ICDs for secondary prevention of sudden death in the older-elderly

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This editorial refers to 'Role of the implantable defibrillator among elderly patients with a history of life-threatening ventricular arrhythmias' by J.S. Healey et al., on page 1746

Unexpected death from cardiovascular causes accounts for 300 000 to 350 000 deaths annually in the United States and is one of the most common modes of death in the elderly.1 Despite advances in the management of cardiovascular diseases, the overall incidence of sudden cardiac death (SCD) in the general population has decreased only marginally and is expected to increase with the aging of the population and increased prevalence of chronic heart disease.1,2 Recent randomized, prospective clinical trials comparing antiarrhythmic drug therapy to implantable cardioverter defibrillator (ICD) have demonstrated the usefulness of ICD in reducing the risk of SCD due to cardiac arrhythmias in those at risk of or resuscitated from cardiac arrest or life-threatening ventricular arrhythmias.2-4 However, none of these trials have focused specifically on the efficacy of ICD in the older-elderly. Overall, the average age of patients in the clinical trials of ICD has been in 60s, ranging from 50s into the high 70s. Data on octogenarian and nona-generians patients are scant, and it is not clear whether the survival benefit observed in the middle-aged and younger-elderly also extends to older-elderly patients with a more limited life span. The impact of ICD on improving survival in the very elderly is difficult to establish because of selection bias in the use of ICD in the elderly, lack of long-term follow-up data and shorter life expectancy due to the high incidence of non-arrhythmic cardiac and non-cardiac deaths in this population. Most published studies in the elderly are retrospective analysis of small number of patients with incomplete follow-up, in which issues related to selection bias have not been fully assessed. Since, the older-elderly constitutes the most rapidly growing segment of the population, it is important to assess the safety, efficacy, and cost effectiveness of these increasingly complex and expensive therapeutic modalities in this population. Because of the limited enrolment in randomized clinical trials and potential selection bias with the use of more expensive devices in ‘healthier’ elderly free of serious co-morbidities and a lower risk of non-cardiac or cardiac death, the efficacy of ICD therapy in the older elderly with limited life expectancy is not clear.

In this regard, Healey et al.5 should be congratulated for providing useful information about the survival outcomes in the older-elderly patients. Using pooled data from the three major randomized ICD secondary prevention trials of SCD,4-8 the authors found no statistically significant reduction in all-cause mortality or arrhythmic death among patients ≥75 years randomized to ICD therapy vs. amiodarone. A total of 1866 patients with a mean age of 63.7 ± 10.4 were included and for this analysis the patients were divided into two groups, ≤75 years or ≥75 years. Two hundred and fifty two patients, 13.5% of the enrolled patients were 75 years or older. There were no significant differences in the baseline left ventricular ejection fraction (~33%), severity of heart failure (~12% NYHA class 3 or 4 patients) history of myocardial infarction, or coronary bypass surgery between the two groups. During the 2.3-year follow-up period, the overall all-cause mortality and arrhythmic death was reduced by ICD in the younger group by 31 and 56%, respectively, but not in the older-elderly (all-cause hazard ratio (HR) = 1.06, 95% CI 0.69–1.64, P = 0.79 and arrhythmic death HR = 0.90, 95% CI 0.42–1.95, P = 0.79]. This was due to high mortality from non-arrhythmic and non-cardiac causes in the older-elderly. These results are similar to what has been reported for the SCD-HeFT, a SCD primary prevention trial but different from Multicenter Automatic Defibrillator Implantation Trial II (MADIT II).4,9 In the SCD-HeFT, in which patients with both ischaemic and non-ischaemic cardiomyopathy with an ejection fraction < 35% were included, the benefit with an ICD was less pronounced in those 65 years or older.4 Whereas, in a retrospective substudy of the MADIT II trial that enrolled 1232 patients with coronary artery disease and left ventricular dysfunction (ejection fraction < 30%), a trend towards improved survival with a higher risk reduction in total mortality was noticed in older-elderly (≥75 years; 16% of the total enrolled patients) than in a well-matched group of patients younger than 75 years.9

