EDITORIAL

ICD therapy: ‘the sickest benefit the most….’: what about the less sick?

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Implantable cardioverter defibrillators (ICDs) have been proven to be highly efficacious in protecting very high-risk cardiac patients from sudden cardiac death and hence enhancing their overall survival. Furthermore, several post hoc sub-study analyses seem to indicate that ICD benefit is predominant in the patients with the highest risk, particularly with depressed left ventricular function. This, in turn, has led some clinicians to question the benefit of ICD therapy in relatively healthy, i.e. ‘less sick’, patients. As these interpretations come entirely from the sub-group analyses of the completed ICD prospective studies, it is important to examine more profoundly the study design, length of follow-up, and outcomes of these studies. Such analysis identifies three primary reasons why the conclusion that ‘less sick’ patients benefit less from ICD therapy may be erroneous: (i) the relatively short follow-up time of the studies (ended as soon as ICD therapy benefit became manifest); (ii) high ‘crossover rate’ from control to ICD therapy; and (iii) predominance of study endpoints (deaths) in the ‘sickest’ patients. The results of several studies, including the most recent and largest ICD study—SCD-Heft—and sub-group analyses of ‘healthier’ patient cohorts in several studies, support the benefit of ICDs in this group of patients, provided the follow-up time is sufficiently long.

KEYWORDS
Implantable cardioverter defibrillator; Sudden death; Left ventricular dysfunction; Heart failure

Introduction

Patients with normal hearts and ‘primary VF’ should undergo implantable cardioverter defibrillator (ICD) therapy, as the treatment of first choice, which was confirmed in the current guidelines for indications for ICDs.1–3 However, there is an ongoing debate whether patients with better left ventricular (LV) function actually benefit from the ICD as much as patients with reduced LV function, or whether they could just as well be treated with amiodarone. The converse of the observation on ICD therapy published by Moss4—that the sickest patients benefit most—would be that the less sick patients do not benefit, and this is the point we wish to examine in this article.

ICD benefit in patients with poor LV function

The term ‘sickest patients’, coined by Moss,4 and used by many others since, refers primarily to patients with depressed LV function. What is the basis for considering that patients with a history of life-threatening ventricular arrhythmias, but with a moderate or good LV function do not derive life-saving benefit from ICDs? Much of this perception comes from the sub-group analyses of the ICD secondary prevention trials: sub-group analysis of the Antiarrhythmics Versus Implantable Defibrillator Implantation Trial (AVID)5 and the meta-analysis6 of AVID and two similar studies, the Cardiac Arrest Study Hamburg (CASH) and the Canadian Implantable Defibrillator Study (CIDS). AVID was by far the largest of these trials (n = 1016 patients), and at a mean of 18 months of follow-up, it revealed a 38% reduction in all-cause mortality (P = 0.02), compared with patients treated almost exclusively by amiodarone.7 The sub-group analysis performed by Domanski et al.5 reported that the ICD benefit was seen primarily in the patients with LV ejection fraction (LVEF) ≤ 0.34. At 2 years of follow-up, patients with LVEF ≥ 0.35 showed no difference in survival between those receiving ICDs or antiarrhythmic drugs, whereas those with LVEF ≤ 0.34 had ~35% lower mortality when treated with ICDs. In a similar retrospective, sub-group analysis of the CIDS study (n = 659 patients), Sheldon et al.8 noted that patients with two or more of the following risk factors—age ≥ 70, LVEF ≤ 0.35, and NYHA III or IV—showed a 50% relative risk reduction when treated with ICDs, whereas those without this combination of risk factors apparently received less or no benefit. In the third of these secondary prevention studies, CASH (n = 288), no sub-group analysis was reported, but data from CASH were included in the meta-analysis.
reported by Connolly et al.,6 which showed a significant reduction in all-cause mortality and in arrhythmic mortality in favour of ICD treatment, for patients with LVEF < 0.35, but not for those with better-preserved LV function. Noting that ICDs have been shown to be extremely effective in patients with very poor LV function, Moss4 made a similar observation from a sub-analysis of the Multicenter Automatic Defibrillator Implantation Trial (MADIT).

