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VIEWPOINT

Extending survival by reducing sudden death with implantable cardioverter-defibrillators: a challenging clinical issue in non-ischaemic and ischaemic cardiomyopathies

Giuseppe Boriani* and Vincenzo Livio Malavasi

Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy

Implantable defibrillators: from a pioneering idea to an evidence-based treatment

The story of the implantable cardioverter-defibrillator (ICD) as an effective tool for reducing sudden death and improving survival in appropriately selected patients has never been simple and since the pioneering era of Michel Mirowski[1] has always been the subject of debate and controversy. In the last 15 years, randomized clinical trials and, as a consequence, evidence-based international guidelines have extended the clinical application of ICDs to increasingly broad patient populations, not only in the setting of secondary prevention of sudden cardiac death, but also in the setting of primary sudden cardiac death prevention (i.e. for patients who are identified as being at risk of life-threatening ventricular tachyarrhythmias, despite no previous history of these events).[2,3] However, primary prevention is a particularly challenging area, as many years may pass before the benefits of the intervention can be perceived within the targeted population, and the financial burden of widespread implementation of such indications may constitute an important limitation in some economic settings.[3,4] Recently, the results of the DANISH trial,[5] focused on ICD implant for primary prevention in patients with non-ischaemic cardiomyopathy, appear to increase the uncertainty on the role of ICD for extending survival and stimulated a new debate on ICD benefit.

Implantable cardioverter-defibrillators in the setting of ischaemic and non-ischaemic cardiomyopathies

The benefits of ICDs implanted for primary prevention of sudden death in patients with left ventricular dysfunction were initially demonstrated in patients with previous myocardial infarction (MADIT I, MUSTT, MADIT II trials),[3] and were then extended to patients with left ventricular dysfunction and heart failure [New York Heart Association (NYHA) classes II and III] of either ischaemic or non-ischaemic aetiology on the basis of the results of the SCD-HeFT trial.[2,6] In all these studies, the primary endpoint was all-cause mortality and this appears absolutely justified as no doubts can arise from using a hard endpoint that is independent of definitions and not affected by the availability or non-availability of specific data related to the terminal event. Moreover, the assumption that prevention of arrhythmic death translates in reduction in all-cause mortality is not always true, as demonstrated in the two trials that evaluated the ICD in the setting of a recent myocardial infarction (IRIS and DINAMIT).[7,8] Both in IRIS and DINAMIT the reduction in sudden death in ICD patients was completely offset by increased non-arrhythmic deaths, thus resulting in no impact on all-cause mortality.[7,8]

Between 2002 and 2005, in the phase of validation of ICD therapy for primary prevention of sudden cardiac death with randomized controlled trials (RCTs), the setting of non-ischaemic cardiomyopathy was not prioritized in comparison with the setting of ischaemic heart disease. Indeed, CAT and AMIOVIRT were studies with a small sample size (<120 patients in each study) and were underpowered to demonstrate a mortality benefit.[9] The trial with the largest number of patients, the SCD-HeFT trial, included both ischaemic and non-ischaemic patients (although a separate analysis was pre-planned).[6] The results of SCD-HeFT showed that the benefit of ICD on all-cause mortality demonstrated in the whole cohort did not reach statistical significance in the non-ischaemic subgroup [hazard ratio (HR) 0.73; 97.5% confidence interval (CI) 0.50–1.07; $P = 0.06$].[5] Moreover, a difference in ICD benefit was found according to NYHA class, as ICD efficacy was demonstrated in NYHA class II, but not in NYHA class III.[6] The DEFINITE trial included 458 patients with non-ischaemic dilated cardiomyopathy, but the effect

*Corresponding author. Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo 71, 41124 Modena, Italy. Tel: +39-059-4225836, Fax: +39-059-4224498, Email: giuseppe.boriani@unimore.it

on all-cause mortality of ICD treatment was non-significant, as compared with the control, despite the significant reduction of sudden death.[10]