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The study by Healey et al.\textsuperscript{5} constitutes the best available randomized trial evidence regarding ICD therapy for secondary prevention of death in older-elderly patients. By limiting their analysis to randomized trial data, the investigators minimized the possible influence of selection bias on outcomes. It appears unlikely that additional secondary prevention ICD randomized trial data will be available in the foreseeable future. The study is also noteworthy because the investigators performed an individual patient data meta-analysis, a design that is considered to be the gold standard among meta analyses. Unlike a conventional meta-analysis in which aggregate trial data are pooled, an individual patient data meta-analysis combines rare patient-level data from different trials in a single database using common definitions and common time points for outcomes. Although this approach can be expensive and labour intensive, individual patient data meta-analyses can yield clinical insights unattainable by single clinical trials or by conventional meta-analyses. Despite its rigorous design, the analysis presented by Healey et al.\textsuperscript{5} does have some limitations. The generalizability of their finding to clinical practice may be limited because of incomplete data regarding patient functional capabilities and severity of coexisting illnesses, such as renal impairment, chronic pulmonary disease, diabetes, or cancer. In addition, their analysis may not be generalizable to the very elderly (> 80 years). The number of older-elderly patients included in their analysis (252) provides only limited statistical power to detect interaction of advanced age and ICD effectiveness. Moreover, information about the type of ICD used with backup ventricular pacing or atrio-ventricular pacing capabilities and percentage time the ventricles were paced in survivors vs. non-survivors was also not accounted. This information is important in view of recent concerns about a potential deleterious effect of backup brady-pacing on cardiac function in ICD recipients due to ventricular desynchrony introduced by pacing from the right ventricular apex.\textsuperscript{10} It is possible that the older-elderly with a higher prevalence of sinus node dysfunction and conduction system disease required more frequent pacing, placing an extra burden on already compromised myocardial functional reserves resulting in cardiac decompensation and heart failure-related deaths.

Is a marginal longevity benefit with an intervention that is expensive and can potentially adversely affect quality of life, generate anxiety, and increase comorbidities justifiable? The true benefit of ICD therapy in the elderly depends not only on the risk from arrhythmias, but also competing risk from other cardiac non-arrhythmic and non-cardiac causes. With the high age-specific and disease-related mortality in the elderly, with increasing number of comorbidities, the life expectancy is short and even an intervention that is 100% effective in preventing arrhythmias will not have a great impact on improving survival. On the other hand, in those at high risk of arrhythmic death with minimum comorbidities, despite advanced age, anti-arrhythmic intervention will reduce mortality to age-specific life-expectancy. In younger patients, this will be longer than the older-elderly. Advanced chronological age alone, therefore, should not be the decisive factor in making a decision on ICD selection for survival benefit but rather lead clinician to carefully consider the risk of non-arrhythmic and non-cardiac deaths\textsuperscript{5} when dealing with an individual patient, in whom 'biological age' may be a more important determinant of survival. The decision regarding selection of devices should also consider the effect on quality of life, risk of complications, and potential adverse effects of devices, such as functional deterioration with ventricular desynchrony in those with heart failure.\textsuperscript{10} Since, a growing proportion of elderly has heart failure, backup ventricular pacing with ICD should be minimized by selecting low minimum rate, programming long AV interval, selecting an ICD with algorithms utilizing automatic mode selection that favours atrial over ventricular pacing, or using ICD with biventricular pacing capabilities.\textsuperscript{4} Clearly, more data is needed in the elderly in this area.

With the continuing rise in medical costs, the number of older-elderly patients and prevalence of cardiovascular diseases in the elderly, the need for evidence-based guidelines in the use of expensive devices, such as ICD, has never been more urgent than before.\textsuperscript{11} The effect of interventions on determining long-term outcomes in the older-elderly will require inclusion of more elderly patients in clinical research studies to truly assess the impact not only on survival improvement but also functional independence and quality of life, so that evidence-based strategies can be applied in a cost-effective manner, to achieve a longer active life free of disability.

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References
Demonstration of clinically silent plaque rupture by dual-source computed tomography

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A 69-year-old woman was admitted because of atypical chest pain. She had hyperlipidaemia and diabetes. ECG and echocardiography showed no abnormal finding. Noninvasive coronary angiography was performed using dual-source computed tomography (DSCT; Somatom Definition, Siemens Medical Solution, Forchheim, Germany). 70 ml of contrast agent was used at 5 mL/s. The collimation was 2 x 64 x 0.6 mm, rotation time was 330 m s, temporal resolution was 83 m s. Cross-sectional images were reconstructed with 0.75 mm slice thickness and 0.4 mm increment. DSCT revealed high-grade stenosis in the middle segment of left anterior descending coronary artery as well as exulceration with a partly calcified atherosclerotic lesion of the left main coronary artery immediately proximal to the bifurcation (Panel A). ‘Plaque map’ analysis which was a comprehensive colour image according to CT number was performed (Panel B). It revealed that within the atherosclerotic plaque material, an enhanced cavity (*) of ruptured plaque forming a double lumen (Panel B). Images showed an eccentric mild stenotic area with a CT attenuation below 70 HU, suggesting fatty plaque and/or thrombus. Some spots under 0 HU (white arrows), were thought to be lipid pools. Some spots of calcification were also detected (black arrows). Invasive coronary angiography demonstrated ruptured plaque on the same position (Panel C). In those findings, the plaque was ruptured silently.

Panel A. Curved multi-planar reformation image of left main coronary artery using DSCT.
Panel B. Consequent images of cross-sectional images of the culprit from the proximal to the distal lesion (upper panels) and Plaque Map (lower panels).
Panel C. Invasive coronary angiography showed moderate stenosis and an exulceration (arrow) in the left main coronary artery, corresponded to DSCT findings.