Editorial

Primary prevention implantable cardioverter defibrillator in patients with reduced ejection fraction: for ischemic or non-ischemic cardiomyopathy or both?

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The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death in patients with heart failure and reduced left ventricular ejection fraction (1,2). These recommendations have been primarily based on clinical trials that mainly included patients with ischemic heart disease as the etiology for heart failure (3-6). In contrast, the body of evidence for primary prevention ICD in those with non-ischemic cardiomyopathy has been less robust. While a meta-analysis of randomized clinical trials conducted more than a decade ago confirmed the mortality benefit of ICD in this population (7), the recently published Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality (DANISH) showed no survival benefit for ICD implantation in this setting (8). These conflicting results generated debate amongst cardiologists regarding the utility of primary prevention ICD in the modern era of guideline directed medical therapy, and particularly in the absence of ischemic heart disease. Since ICD implantation is not without risk (e.g., short- and long-term device related infections, and inappropriate device therapies), as well as the considerable cost related to the device, it is important to identify those who will gain the most benefit.

In this context, Kolodziejczak *et al.* conducted a meta-analysis of randomized trials to evaluate the role of prophylactic ICD compared with conventional therapy for mortality prevention in patients with ischemic and non-ischemic cardiomyopathy (9). The analysis included 11 trials with 8,716 patients; 4 trials (1,781 patients) evaluated patients with non-ischemic cardiomyopathy, 6 trials (4,414 patients) with ischemic cardiomyopathy, and 1 trial (2,521 patients) with both types of cardiomyopathy. This analysis demonstrated a 19% reduction in all-cause mortality with ICD compared with conventional therapy in the overall population [hazard ratio (HR) =0.81; 95% confidence interval (CI), 0.70–0.94; P=0.043]. A similar reduction was noted in patients with non-ischemic cardiomyopathy (HR =0.81; 95% CI, 0.72–0.91; P=0.006), and a similar effect in patients with ischemic cardiomyopathy; however, this did not reach statistical significance (HR =0.82; 95% CI, 0.63–1.06; P=0.063). Similarly, ICD was associated with 59% reduction in the risk of sudden cardiac death (SCD) compared with conventional therapy in the overall population (HR =0.41; 95% CI, 0.30–0.56; P=0.001). The benefit was noted in patients with ischemic cardiomyopathy (HR =0.39; 95% CI, 0.23–0.68; P=0.012), but did not reach statistical significance in those with non-ischemic cardiomyopathy (HR =0.44; 95% CI, 0.17–1.12; P=0.064). Cardiac and non-cardiac mortality rates were similar in the overall population and in the analyses according to the etiology of cardiomyopathy. Subgroup analyses demonstrated that the benefit of ICD placement was consistent across different study-level variables, including age, sex, symptoms, systolic function and QRS duration; however, there was evidence of significant effect modification by diabetes status (i.e., benefit was seen in those with no diabetes) and timing of ICD placement after myocardial infarction or coronary by-pass surgery (benefit was noted when implantation did not

occur within 40 days of myocardial infarction or at the time of by-pass surgery).

Despite the potential criticism that might arise from analyzing trial-level data, rather than patient-level data, and that the trials included in this study span across a decade, this meta-analysis by Kolodziejczak *et al.* was well conducted and supports the benefit of ICD in the primary prevention of all-cause mortality and SCD in patients with heart failure with reduced ejection fraction (9). In the ischemic cardiomyopathy trials, the reduction of all-cause mortality did not reach statistical significance, probably due to the inclusion of the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and the Immediate Risk Stratification Improves Survival (IRIS) trial (which evaluated early post–myocardial infarction patients), and the Coronary Artery bypass graft (CABG)-Patch trial (which evaluated immediate post-coronary by-pass patients) (10-12). Analysis of the remainder of the ischemic cardiomyopathy trials demonstrated a statistically significant 28% reduction in all-cause mortality reduction with ICD placement (HR =0.72; 95% CI, 0.65–0.81; P=0.001). These findings are in line with the ESC and ACC/AHA guideline recommendations (1,2), and are well accepted. In contrast, although the analysis of non-ischemic cardiomyopathy trials similarly remained in support of the current guidelines, it is important to try to understand the possible reasons for the disagreement with the DANISH trial results (8), to help direct future research towards addressing these knowledge gaps. The first plausible explanation is the effect of age and co-morbidities on the mortality benefit derived from ICD placement. ICD is very effective in preventing SCD, as demonstrated by the magnitude of risk reduction demonstrated in the current and other recent meta-analyses (13). However, ICD placement does not prevent death from other cardiac and non-cardiac causes, which may explain the lack of all-cause mortality benefit despite significant reduction of SCD in the DANISH trial. Logically, this disconnect would become more evident with advanced age and increased co-morbidities. In the DANISH trial, one-third of the patients were ≥68 years. Subgroup analysis of the DANISH trial demonstrated a mortality benefit with ICD in younger patients (i.e., age <68 years) (HR =0.64; 95% CI, 0.45–0.90; P=0.01). Although the current meta-analysis did not show a statistically significant interaction between treatment and age (<65 *vs.* ≥65 years) in the overall population (ischemic and non-ischemic), a recent dedicated meta-analysis of the non-ischemic cardiomyopathy trials suggested a possible effect modification by age, with potential benefit in those <60 years as compared with older patients (≥60 years) (13). Second, cardiac resynchronization therapy (CRT) has been shown to reduce the risk of mortality in select patients with cardiomyopathy. In the DANISH trial, 58% of the patients had CRT in place, which may have contributed to the attenuated mortality benefit of ICD therapy. In a large observational study with ~5,300 patients who had CRT implanted, ICD was associated with a lower risk of all-cause mortality at 44 months in those with ischemic cardiomyopathy, but not in those with non-ischemic cardiomyopathy (14). Finally, the improved adherence to guideline directed medical therapy in the DANISH trial compared with older trials might have also contributed to the reduced incidence of cardiac deaths (e.g., beta-blocker therapy was as low as 3.8% in the CAT trial, compared with ~92% in the DANISH trial).

In summary, the meta-analysis by Kolodziejczak *et al.* provides further evidence to support the current ESC and ACC/AHA guidelines for primary prevention ICD in patients with heart failure with reduced ejection fraction irrespective of the underlying etiology (i.e., ischemic or non-ischemic origin) (1,2). Taking into account the DANISH trial (8) results, which sparked some controversies regarding primary prevention ICD in patients with non-ischemic cardiomyopathy, future research efforts should explore the utility of ICD therapy in the elderly. An ongoing clinical trial, the I-70 (Efficacy and Safety of Implantable Cardioverter-Defibrillator Implantation in the Elderly) trial (ClinicalTrials.gov, NCT02121158), is exploring the mortality benefit of ICD placement in the context of declining SCD in those >70 years.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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