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REVIEW TOPIC OF THE WEEK

Mode of Death in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Little is known about specific modes of death in patients with heart failure with preserved ejection fraction (HFpEF). Herein, the authors critically appraise the current state of data and offer potential future directions. They conducted a systematic review of 1,608 published HFpEF papers from January 1, 1985, to December 31, 2015, which yielded 8 randomized clinical trials and 24 epidemiological studies with mode-of-death data. Noncardiovascular modes of death represent an important competing risk in HFpEF. Although sudden death accounted for ~25% to 30% of deaths in trials, its definition is nonspecific; it is unclear what proportion represents arrhythmic deaths. Moving forward, reporting and definitions of modes of death must be standardized and tailored to the HFpEF population. Broad-scale systematic autopsies and long-term rhythm monitoring may clarify the underlying pathology and mechanisms driving mortal events. There is an unmet need for a longitudinal multicenter, global registry of patients with HFpEF to map its natural history. (J Am Coll Cardiol 2017;69:556-69) © 2017 by the American College of Cardiology Foundation.

Despite the increasing prevalence and attendant clinical and economic burden of heart failure (HF) with preserved ejection fraction (HFpEF) globally (1,2), little is known about how these patients die. To date, drug and device trials targeting these patients have failed to alter their disease trajectory. The lack of success of these therapeutic programs may be, in part, a result of the marked heterogeneity in the clinical profiles of this complex entity (3,4). However, inadequate understanding of the specific cardiovascular (CV) and non-CV mechanisms driving terminal events also renders therapeutic development difficult, because successful interventions typically modulate

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pathophysiologies and outcomes that are relevant to the study patients in whom they are being tested (5). To date, clinical trials of HFpEF patients report considerable CV mortality rates, just below those of heart failure with reduced ejection fraction (HFrEF) patients (6). Furthermore, trial data suggest that sudden death (SD) and HF death account for the majority of CV mortality in HFpEF (6). It remains unclear, however, whether death due to SD or worsening HF in HFpEF shares the same clinical and mechanistic relevance as in HFrEF. There has been overwhelming evidence to suggest that ventricular arrhythmias are prevalent and account for the majority of SD in HFrEF patients (7). On the contrary, the burden and impact of ventricular arrhythmias in HFpEF have not been defined (8), and thus the underlying mechanism of SD may be different in these patients.

In addition, clinical experience suggests that HF death in HFpEF is not classic "pump failure," as in HFrEF, but in many cases, involves progressive pulmonary hypertension, right ventricular failure, and/or renal venous congestion and worsening renal function with ensuing multiorgan dysfunction. Differential classification of events as SD or pump failure in HFrEF and HFpEF may influence the intended versus the actual impact of a therapeutic intervention on outcomes. If such mechanistic differences were validated, this would suggest that the definitions of modes of death should be tailored to each specific disease state. Without knowledge of the modes of death in granular detail, advances in effective therapeutics for HFpEF and appropriate clinical trial design may continue to be limited. As such, we conducted a broad-scale systematic review of cause-specific mortality in patients with HFpEF across contemporary randomized controlled trials (RCTs) and epidemiological studies conducted over the last 30 years.

SYSTEMATIC REVIEW OF MODE OF DEATH IN HFpEF

SEARCH STRATEGY. We identified key studies exploring mode of death in HFpEF published in English between January 1, 1985, and December 31, 2015, by systematically searching the PubMed and EMBASE databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram summarizing the search strategy and selected studies in this systematic review is presented in Figure 1. Initial evaluation was of the study titles and abstracts alone, followed by a more rigorous manual screen in duplicate of all full texts by 2 independent authors (M.V. and R.B.P.). References were considered if they included patients with the clinical syndrome of HF and applied an ejection fraction (EF) cutoff of at least 40% or above to define HFpEF. Only studies that enrolled or included stably preserved EF were analyzed (i.e., studies evaluating patients with recovered EF were excluded). Studies were required to have at least 1 month of follow-up, and as such, studies limited to the in-hospital setting were excluded. Other key exclusion criteria included: 1) papers not reporting specific EF thresholds or applying EF cutoffs lower than 40% to define HFpEF; 2) studies of subgroups within HFpEF (to avoid bias); 3) studies assessing only nonmortality endpoints; 4) investigations that provided data on total mortality alone, without details of the specific mode or cause of death; and 5) secondary or post hoc analyses of original studies to limit duplication. Some studies may have had more than 1 reason for exclusion, but the main violation of the eligibility criteria was tabulated for the purposes of the PRISMA figure.

Studies were analyzed separately on the basis of their primary study designs: RCTs and epidemiological studies. When available, CV deaths were subclassified by specific causes, including HF, SD, sudden cardiac death (SCD), myocardial infarction (MI), stroke, procedural, or other CV. Similarly, when described, non-CV deaths were subclassified by specific causes, including cancer, infection/sepsis, respiratory, renal, gastrointestinal, diabetes, trauma, suicide, or other non-CV. Cause-specific mortality was expressed separately as a proportion of total CV and non-CV deaths. When sufficient data were available, cause-specific mortality was also reported as a proportion of total deaths.

STUDY SELECTION. The initial search strategy yielded 1,608 unique papers published between January 1st, 1985, and December 31st, 2015 (Figure 1). After manual screen of the titles and abstracts, 548 were excluded because they were not original investigations, and 121 were not available in English. Full texts of the remaining papers (n = 939) were reviewed in duplicate, and after further relevant exclusions (detailed in Figure 1), we identified 320 HFpEF studies with mortality data. Of these, 32 studies (8 RCTs and 24 epidemiological studies) included sufficient mode-of-death data, and were selected for final inclusion in this systematic review.

DEFINITIONS OF SD, SCD, AND HF DEATH. Four of the 8 HFpEF RCTs (50%) included data on SD or SCD, and 5 of 8 (62.5%) included data on HF death.

ABBREVIATIONS AND ACRONYMS

CV = cardiovascular
EF = ejection fraction
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
ICD = implantable cardioverter-defibrillator
MI = myocardial infarction
RCT = randomized controlled trial
SCD = sudden cardiac death
SD = sudden death