JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 69, NO. 5, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.10.078

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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Manuscript received October 3, 2016; accepted October 26, 2016.

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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.

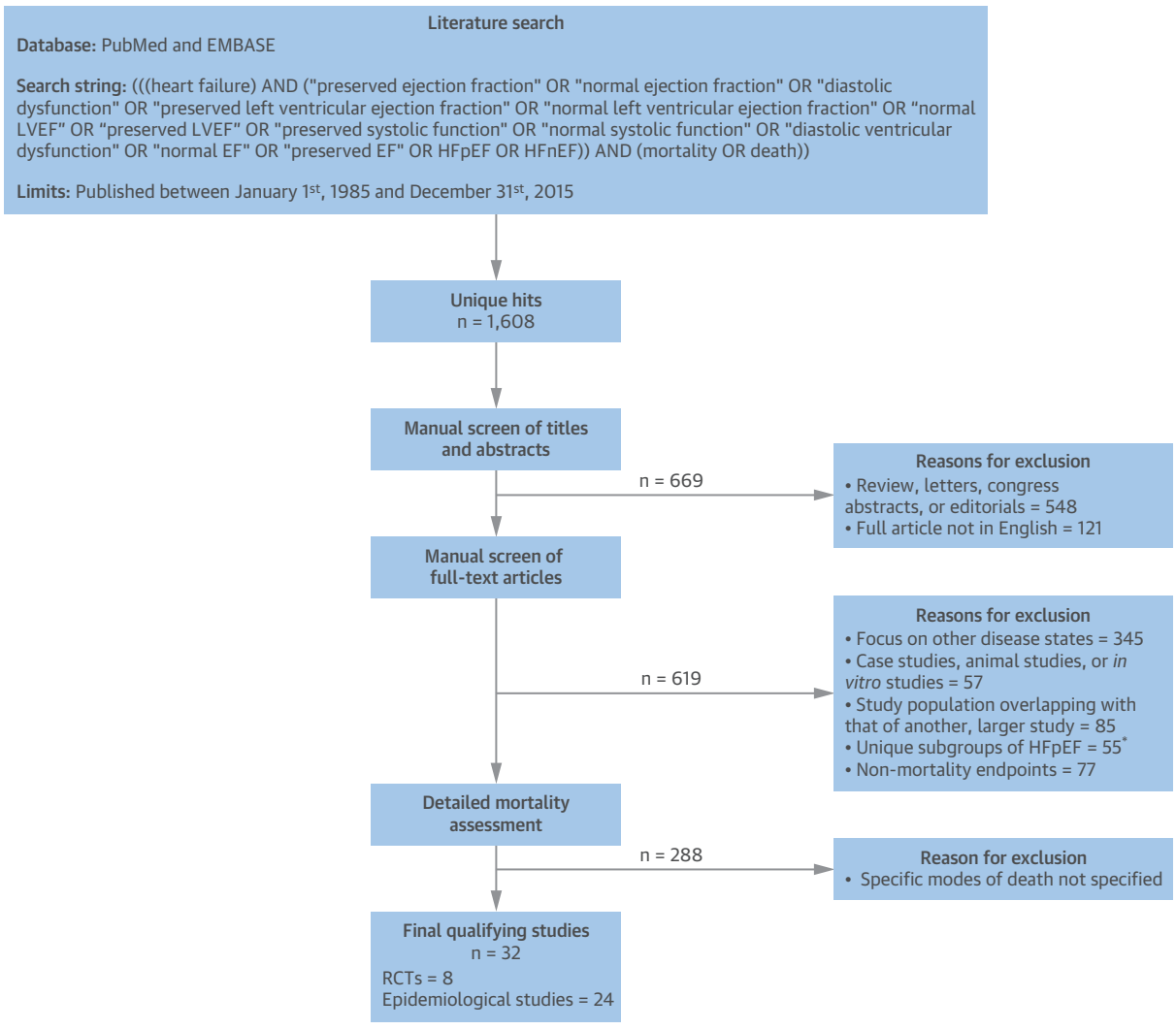
STUDY SELECTION. The initial search strategy yielded 1,608 unique papers published between January 1st, 1985, and December 31st, 2015 (Figure 1). After manual screen of the titles and abstracts, 548 were excluded because they were not original investigations, and 121 were not available in English. Full 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

FIGURE 1 PRISMA Flow Diagram of Systematic Searches and Selection Process



*Examples of specific subpopulations include 100% male or female populations, pediatric populations, or populations receiving or eligible for a particular treatment. EF = ejection fraction; HFnEF = heart failure with normal ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

Of the 24 epidemiological studies, 5 (20.8%) reported data on SD or SCD and 7 (29.2%) reported data on HF death.

The specific definitions of SD, SCD, and HF death were variable across trials (**Table 1**). Compared with the earlier CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity)-Preserved (9) and DIG (Digitalis Investigation Group)-Ancillary (10) studies, more contemporary RCTs, such as the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study (11), provided more granular details regarding timing and circumstances surrounding SD. However, none of the included HFpEF trials defined SCD specifically; rather, they defined the broader syndrome of SD. The I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study) (12) study collected information on the presence of CV symptoms before a mortal event, but did not delineate a timeframe or duration of symptoms to qualify the SD, and these data were unknown in 46% of enrolled patients (12).