A meta-analysis including CAT, AMIOVERT, DEFINITE and the non-ischaemic cohort of SCD-HeFT found a statistically significant benefit of ICD therapy on all-cause mortality (relative risk 0.74; 95% CI 0.58–0.96; $P = 0.02$)[11] and this was the basis for the recommendations of international consensus guidelines.[12,13] However, on the basis of data from these trials, the NICE guidelines on ICD use issued in 2006 did not cover the use of ICDs for non-ischaemic cardiomyopathy,[14] a decision that was more recently revised, including non-ischaemic cardiomyopathy among the indications for an ICD for primary prevention, in the presence of left ventricular dysfunction and heart failure.[1] The Danish Cardiac Society also limited the indication for ICD in primary prevention to ischaemic patients but, in parallel, promoted a randomized study, the DANISH trial.[5]

The DANISH trial: impact on general knowledge of the benefits of implantable cardioverter-defibrillators

The DANISH trial, published in 2016,[5] evaluated the impact of ICD implant in the setting of symptomatic heart failure with systolic dysfunction (left ventricular ejection fraction ≤35%) due to non-ischaemic cardiomyopathy. In a follow-up of more than 5.5 years, no survival benefit emerged in the ICD group as compared with usual care in the entire population (HR 0.87; 95% CI 0.68–1.12, $P = 0.28$), although a significant reduction in the risk of all-cause mortality was found in the subgroup of patients younger than 68 years, with a 36% relative risk reduction (HR 0.64; 95% CI 0.45–0.90, $P = 0.01$). It is noteworthy that 58% of patients received cardiac resynchronization therapy (CRT) but no significant interaction was found on ICD effects. In this study, sudden cardiac death was actually significantly reduced by the ICD in the whole group assigned to ICD treatment, as it was halved as compared with controls (HR 0.50; 95% CI 0.31–0.82, $P = 0.005$), but sudden cardiac death accounted for only 35% of all-cause mortality in the control group. Overall, 31% of deaths were attributed to non-cardiovascular causes (36% in the ICD group and 27% in the control group) and this type of death could have represented a competing risk with sudden cardiac death, with a much higher influence in the elderly, in whom multiple co-morbidities could presumably affect outcomes.

The findings of the DANISH trial on the age dependency of ICD benefit need to be considered within the overall scenario of evidence provided by the other randomized trials on ICDs in primary prevention. *Figure 1* provides an analysis of the efficacy of ICD vs. control in the setting of primary prevention in patients with heart failure, including all the randomized trials where the efficacy on all-cause mortality was analysed, stratified by age. The stratification by age, as shown in *Figure 1*, was done by considering older patients, corresponding to elderly age (≥65–70 years) vs. younger patients. The meta-analysis that we performed according to a random-effects model and that we present in *Figure 1* shows that the benefit of ICD on all-cause mortality is confirmed in younger patients (< 65–70 years) with a relative risk reduction of 32%, with important statistical significance. This meta-analysis, including both patients with ischaemic and non-ischaemic aetiology, highlights the contribution of the DANISH trial, as the benefit of ICD treatment in the elderly is no longer detectable, as compared with a previous meta-analysis,[16] performed before the DANISH trial. This situation is absolutely clear in the sensitivity analysis that we report in the supplementary material online, *Appendix S1*, in which the removal of every specific study never affected the estimated efficacy of ICDs in younger patients, while removal of the DANISH trial completely changed the estimated effect of ICDs in the elderly (moving from no effect to beneficial). Recently a meta-analysis focused only on non-ischaemic cardiomyopathy and therefore limited to DEFINITE[10] and DANISH[5] trials similarly showed that the use of ICDs in primary prevention was associated with a significant benefit on all-cause mortality in younger, but not in older, patients.[17] Other recently published meta-analyses updated the evaluation of ICD efficacy in the setting of primary prevention of sudden death for non-ischaemic cardiomyopathy[18,19] and found that overall the efficacy of ICD was confirmed even after inclusion of the DANISH trial, but the investigators did not include an analysis stratified by patient age.

