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EDITORIAL COMMENT

Who Benefits From Implantable Cardioverter-Defibrillators?

Integrating Absolute, Proportional, and Competing Risk*

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We commonly use absolute risk to determine candidacy for therapy in cardiovascular disease. For example, in patients with atrial fibrillation, annualized stroke estimates guide decision making for anticoagulation (1) and for patients with coronary heart disease, 10-year cardiovascular event risk serves as the basis for statin qualification (2). Inherent in this formulation of risk is the concept of absolute risk reduction and its inverse form, number needed to treat. The higher the absolute risk, the greater the absolute risk reduction and the lower the number needed to treat to benefit 1 patient.

At least 1 arena where this concept has not proven consistently true is the prevention of sudden cardiac death with implantable cardioverter-defibrillators (ICDs) (3). Given that ICD therapy is designed to treat potentially fatal ventricular arrhythmias, it would seem sensible that the greatest mortality benefit of ICD therapy would be in those at highest absolute risk of arrhythmic death (4). However, a key missing consideration in this formulation of ICD benefit is the impact of the competing risk of nonsudden deaths, which mitigate the potential lifesaving benefits of ICD therapy. The implications of competing risk are not just theoretical. The majority of patients undergoing ICD implantation never use their device and a recent study of US Medicare ICD recipients found that 50% had either died or were enrolled in hospice within 5 years of implantation (5). Indeed, the fact that those at increased risk of sudden death are also at increased and excessive risk of nonsudden death (6) poses a significant challenge to the traditional absolute risk paradigm by effectively uncoupling absolute sudden death risk and ICD survival benefit.

The question of who benefits from ICD therapy is increasingly important, particularly in light of the DANISH (Danish Study to Assess the Efficiency of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality) study (7), which found no survival advantage to ICD implantation in patients with a low ejection fraction, nonischemic cardiomyopathy, and no history of ventricular arrhythmia. Beyond questions of efficacy in particular subgroups, ICD implantation is associated with both short- and long-term device complications (8), inappropriate shocks leading to decreased quality of life and morbidity (9), as well as considerable cost. With an aging population and anticipated increase in global rates of incident heart failure (HF), the clinical and financial implications of maximizing ICD benefit will only intensify.

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In this issue of the *Journal*, Bilchick et al. (10) integrate concepts of absolute and competing risk to identify patients who may benefit most from primary prevention ICD implantation. They estimate the impact of ICD implantation on survival by comparing mortality in ICD recipients from the United States National Cardiovascular Data Registry (N = 87,914) and a control cohort of HF patients without ICDs (N = 10,932). After adjusting for baseline differences between the groups, they estimated that ICD therapy was associated with 25% lower risk of death. They

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then explored whether the efficacy of ICD therapy differed according to total mortality risk (estimated using the Seattle Heart Failure Model [SHFM]) or proportional sudden death risk (estimated using the Seattle Proportional Risk Model [SPRM]). There was evidence of effect modification for both, suggesting that the magnitude of survival benefit for ICD therapy differed across strata of both total mortality and proportional sudden death risk. When assessed continuously, the magnitude of survival benefit associated with ICD therapy increased as the proportional risk of sudden death increased.

To identify subgroups with differential ICD benefit, they stratified the cohort by median 1-year total mortality risk and then by median proportional risk of sudden death. Those with a higher proportional risk of sudden death had the greatest ICD benefit independent of estimated total mortality (30% to 40% relative reduction in mortality), with the greatest life years gained in those with the combination of low predicted 1-year total mortality (<6%) and high proportional risk of sudden death (>57%). Conversely, patients with low proportional sudden death risk were predicted to benefit less from ICD therapy, with the combination of low total mortality risk and low proportional sudden death risk associated with no survival benefit.

While this ambitious and timely study integrates nuanced concepts of absolute and proportional risk, there are several caveats to consider. First, as the authors acknowledge, this is an observational study with collation of an ICD cohort and historical HF controls. Despite multivariable adjustment, major differences in medication use (β-blockade, renin-angiotensin-aldosterone system digoxin) and HF class between the ICD and HF control groups raise concerns regarding comparability. Replication of this approach within randomized ICD trials would be of significant value and needed before clinical implementation. Second, the study excluded patients undergoing cardiac resynchronization therapy (CRT), who accounted for nearly 40% of eligible patients in the final selection of the ICD cohort. To the extent that CRT-induced reverse remodeling modifies the risk of both arrhythmic and non-arrhythmic death (11), the generalizability of these findings, and the fidelity of the SPRM or SHFM estimates in this substantial population is uncertain. Third, it is worth understanding the relationship between the risk models presented (SHFM, SPRM). These authors have previously shown that an increasing SHFM (total mortality) score is not only associated with an increasing absolute risk of sudden death, but is also inversely related to the proportional risk of sudden death (6). This overlap between the risk captured by the SHFM and SPRM may explain some of the non-intuitive findings in this study including, for example, why participants with low proportional risk of sudden death but higher total mortality (i.e., high absolute risk sudden death) were still predicted to benefit from ICD. Given that the mechanism of survival benefit for ICD therapy is via its effect on sudden death, more direct modeling of absolute sudden death risk (as opposed to total mortality) may have yielded greater clarity to the interaction of absolute and proportional risk with ICD benefit.

By highlighting the need to look beyond absolute risk, Bilchick et al. (10) have offered us an important step forward in sudden death prevention. Organizing their results somewhat differently, for patients at lower overall mortality (<6% per year), the proportional risk of sudden death had the most extreme implications – with the greatest ICD benefit accruing to those at high proportional risk and no ICD benefit for those at low proportional risk. By comparison, for patients at high all-cause mortality risk, ICD therapy was efficacious regardless of proportional sudden death risk, although there appeared to be a numerically greater benefit as sudden death accounted for a greater proportion of mortality. This alternative formulation has specific relevance to patient selection in ICD trial design. As absolute rates of both total and arrhythmic mortality in ICD trials have consistently declined in the last 20 years, enrichment for the proportional risk of sudden death may be increasingly important. Indeed, this likely explains the post hoc findings of the DANISH investigators (7) who identified no survival benefit in the overall cohort (low mortality, low proportional risk) but did find benefit in younger individuals (low mortality, higher proportional risk).

Looking ahead, our contemporary “one size fits all” approach to ICD implantation does not appear to be a clinically or cost-effective strategy in sudden death prevention. Although ICDs are clearly efficacious for the treatment of ventricular arrhythmias (i.e., “insurance policy”), these devices do not directly ameliorate the substrate of arrhythmic risk (i.e., “maintenance plan”). In that context, therapies which target upstream drivers of sudden death – such as worsening HF or adverse left ventricular remodeling – may provide synergistic survival benefits for ICD eligible patients by targeting both arrhythmic and nonarrhythmic modes of death. For example, HF pharmacotherapy associated with reduction in HF risk has shown consistent and significant reduction in both HF and arrhythmic mortality (e.g., 20% reduction in sudden death with

sacubitril/valsartan compared to standard goal directed medical therapy) (12). By broadening the scope of sudden death prevention tools, we could begin to consider more flexible and individualized approaches to risk reduction. For example, staged strategies deploying pharmacotherapy or CRT pacing first to modify absolute and proportional sudden death risk may help guide subsequent decision making regarding ICD implantation. For now, this study leaves us with an important lesson: while you can only die once, there is more than 1 way to die—understanding the difference is key.

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