What these studies have established is that the ICD is indeed remarkably effective in patients with very poor LV function, quite in contrast to the prevailing notion a few years ago.9,10 No doubt that improved medical management of heart failure, with beta-blockers and angiotensin-converting enzyme inhibitors, and technological improvements in ICDs—replacing the need for thoracotomy as in the early years and enabling pacemaker-like insertion—have contributed to this result. In essence, reducing patients’ risk of dying from heart failure enhances the ICD’s opportunity to interrupt malignant VT/VF episodes.

But does this mean that patients at risk of such arrhythmias, but generally enjoying better health, do not benefit from ICD therapy? Does it mean that the ICD should not be recommended for patients with better LV function? On the basis of ‘evidence-based medicine’, there is as yet no science that establishes the lack of ICD benefit in healthier patients. All the data reported earlier have come from retrospective, sub-group analyses. Quoting from the article of Domanski et al.,5 ‘only a suitably powered, randomized trial can answer this question’. In other words, the intriguing results that we have reported earlier may establish the hypothesis for conducting such trials, but are not in themselves proof of anything.

Critical review of the conclusions on ICD benefit in ‘less sick’ patients

As shown earlier, it has been argued that patients with well-preserved ventricular function may not benefit from an ICD and, therefore, do not need an ICD. Is this conclusion correct? Or is the result of this analysis the simple consequence of the study design of the studies cited? We will focus on three reasons why the conclusions concerning lack of ICD benefit in ‘less sick’ patients may be erroneous: (i) short time of follow-up; (ii) high crossover rate; and (iii) predominance of study endpoints (deaths) in the ‘sickest’ patients.

Relatively short time of follow-up

Prospective ICD studies, with mortality as the primary endpoint, must, of necessity, be stopped as soon as there is clear evidence of harm to either randomized group. This overriding requirement has shortened the duration of these studies, e.g. the mean follow-up was 18 months in AVID. This point may be critically important, especially for younger, healthier patients. In such patients, it often takes many months, even years before a second or subsequent life-threatening VT/VF episode occurs.11 In healthier patients, the time required to show ICD benefit may be well beyond the duration of the studies cited earlier. This fact is illustrated by the CASH trial, where patients in their 9th year of follow-up still had a one-fourth reduction in mortality when treated with ICDs.12 The reduction in mortality for patients treated with ICDs in CASH was 41.9, 39.3, 28.4, 27.7, 22.8, 11.4, 9.1, 10.6, and 24.7%, at 1–9 years of follow-up, respectively. We carried out a sub-group analysis in CASH on 30 patients with normal hearts (median LVEF 65%), and during the first 8 years, not one of the nine patients randomized to ICDs died, whereas there were 5 deaths among the 21 randomized to metoprolol or amiodarone. One of the CIDS investigator centres recently concluded on the basis of their 11-year follow-up on 60 patients that ‘the benefit of the ICD over amiodarone increases with time; most of amiodarone-treated patients eventually develop side effects, have arrhythmia recurrences, or die’.13 The authors especially emphasize that it was the long follow-up time that enabled them to observe ‘...the superiority of ICD over amiodarone...increases over time’. This observation, on the continued divergence of the survival curves over time, is not limited to the CIDS study. Salukhe et al.4 very recently reported exactly the same phenomenon in all eight ICD trials they had analysed and concluded that ICD benefit ‘...is dramatically dependent on the time window over which the benefit is assessed’. The practical implication of this time-of-follow-up concept is that most patients will benefit from their implanted ICDs within 5–7 years of expected lifetime of their device.

High crossover rate

Another major fault with the conclusions reported previously may be related to patients’ crossing over to ICDs. The CIDS trial, as illustrated in the just-stated example, had an overall 21.4% rate of crossovers from amiodarone to ICDs at 5 years.4 In AVID, 24.3% of the patients assigned to antiarrhythmic drugs had crossed over to ICDs by 3 years.7 Furthermore, patients with the worst LVEF had the highest rate of crossovers: 38.7, 30.3, and 18.5% for LVEF <0.20, 0.20–0.34, and >0.34, respectively.5 Such crossovers, made necessary because of recurrences of VT/VF and/or side effects of antiarrhythmic drugs, increase with time (thus reinforcing our first argument) and with poorer LVEF. In an intention-to-treat analysis, the patients randomized to antiarrhythmic drugs, then crossed over to ICDs, are still considered for analysis purposes to be in their assigned treatment group. Thus, whatever life-saving benefit they may get from ICDs subsequent to the crossover will be attributed to the drug limb.