Pharmacological treatments and the concept of 'optimized medical treatment'

Any controlled evaluation of the efficacy of ICD in patients with left ventricular systolic dysfunction and heart failure has to consider that a series of drugs exerts favourable effects on outcome that also include a reduction in the risk of sudden death.[20] As known, these agents include beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blocking agents, and aldosterone antagonists, and the evolution of evidence has led, with time, to consider these agents as essential components of the 'optimized medical treatment' that should be applied to any patient with systolic dysfunction, thus proposing the ICD implant as a way to reduce the residual risk of sudden cardiac death.[20,21] The full implementation of all these agents in daily practice occurred with time and was often not fully complete or variable, when considering that the trials evaluating ICD efficacy that were published around 15 years ago compared with most recent trials. It is possible that differences in pharmacological treatments may explain at least part of the heterogeneity found for the elderly in the meta-analysis that we performed on the efficacy of ICDs on all-cause mortality (*Figure 1*). Other meta-analyses have also found some heterogeneity in ICD efficacy.[19,22] According to recent data from the PARADIGM-HF trial,[23] treatment with sacubitril/valsartan is associated with a reduction in both sudden cardiac death and death from worsening heart failure as compared with enalapril; this evidence further updates the composition of 'optimized medical treatment' for patients with left ventricular systolic dysfunction.[24,25]

