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EDITORIAL COMMENT

Patient outcome after implant of a cardioverter defibrillator in the 'real world': the key role of co-morbidities

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This article refers to 'The impact of co-morbidity burden on appropriate implantable cardioverter defibrillator therapy and all-cause mortality: insight from Danish nationwide clinical registers,' by A.C. Ruwald *et al.*, published in this issue on pages 377–386.

The use of implantable cardioverter defibrillators (ICDs) has significantly evolved in the last decades, following the pioneering experiences of Mirowski ~35 years ago and related to very selected patients with a history of multiple cardiac arrests.[1] In a landmark trial on secondary prevention, the AVID trial, the ICD was found to be associated with a survival benefit, as compared with the control treatment group, which was affected by an occurrence of all-cause mortality of ~25% at 2 years and 36% at 3 years.[2] In the setting of primary prevention, the efficacy of ICDs was initially established in patients with previous myocardial infarction and LV dysfunction (MADIT I, MUSTT, and MADIT II trials),[1,3] and was then extended to patients with LV dysfunction and heart failure (NYHA class II and III) of either ischaemic or non-ischaemic aetiology (SCD-HeFT trial).[3] In terms of relative risk, the benefits of ICD therapy were additional to optimized pharmacological treatment, and appeared even greater in primary than in secondary prevention trials (*Figure 1*).

These findings were progressively translated into the recommendations for ICD implantation provided by consensus guidelines. Despite the solid evidence of benefit, the implementation of ICD therapy in the 'real world' was quite heterogeneous, and both financial and cultural issues could be considered in interpreting the extremely variable implant rates found in western countries and within Europe.[4]

While the evidence in support of a benefit of the ICD in improving survival is quite solid in appropriately selected patients with ischaemic heart disease, some degree of uncertainty has always characterized the setting of non-ischaemic heart disease. The most recent guidelines on management of ventricular tachyarrhythmias and prevention of sudden cardiac death (SCD) reported that ICD therapy is recommended to reduce SCD in patients with symptomatic heart failure (NYHA class II–III) and LVEF ≤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. In these guidelines, the class and strength of the recommendation for ICD implant was IA for ischaemic and IB for non-ischaemic aetiologies, respectively.[5]

Recently a randomized controlled trial performed in Denmark evaluated the impact of ICD implant in the setting of symptomatic systolic heart failure (LVEF ≤35%) not caused by CAD.[6] In a follow-up of >5.5 years, no survival benefit emerged in the ICD group as compared with usual care taking into account the whole cohort (*Figure 1*), although a significant reduction in the risk of all-cause death was found in the subgroup of patients younger than 68 years (36% relative risk reduction). It is noteworthy that 58% of patients received CRT but no significant interaction was found on ICD effects. In this study, SCD was actually significantly reduced by ICD treatment, since it was halved as compared with controls, but it accounted for only 35% of all-cause mortality in the control group. Overall, 31% of deaths were attributed to non-cardiovascular causes, and this type of death could have represented a competing risk with SCD, with a much higher influence in the elderly, where multiple co-morbidities presumably could strongly affect outcomes.

In this issue of the journal, Ruwald *et al.* report on data from the Danish registry taking into account patients implanted with an ICD from 2007 to 2012 in the setting of primary prevention (1873 patients) or of secondary prevention (2461 patients) of SCD.[7] Patients implanted with a biventricular ICD for CRT were not included. At a mean follow-up of 2.5 years, an increasing co-morbidity burden (as detected through administrative and drug prescription data) was not associated with increased risk of appropriate ICD therapy, in terms of delivered shock or antitachycardia pacing. However, as expected, an increasing co-morbidity burden