Predominance of study endpoints (deaths) in the ‘sickest’ patients

In the studies whose post hoc sub-group analyses led to the ‘sicker patients benefit most’ hypothesis, the patients with lower LVEF experienced significantly more events—more than double within the same follow-up period when compared with patients with better-preserved LV function. Therefore, the study endpoints were predominantly determined by the cohort with low LVEF (and higher event rate) and less so by that with good LVEF (and lower event rate). As a consequence of the high event rate in patients with poor LV function, the absolute benefit of the ICD was so high that it led to (premature) termination of the trials. For example, patients with better-preserved LV function in the secondary prophylaxis studies may have received a similar relative benefit from the ICD to individuals with low ejection fraction, but the absolute benefit would be...
expected to be lower given the substantially lower event rate. Within the relatively short time prior to trial termination (e.g. 18 months in AVID), the patients with good LV function had experienced an event rate too low to be improved by any intervention. This phenomenon was amplified by the fact that the trials were dominated by patients with poor LV function, e.g. two-thirds of patients enrolled in AVID had LVEF $\leq 0.34$.

Discussion

Most patients considered for ICD therapy have concomitant risks: on the one hand, heart failure or other risk related to their cardiomyopathy of ischaemic or non-ischaemic origin; on the other, arrhythmic causes leading to VT/VF. A fact that may be overlooked in the ‘sickest patients benefit most’ concept is that the ‘less sick’ patients have little risk beyond that of an arrhythmic death. In other words, if an ICD protects them from cardiac arrest, such patients should have excellent prognosis, as they have little other risk. A perfect illustration of this fact is the ‘Defibrillators versus B-Blockers for Unexplained Death in Thailand (DEBUT)’ study that reported 18% deaths by 3 years in the B-Blocker group and no deaths in the ICD group.\(^5\) In fact, this result is very similar to the experience we reported earlier with the CASH sub-group with normal hearts, in which we also had no deaths until the 9th year for patients randomized to ICDs vs. five (24%) in the control group. Very similar results have been reported for patients with the Brugada syndrome and with Long QT syndrome, treated with ICDs.\(^\text{16,17}\) For the latter two studies, the Kaplan–Meier curves for the patients’ actuarial survival, compared with the rate of appropriate ICD interventions (Figure 1), show clearly that patients with normal ventricular function attain nearly 100% survival over a long follow-up period, during which the ICD nevertheless intervenes frequently (but often, many years after the initial implantation). Perhaps, the most persuasive argument supporting the usefulness of ICD therapy in ‘healthier’ patients comes from the recently completed landmark study, Sudden Cardiac Death in Heart Failure (SCD-Heft), conducted on 2521 patients in NYHA II and III heart failure.\(^\text{18}\) The subgroup analysis from that trial indicated that it was the patients in the NYHA class II who derived the predominant life-saving benefit from ICD therapy (hazard ratio 0.54 when compared with hazard ratio 1.16 for patients in NYHA III). The SCD-Heft survival curves (Figure 2), comparing ICD with amiodarone with placebo, only started separating at 18 months, further supporting the earlier cited conclusions by Salukhe et al.,\(^\text{14}\) concerning the importance of long follow-up time. The pharmaceutical trials in heart failure have also accentuated this point well by showing that the risk of sudden death is relatively highest in the patients in the better (lower) NYHA classes, whereas the risk of dying from heart failure dominates for patients in the NYHA classes III and IV.\(^\text{19,20}\)

We know that patients with well-preserved LV function have a better chance of surviving an episode of VT/VF, but that fact does not translate into a lesser need to protect them, when and if such an arrhythmia occurs again. Herein lies the answer to the question posed by the title of this article: if and until appropriately powered

![Figure 1](https://academic.oup.com/europace/article-abstract/8/7/508/480829/729584/98202) by guest on 28 December 2018

\(^5\) Zareba et al. 17.
prospective studies demonstrate the contrary, there is no reason to deprive a patient an ICD, who is otherwise considered an appropriate candidate, simply on the basis of his/her being ‘less sick’.

References