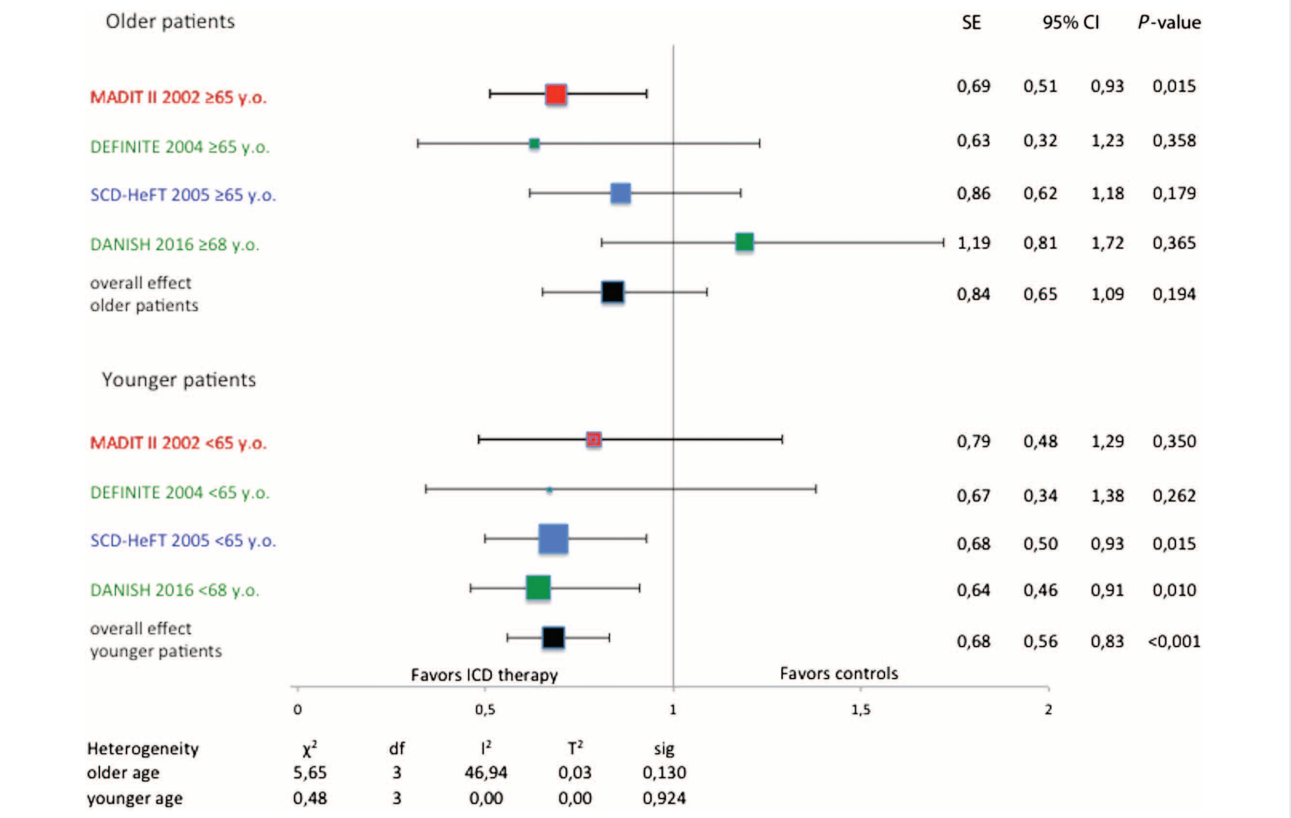

Figure 1 Meta-analysis (performed by the authors according to a random-effects model) including literature data on implantable cardioverter-defibrillators (ICDs) in the setting of primary prevention of sudden cardiac death, with estimate of the efficacy on all-cause mortality vs. control, stratified by age (≥65–70 vs. < 65–70). The trials that enrolled patients with ischaemic heart disease are in red, the trials that enrolled patients with non-ischaemic cardiomyopathies are in green and the trials including both aetiologies are in blue. A significant benefit of ICD vs. controls is found in younger patients, but not in older patients. In older patients there is a significant heterogeneity of the effect of ICD on all-cause mortality. The sensitivity analysis is reported in the supplementary material online, *Appendix S1*. CI, confidence interval; SE, standard error.

Finally, the evaluation of more than 40 000 patients with heart failure with systolic dysfunction, enrolled in 12 trials and performed over the last 20 years showed that rates of sudden death have declined substantially over time, a finding consistent with the cumulative benefit of evidence-based medications.[26] Actually, we do not know to what extent the benefit of ICD treatment found in randomized trials performed 10–15 years ago are still valid in light of the improvement in pharmacological and non-pharmacological treatments (e.g. revascularization). This situation constitutes a limitation to be considered when comparing most recent trials (i.e. the DANISH trial) with previous trials. However, these limitations are also important for any treatment applied to patients concurrently treated with other therapies that are subject to evolution and improvement over time.

Interpretation of the DANISH trial and clinical implications

The evidence of an important degree of age dependency for ICD benefit and the issue of competing risk of death related to co-morbidities are topical issues. Independently of the effects of ICD treatment, variations in the causes of death at increasing age deserve attention. Although the incidence of sudden death slightly increases with age, the proportion of deaths with the characteristics of sudden death diminishes markedly at increasing age, as a result of non-arrhythmic cardiovascular causes of death or even of non-cardiac causes of death.[27]

As a consequence of change in the prevailing determinants of death at increasing age it is quite normal that the benefit of ICD shows some age dependence. A meta-analysis of five RCTs on ICDs showed that the benefit of ICD therapy is attenuated at increasing age and that this finding may be related to an accompanying increase in the burden of co-morbid illness, even in the quite selected setting of RCTs.[28]

Co-morbidities are important determinants of outcomes in heart failure patients. The importance of co-morbidities as strong determinants of outcomes is also very clear in real-world registries.[29–31] In a regional registry from Italy that enrolled consecutive patients implanted with ICD and CRT-D devices, co-morbidities proved to be independent predictors of the risk