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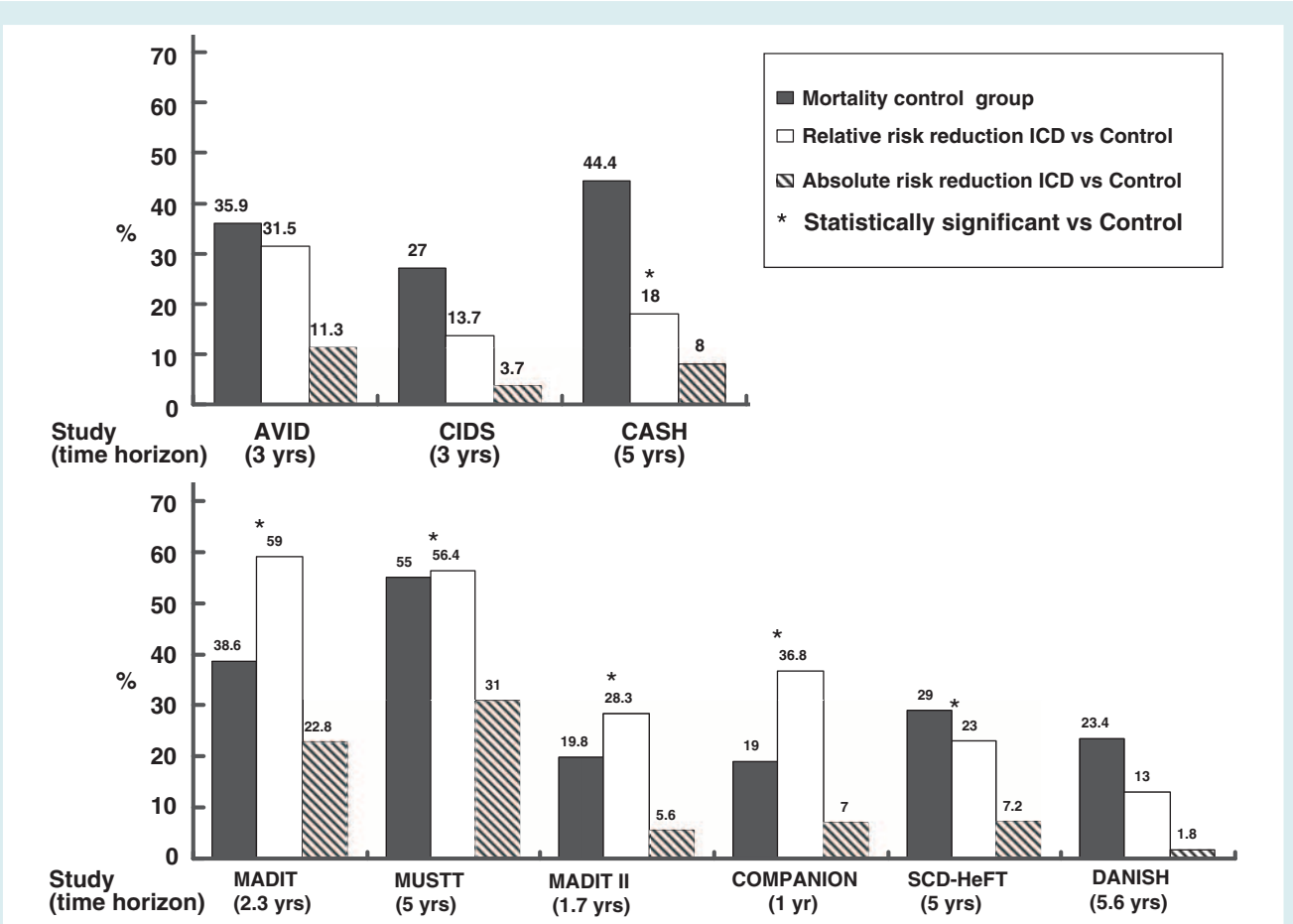

Figure 1 Results of randomized controlled studies that evaluated the efficacy of implantable cardioverter defibrillators (ICDs) in the setting of secondary prevention (top) and primary prevention (bottom) of sudden cardiac death. The bars show the overall mortality risk recorded for the control groups (during the given study periods), alongside the reductions in relative risk and absolute risk recorded in the corresponding ICD intervention groups.

was associated with increased mortality, with a higher proportion of patients dying without evidence of delivered device therapy for ventricular tachyarrhythmias. In particular, AF, diabetes, COPD, chronic renal disease, and peripheral vascular disease were independently associated with increased risk of death in both primary and secondary prevention ICD patients. Primary and secondary prevention patients had a similar 4-year cumulative risk of death of 7% if no co-morbidities were present at implant, but the risk of death progressively increased up to 52% in patients with three or more co-morbidities.[7]

