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Implantable cardioverter-defibrillator therapy in the elderly: The continuing quest for data

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Sudden cardiac death (SCD) remains a leading cause of mortality worldwide. In the United States, deaths attributed to SCD are estimated at 310,000 per year, overwhelmingly as a result of ventricular tachyarrhythmias (VT) [1]. Heart failure (HF) represents the most common substrate for VT; and the risks of these arrhythmias, as well as of SCD, increase as ejection fraction decreases among patients with both ischemic and non ischemic heart disease. The substrate for malignant VT is facilitated by fibrosis and dilation that occur in these diseased states. This potential electrical instability can be further triggered and exacerbated by sympathetic excitation in the presence of congestive HF [2–4]. The incidence, prevalence and mortality rate of HF are all known to increase with advancing age. Those 75 to 84 years of age have double the annual rates of HF events as compared with those 65 to 74 years of age, and those older than 85 have four-fold annual rates of HF events as compared with those aged 65 to 74. The prevalence of HF is 2–3% in the total population, but in those older than 75 it rises to 10–20% [5, 6]. In patients with HF, their one-year mortality rate increases by 60% to 70% per decade [7, 8].

To date, multiple randomized clinical trials have demonstrated a significant reduction in the risk of death with an implantable cardioverter--defibrillator (ICD) among patients with a left ventricular ejection fraction < 30–40% [9–13]. However, the patient population enrolled in these studies consisted mainly of young patients, with a mean age of 52–64 years, and data on the benefit of ICDs among older age groups remains limited and at times controversial. The effects of older age on ICD benefit could be potentially related to two opposing factors: (1) elderly patients have more co-morbidities than their younger counterparts, thus, the proportion of patients dying due to VT and SCD decreases with advancing age; and (2) the incidence, prevalence and mortality rate of HF increase with advancing age, so that any proven beneficial therapy (e.g. ICD implantation) in patients with HF might be associated with a greater survival benefit in this population.

In their article in this issue of *Cardiology Journal*, Kong et al. [14] report the results of a meta-analysis investigating the effectiveness of ICD among patients aged over 65 and among patients aged over 75. Their meta-analysis focused on the five studies that are considered most relevant to primary prevention ICD therapy, namely MADIT (Multicenter Automatic Defibrillator Implantation Trial) [9], MUSTT (Multicenter Unsustained Tachycardia Trial) [10], MADIT-II [11], DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) [12], and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) [13]. Many of these trials did not include a pre-defined age limit. Primary prevention ICD therapy was associated with a significant 40% reduction (95% confidence interval [CI] 22–55%) in all-cause mortality among patients ≥ 65 years old and with a significant 27% (95% CI 3–49%) reduction in all-cause mortality among patients ≥ 75 years old. Similar results were found when the MUSTT trial, where ICD therapy was not randomized, was excluded. It should be noted that the authors excluded five other randomized clinical trials: CAT (Cardiomyopathy Trial) and AMIOVIRT (Amiodarone Versus Implantable Cardioverter Defibrillator Trial) which were small studies that were excluded due to lack of estimates of ICD effect based on age; and DINAMIT (Defibrillator in Acute Myocardial Infarction Trial),

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CABG-PATCH, and IRIS (Immediate Risk Stratification Improves Survival) which enrolled patients early post-myocardial infarction or coronary artery bypass grafting (i.e. patients not included in the current guidelines for primary prevention ICD).

Moreover, the authors provided a comprehensive review of the literature and summarized the results of substudies and non-randomized trials investigating the effectiveness of ICD among older patients. The authors showed consistent results demonstrating that primary prevention ICD among high risk older patients (≥ 65 or ≥ 75 years) is associated with greater survival rates, but not associated with significantly increased risk for procedural or post-procedural complications. Importantly, the authors also attempted to address the question as to whether ICDs affect quality of life differently among older and younger patients. Although they found only limited data, older patients did not experience a significant decrease in quality of life.

The overall beneficial effects of primary ICD implantation in the older age groups as shown in this meta-analysis and review of literature, however, should be interpreted with caution due to the following limitations: (1) analysis of data on elderly patients enrolled in randomized control trials might not reflect 'real world' practice, as very high risk elderly patients with multiple co-morbidities, particularly with advanced renal dysfunction, are often excluded from ICD randomized control trials; (2) given the low number of octogenarians and nonagenarians enrolled in these studies, conclusions could not be made for these important, and growing, subgroups of patients; (3) the current meta-analysis provides data on the effect of old age on ICD benefit by employing mainly univariate analyses; to explore the effectiveness of ICD among young and elderly patients, it is important to neutralize the effects of co-morbid conditions by adjusting for clinical variables or by setting sudden cardiac death as the primary end point instead of all-cause mortality; (4) intrinsic inadequacies of a meta-analysis should be realized and applied to the interpretation of the analyzed data.

The importance of risk factors and co-morbidities for the assessment of ICD effectiveness was previously shown in a MADIT-II substudy [15], where five simple clinical parameters (comprising age, heart failure functional class, blood urea nitrogen, QRS duration, and atrial fibrillation) were found to stratify patients into a low-risk group (with none of the five clinical risk factors) who did not derive a significant survival benefit from the ICD; an intermediate-high risk group (≥ one risk factors) who derived a pronounced benefit from primary ICD implantation; and a very high risk group (with advanced comorbidities), in whom the benefit of the ICD was attenuated. Although Kong et al. [14] have provided data from substudies of clinical trials showing that by multivariate analyses the effects of age on ICD benefit were consistent with the main results of the univariate results of the meta-analysis, it should be noted that the variables included in each substudy model are different, and thus it is difficult to evaluate the overall isolated effect of age on ICD benefit.

In trials assessing medical therapy, the derived benefits from the study medication may only be expected if 'targeted' dosing is applied and proper patients are selected. One may not extrapolate the data to lower doses or in improperly selected patients. The same principle should be remembered in patients being considered for device therapy, especially one as expensive as ICD. Inclusion and exclusion criteria incorporated in these studies need to be kept in mind when clinical decisions for device therapy are made.

Until there is randomized data on the effectiveness of ICD as primary prevention therapy in elderly patients, the debate about the risk/benefit balance is sure to persist. The existing guidelines for ICD therapy may well prevent such trials from being carried out, as it may be difficult to justify withholding device therapy in the control group. The cost issues of such therapy in this population are also critical subjects that societies need to ponder; in many regions in the world, the expenses related to the therapy alone are prohibitive.

Within these confines, the current study adds to the accumulating data showing that age does not attenuate the benefit of ICD therapy, thus supporting the opinion that appropriate risk assessment before ICD implant among appropriately selected patients should not be withheld from the elderly patients based on age alone.

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