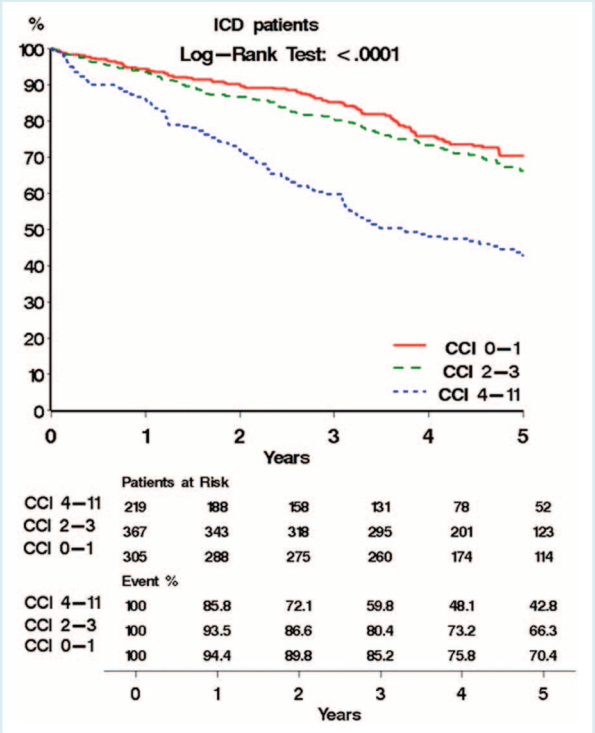

Figure 2 Data from a regional registry in Italy. Long-term outcome (Kaplan–Meier curve of survival free from death/cardiac transplant) in patients implanted with an implantable cardioverter-defibrillator (ICD) according to number and severity of co-morbidities, as expressed by Charlson co-morbidity index (CCI). Modified from Boriani *et al.*[32].

of death or cardiac transplant[32] (*Figure 2*). An analysis from the Danish national registry reported that an increased burden of co-morbidities was associated with increased mortality, with a higher proportion of patients who died without ever having experienced ICD shocks to terminate ventricular tachyarrhythmias.[33,34] Some temporal trends may also have an influence on the mode of death, as a reduction in the proportion of cardiovascular vs. non-cardiovascular causes of death was observed in the last three decades among patients enrolled in trials on heart failure.[35]

The evaluation of the patient's life expectancy and the potential role of co-morbidities in reducing the benefit of a strategy, like the ICD, that is merely able to terminate ventricular tachyarrhythmias and therefore may potentially condition only arrhythmic deaths, is a true clinical challenge. The most recent guidelines on the management of ventricular tachyarrhythmias and prevention of sudden cardiac death released by the European Society of Cardiology reported that ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (NYHA classes II and III) and left ventricular ejection fraction ≤35% after ≥3 months of optimal medical therapy, provided that the candidates are expected to survive for at least 1 year with good functional status.[36] The indication to select candidates for ICD after a clinical estimate resulting in at least 1 year of life expectancy with good functional status is difficult to apply in many cases, in view of the difficulties in making a precise prediction of outcome. This aspect is not addressed specifically in guidelines, leaving this difficult task to an undefined clinical judgement. Moreover, an upper limit of age for candidacy for ICD has never been suggested and this situation leaves a great margin of variability in candidate selection. It is noteworthy that the document on appropriate use criteria for candidacy for ICD or CRT-D implant released by the American College of Cardiology Foundation in collaboration with the Heart Rhythm Society, written as a result of an evaluation by expert physicians of a series of potential clinical scenarios, rated the implant of an ICD for primary prevention of sudden death in patients with left ventricular ejection fraction ≤30% on guideline-directed medical therapy if the patient's age was between 80 and 89 years as 'may be appropriate'. The same rating was released for patients aged ≥90 years in NYHA class II or III.[37] The same document also rated the implant of an ICD in a patient with chronic kidney disease on dialysis as 'may be appropriate', a setting in which the high risk of non-sudden death coupled with lack of specific evidence of benefit make clinical decision-making very uncertain.[38]

It is highly probable that age acts as a surrogate measure for the absence/presence of co-morbidities that may have a major impact on survival and may condition competing risks with regard to the risk of arrhythmic death. The additional impact of multiple co-morbidities on outcomes is clearly shown by an analysis of data from four ICD trials, showing that the benefit of ICD treatment on mortality decreases with the increasing number of co-morbidities.[39] The Seattle Proportional Risk Score has been found to predict the proportion of sudden vs. non-sudden death and predict the benefit of ICD according to the estimated conditional probability of sudden death.[40] A greater relative ICD benefit on sudden death and total mortality emerged in those patients with a higher predicted proportion of mortality from sudden death. This provides an interesting tool for improved patient targeting for use of ICDs in primary prevention[40] or for deciding whether CRT should include, or not, the defibrillation capability.[41] In addition, the growing use of CRT associated with defibrillation,[42] as well as the growing adoption of subcutaneous ICDs that occurred in recent years[43] make assessment of the appropriate targeting of this specific type of implanted device necessary.