There are complex inter-relationships between heart failure and co-morbidities, including also pathophysiological interactions, with a marked impact on outcomes, in terms of mortality and hospitalizations that can be more appropriately evaluated in observational studies and registries focused on the 'real world'.[8–10] In unselected patients with heart failure, analysis of data derived from administrative data sets indicates that patient characteristics and treatment patterns differ from those reported by randomized clinical trials, and outcomes are particularly severe, with rehospitalizations within 1 year after an admission for heart failure occurring in 57% of patients, with 49% of them due to non-cardiovascular morbidities.[11] The impact of co-morbidities can be evaluated with different approaches, quite commonly using the Charlson co-morbidity index, that can be assessed even using administrative data.[8] Ruwald *et al.*[7] did not apply this approach and limited the assessment of co-morbidities to conditions not related to an ICD indication, thus excluding previous myocardial infarction and heart failure.

In a regional registry from Italy including consecutive heart failure patients who underwent a first implant of an ICD, survival free from death/cardiac transplant was ~62% at 5 years.[8] Co-morbidities, as evaluated by means of the Charlson co-morbidity index, had a significant impact on outcomes in terms of mortality/heart transplant, hospitalizations, and days spent alive and out of hospital. Also, patient age, implant during urgent, unplanned hospitalization, and a higher NYHA class had a significant negative impact on both hospitalizations and mortality.

These data suggest the need to consider age as an important factor affecting patient outcome and therefore the potential benefit of ICDs on sudden death. In a meta-analysis of five randomized

controlled trials evaluating the ICD in primary prevention, which had the limitation of a small sample of patients aged ≥75 years, the results showed that at a median follow-up of 2.6 years the benefit on survival, but not on hospitalizations, was significantly attenuated with increasing age.[12]

Among the various co-morbidities that can be present in a potential candidate for ICD therapy, chronic kidney disease is particularly challenging, since it can markedly influence both the decision to implant an ICD and the post-implant outcome.[13] In the absence of dedicated randomized trials, there is still uncertainty about the benefit of the ICD for primary prevention of SCD in chronic kidney disease patients, especially in those with more advanced stages of renal dysfunction, and a thorough assessment of individual risk/benefit of ICD therapy is needed.[13]

In the study by Ruwald *et al.*,[7] an increasing co-morbidity burden was not associated with increased risk of appropriate ICD therapy, and this suggests a limited impact of co-morbidities in modulating cardiac arrhythmogenesis. However, when more co-morbidities were present, there was an increased chance of observing lack of appropriate ICD therapy prior to death (this occurred in 72% of primary and 45% of secondary prevention patients with a high co-morbidity burden).[7] This observation suggests a series of considerations, focused on potential improvement in patient selection, but also on the need to address this issue in observational studies using pre-defined device programming of detection settings and device therapies (antitachycardia pacing, shocks). It is also worth considering that delivery of appropriate device shocks is associated with worsening of the outcome, with a consistent five-fold increase in the risk of mortality as compared with patients without any shock, with heart failure constituting the main cause of subsequent death.[14] Worsening of the outcome after delivered ICD therapy was not observed when antitachycardia pacing was the effective treatment delivered for ventricular tachyarrhythmias; however, prognosis was indeed better in patients without arrhythmic episodes.[15] In this perspective, the arrhythmia itself should be considered as a powerful marker of underlying cardiac disease progression, in a complex inter-relationship between the rhythm and the myocardial mechanical performance.[15]

We are facing a progressive ageing of the population, and this is reflected in the candidacy for interventional procedures. As found in the Danish registry, there is a trend towards increasing patients age at implant in primary prevention indications.[7] This is an additional observation that stresses the importance of further evaluations of patient outcome after ICD implant, of its determinants, and of the many modulating factor that may interact in a complex and dynamic way. Since randomized trials obviously imply some patient selection, collection of high-quality 'real-world data' appears mandatory and should represent one of the next targets of our community.[16–19]

The issue of co-morbidities is crucial in all the aspects of heart failure management, even beyond selection of ICD candidates, and supports the need for a holistic, patient-centred clinical approach taking into account the available scientific knowledge, the individual patient context and expected outcome, as well as patient preferences and values. The famous quote of Sir William Osler, dated 1904, turns out always to be valid: 'It is much more important to know what sort of patient has a disease than what sort of disease a patient has.'

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