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EDITORIAL COMMENT

Trying to Make Progress on Survival in a Complicated Area

Sudden Death in HFpEF*

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When I was in medical school, there was at least the urban legend that a criteria for a chief of medicine position was to be "able to function in a world of ambiguity." Since "ambiguity" is defined as doubtfulness or uncertainty of meaning, it is worth keeping this in mind while considering the paper by Vaduganathan et al. (1), which involves fatal events categorized as sudden in subjects with heart failure with preserved ejection fraction (HFpEF). The clinical entity, HFpEF, has its own ambiguity given the difficulties of diagnosis, heterogeneous pathophysiology, comorbidities, older cohort, and so on—but efforts to better understand sudden death, reported as the leading mode of death in HFpEF clinical trials, and consider possible interventions is necessary. It will also be challenging.

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SUDDEN DEATH IN HFpEF

Sudden death definitions vary—some say all death is sudden—however, events should be not only sudden, but also unexpected. Unfortunately, this categorization has been fraught with uncertainty in both heart failure and arrhythmia clinical trials, since these are overwhelmingly outpatient events about which little documentation often exists. For primary prevention, sudden death events have been most commonly evaluated in heart failure with reduced ejection fraction (HFrEF), where they represent ~40% of all-cause mortality in mild-to-moderate heart failure patients, and the assumption has been that they are predominantly tachyarrhythmic episodes. However, in large heart failure clinical trials, while the assumption of tachyarrhythmia for sudden death events is usually unproven, intracardiac implantable cardioverter-defibrillator (ICD) therapy in SCD-HEFT (Sudden Cardiac Death in Heart Failure Trial) reduced these "presumed tachyarrhythmic" events by 60.2% (Online Ref. 1). There have also been significant sudden death reductions with guideline-based medical therapies, such as aldosterone antagonists, beta-blockers, and the neutral endopeptidase inhibitor/angiotensin receptor blocker combination, although not quite to this degree. In HFpEF, sudden death events are a smaller target, although usually still the largest mode of death category: reported analyses from CHARM Preserved 3 (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity) (Online Ref. 2) and I-PRESERVE 4 (Irbesartan in Heart Failure With Preserved Systolic Function) (2), as well as other smaller databases, indicate that sudden death represents 20% to 25% of fatal events. As in HFrEF, how close the clinical trial results are to "real world" sudden death events is hard to be certain, but one could assume that, as usual, the issues will be even more complex in HFpEF. For example, the above clinical trials reported that approximately 60% of overall deaths were cardiovascular (CV) (and 40% of CV deaths were sudden). However, epidemiological data from Olmstead County (Online Ref. 3) indicates that the proportion of CV deaths declined from 69% to 40%, in an HFpEF cohort, then making sudden death events a smaller target. Could this be so? "Real-world" reports of HFpEF patients are usually older with more comorbidities than those in clinical trials, and therefore noncardiovascular, invariably nonsudden, fatal events would likely be increased. It is also true that the proportion of sudden/nonsudden events also relates to how one considers a "sudden death" event: is it really a sudden unexpected death? Certainly in a

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population of older individuals with significant comorbidities, a death may be sudden but not necessarily unexpected or for that matter cardiac. For example, an 85-year-old patient with significant renal insufficiency in an assisted living facility dies. As above, is this a sudden unexpected death? Pushing a little further, would it be a sudden cardiac death? Issues such as this have led then to the concept of risk stratifying individuals who might have higher fatal cardiac event rates, and more likely sudden unexpected, presumably cardiac, fatal events and therefore might benefit from an intervention such as an ICD.

RISK STRATIFICATION FOR SD

A number of risk stratification models have been presented in HFrEF with careful consideration of the concept of competing risk between sudden and nonsudden fatal events. In general, separation by scores is often best with pump failure events, but clustering by scores persists with SDs making the differentiation of the risk difficult. Fewer reports exist for HFpEF patients largely due to the lack of large clinical trials until recently. A previous analysis from the I-PRESERVE database provided a model that included age, gender, diabetes mellitus or myocardial infarction history, left bundle branch block, and lnN-terminal proBNP, which identified a higher risk cohort that the authors considered might be a group to test for benefit from ICD use (3). Further analyses are sure to be forthcoming from the large clinical trials that have finally occurred in this population.

POTENTIAL THERAPY

Interventions for SD in HFpEF and in HFrEF, apart from an ICD, that have reduced all-cause mortality have done so by reducing the 2 major fatal categories: SD and pump failure deaths. This concept was reinforced by a recent report of a decline in reported SD events in HFrEF, largely without ICD therapy, using guideline-based therapy (4). Unfortunately, effective treatments such as in HFrEF are currently not available for HFpEF, and optimism has to be tempered given the pathophysiologic heterogeneity. What about ICD implantation in HFpEF patients? Certainly, this therapy is well established in the medical trials in HFrEF as primary prevention, although estimates indicate that perhaps only 20% to 25% of "guideline eligible" patients receive an ICD. Further, electrophysiologists have wondered about conundrums involving ICD use in such patients. For example, a disconnect has been reported, even in clinical trials, between shocks and mortality benefit. Additionally, electrophysiologists have also reported the relatively low number of patients who receive a shock: 19% in 2.59 years (SCD-HeFT/MADIT [Multicenter Automatic Defibrillator Implantation Trial]) (Online Ref. 4); and in a real-world assessment two-thirds of patients with an initial generator exchange had not received a shock and only one-fourth of these did afterward (Online Ref. 5). Considering whether ICD therapy might be effective in a HFpEF population, recent reports suggest additional hurdles. In the recent DANISH (Danish Study to Assess the Efficacy of ICDs in Patients With Non-ischemic Systolic Heart Failure on Mortality) study, ICD therapy did not reduce all-cause mortality in the nonischemic cohort and this was particularly apparent with patients older than 70 years (5). HFpEF patients more commonly have a nonischemic etiology and are older. The competing risk of non-SD events looms larger in such patients who often have important comorbidities. For example, multiple reports now show a lack of benefit and, in fact, some harm of ICDs in patients with HFrEF and chronic kidney disease. Reports such as these have led to suggestion that even in HFrEF patients there should at least be careful patient discussion and perhaps a further look at risk stratification strategies, which would be even more pressing in a HFpEF population.

Vaduganathan et al. (1) note the difficulties in establishing a firm number of SD events in trials with different definitions and limited information. It provides a model but is limited by the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function trial) database, with suitable subjects analyzed only from the Americas region due to enrollment and protocol conduct issues in other geographic regions. Although well analyzed, this then limited the number of SD events with a resulting model of modest predictive value and only 2 independent covariates (male sex and insulin-treated diabetes mellitus). More substantial analyses are necessary to move forward with potential risk stratification of SD events and then consideration of clinical trials for ICD therapy. However, as noted above, even if there were a strong signal seen, there would have to be care to the application of such results in a real-world setting so as to maximize benefit and not harm.

How to proceed in a world of ambiguity? Vaduganathan et al. (1) keep a dialogue going regarding potential approaches to improve survival in HFpEF where we struggle to find a way forward.

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APPENDIX For additional references, please see the online version of this paper.