The results of the DANISH trial should, in our view, stimulate more studies dedicated to improving outcome prediction in the elderly, as well as in any case of patients with multiple co-morbidities, two settings in which the knowledge of just one branch of medicine may make accurate estimation of the outcome very difficult. In the case of elderly patients, decision-making can be easy at the extremes of the grey zone. For instance, ICD should obviously be considered in elderly patients with non-ischaemic cardiomyopathy when biological age, in view of lack of co-morbidities or functional impairment, conditions a better outcome as compared with actual age. In contrast, severe co-morbidities and age > 80 years should discourage the implant of an ICD for primary prevention of sudden cardiac death. Multidisciplinary teams have been proposed for improvement of patient management and decision-making in different settings and can certainly have a role in proposing a multidimensional approach to a complex decision on appropriate management of heart failure,

including candidacy for ICD implant. In any case, the setting of patients younger than 65–70 also has to be approached in specific cases with the aid of a multidisciplinary team of experts. Patients with muscular dystrophies with a high risk of respiratory insufficiency, patients with severe obesity or severe chronic kidney disease, and patients with previous cancer treated with chemotherapy are very problematic cases for physicians. The activity of a multidisciplinary team should also include the evaluation of the psychological aspects of ICD recipients in order to minimize the risk of psychological distress that may derive from ICD shocks or device-related complications.[44] While a multidisciplinary assessment has been proposed in heart failure guidelines,[45] its role in decision-making for ICD implant is not specifically stressed.

In interpreting the results of the DANISH trial, the heterogeneity of non-ischaemic cardiomyopathy should also be a matter of consideration. The wide spectrum of the disease, often genetically determined,[46] as well as the variable severity of the disease according to aetiology[47] condition, a variability in outcome, as compared with ischaemic heart disease, may make it more difficult to precisely assess the benefit of ICD in the setting of left ventricular dysfunction. Randomized trials are ongoing in order to assess the incremental value of selecting candidates for ICDs on the basis of quantification of myocardial fibrosis with cardiovascular magnetic resonance imaging[48] or using a scintigraphic assessment of sympathetic innervation of the myocardium.[49]

Conclusions

The DANISH trial had the merit to explore the complex setting of non-ischaemic cardiomyopathy by means of a RCT and this aspect is of great value as, in this setting, the benefit of ICDs was not well defined. Even if the picture is not completely clear, we now have more specific information on how age may influence the benefit of an ICD on all-cause mortality in the setting of primary prevention of sudden cardiac death. Below the age of 65–70, implantation of an ICD appears to be beneficial in non-ischaemic cardiomyopathy according to the recommendations of current guidelines, even if this is derived from subgroup analysis. Future guidelines will have to focus on this point better in light of the results of the DANISH trial, as well as the results of several analysis derived from this study combined with the previous ones. As age is only one component of patient characterization, it is absolutely vital to improve outcome prediction according to more detailed evaluations of patient status, in addition to age, and taking into account renal function, diabetes, other co-morbidities and functional status, especially when these factors appear to have a major impact on outcomes. In these conditions, clinical judgement may benefit from the contribution of experts who interact in multidisciplinary teams. Finally, prospective registries targeted to assess outcomes at 3–5 years and beyond can have an important role in improving our knowledge and in providing the basis for future trials targeted on specific groups of patients characterized by important co-morbidities (e.g. moderate to severe chronic kidney disease).

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Sensitivity analysis.

Conflict of interest: G.B. reported speaker's fees of small amounts from Medtronic, Boston and Biotronik. V.L.M. reported no conflict to disclose.

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