded expanding it into a full trial. SCD-Heft, with nearly half NICM patients, did show a positive outcome for ICDs, probably aided by the large size of the study and the very long follow-up. As a matter of fact, the survival curves only started diverging at 18 months, so a study terminating earlier, and/or with fewer patients may not have achieved a positive result.

It was also clear that in patients with active ischaemia and/or those enrolled very shortly following infarction, ICD therapy was not able to reduce all-cause mortality, despite lowering the arrhythmic mortality in both studies. In patients such as in CAGB-Patch, already scheduled to undergo revascularization, the ICD may eventually be of help (as demonstrated clearly in MADIT, MUSTT, and MADIT II), i.e. in those patients who—subsequent to their revascularization—continue to manifest the risk stratifiers used in these studies. A reasonable strategy in such patients might be to re-evaluate them, say, 6–8 weeks after revascularization and decide then if there is a need for ICD implantation. In DINAMIT, the patients' slight improvement of LVEF from 0.28 at baseline to 0.30 by 6–8 weeks post-infarction may have been one of the explanations for their lower overall risk than patients with LVEF ≤0.25, as in MADIT, MUSTT, MADIT II, and SCD-Heft. We believe that waiting 4–6 weeks post-MI to re-evaluate the patients, as in MADIT, MADIT II, and MUSTT, allows them to achieve a more stable physiological and electrophysiological situation, which permits a more meaningful evaluation of their risk and need for therapy (in MADIT, MADIT II, and MUSTT, respectively, zero, and 17% of patients were enrolled <1 month of MI). This same observation was certainly taken into account by the Centers for Medicaid and Medicare Studies, in excluding ICD insurance coverage to patients who '...had an acute MI within the past 40 days'.

**Conclusions and clinical implications**

It is important to emphasize that also these non-positive ICD trials have contributed to the overall knowledge base, which now helps select patients for whom ICDs provide substantial benefit: cohorts with relatively high risk of all-cause mortality and, in particular, with high risk of arrhythmic mortality. At the same time, we have to accept the lessons learned from randomized controlled trials such as CAGB-Patch and DINAMIT that with regard to eventual ICD therapy, we might have to wait at least 6 weeks after a patient's myocardial infarction before evaluating such a patient for ICD implantation. A final implication of the overview of all the completed ICD trials is that it will be very difficult to visualize other populations for future ICD trials. It is not that all the questions have been answered, but repeating trials in high-risk populations will be ethically difficult, and in lower-risk populations (e.g. long QT syndrome), would require such large sample size and long follow-up that they might be practically impossible.

**References**


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