The CHARM-Preserved (9), DIG-Ancillary (10), and TOPCAT (11) studies defined HF death as a death in

TABLE 1 Variation in Definitions of SD and HF Death

Trial or Society (Ref. #)	Criteria for SD	Criteria for HF Death
CHARM-Preserved (9)	The unexpected death of a stable patient	Death in the setting of clinical progressive HF, with no other apparent cause
DIG-Ancillary (10)	Data not available for this trial	Death in the setting of clinical progressive HF, with no other apparent cause
I-PRESERVE (12)	An unexpected death in a previously clinically stable patient. Patients in this category had recent human contact before the event. Includes patients who, after attempted resuscitation, became comatose and then died. Patients who had been out of contact for prolonged (generally >1 week) or unknown periods of time were classified as unknown. When sufficient information was available, SD was subcategorized as with or without preceding cardiovascular symptoms.	Death as a result of worsening or intractable HF. The death usually occurred during hospitalization, at a nursing home, or while in hospice care. When sufficient information was available, HF was subcategorized as with or without low output and/or congestion. Low output was indicated by fatigue, signs of vasoconstriction, pre-renal azotemia, need for vasopressors, low cardiac output, or hypotension. Congestion was indicated by symptoms and signs on physical examination, chest x-ray, and invasive/noninvasive measurements.
TOPCAT (11)	SD Death that occurred unexpectedly in an otherwise stable subject. Further subclassification of SD was as follows: a) witnessed; and b) last seen ≥1 and <24 h Presumed SD Death that occurred unexpectedly in an otherwise stable subject in which the subject was last seen ≥24 h before death and circumstances are suggestive of SD	Death occurring within the context of clinically worsening symptoms and/or signs of HF, without evidence of another cause of death. If worsening HF is secondary to MI, then MI should be listed as the primary cause of death, given that the subject has an MI within 14 days of death.
TIME-CHF (14)	1. Witnessed death in the absence of pre-existing circulatory failure 2. Unwitnessed death in the absence of pre-existing circulatory failure 3. Patients resuscitated from cardiac arrest in the absence of pre-existing circulatory failure	The presence of at least 1 of the following at the time of death: 1) cardiogenic shock (hypotension resulting in a failure to maintain normal renal or cerebral function for >15 min before death; 2) pulmonary edema sufficient to cause tachypnea and distress; 3) HF symptoms requiring continuous intravenous therapy or oxygen administration; or 4) confinement to bed due to HF symptoms.
PARADIGM-HF (24)	SD Death that occurred unexpectedly in an otherwise stable patient. Further subclassification of SD based on timing of last seen alive: a) within 1 h; or b) between 1 and 24 h. Presumed SD Death that occurred unexpectedly in an otherwise stable patient in which the patient was last seen ≥24 h before death	Death in the context of clinically worsening signs or symptoms of HF with no other apparent cause, death as a consequence of surgical procedure to treat HF, or death after referral to hospice for HF.
MADIT (7)	Arrhythmic death Abrupt collapse accompanied by cessation of pulse without prior circulatory collapse	Data not available for this trial
NHLBI and HRS Working Group Definition (28)	Established SCD An unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse. If unwitnessed, occurring within 1 h after the onset of symptoms Probable SCD An unexpected death without extracardiac cause that occurred within the previous 24 h. In any situation, the death should not occur in the setting of a prior terminal condition.	Data not available for this trial
CDISC (30)	SCD 1. Death witnessed and occurring without new or worsening symptoms. 2. Death witnessed within 60 min of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI. 3. Death witnessed and attributed to an identified arrhythmia. 4. Death after unsuccessful resuscitation from cardiac arrest. 5. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac etiology. 6. Unwitnessed death in a subject seen alive and clinically stable ≤24 h before being found dead, without any evidence supporting a specific non-CV cause of death.	Death in association with clinically worsening symptoms and/or signs of HF, regardless of HF etiology.

CDISC = Clinical Data Interchange Standards Consortium; CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CV = cardiovascular; DIG = Digitalis Investigation Group; HF = heart failure; HRS = Heart Rhythm Society; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction Study; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NHLBI= National Heart, Lung, and Blood Institute; PARADIGM-HF = Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; SCD = sudden cardiac death; SD = sudden death; TIME-CHF = Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

the setting of worsening HF without apparent alternative cause. The I-PRESERVE study further defined HF death on the basis of perfusion and congestion status; however, data on these elements were unavailable in 15% of patients (12).

CV VERSUS NON-CV CAUSES OF MORTALITY. Of the study designs, the RCTs (9–16) presented more comprehensive cause-specific data, with relatively low reported rates of unknown or unadjudicated causes of mortality. Early RCTs (10,13) included ~800 patients with HFpEF, whereas more recent trials enrolled more than 3,000 patients with HFpEF, and included more specific breakdowns of CV and non-CV deaths (11,12). Available follow-up times over which cause-specific events were captured ranged from 1 to 50 months. Across the 8 contemporary HFpEF RCTs, CV-related causes consistently accounted for approximately 60% to 70% of total deaths, whereas 20% to 30% of deaths were attributed to non-CV causes (**Figure 2**).

The epidemiological studies were highly variable in terms of sample sizes of patients with HFpEF (ranging from 28 to 2,316) and settings of enrollment, but had consistently longer durations of average follow-up compared with the RCTs (ranging from 12 to 116 months) (**Table 2**). Compared with the RCTs, the epidemiological studies had a wider range of CV-specific mortality (as a proportion of total mortality, 14% to 83%). CV causes accounted for a median of 58.5% of total mortality in the included epidemiological studies (**Table 2**).

CAUSE-SPECIFIC CV MORTALITY. Data on individual components of CV deaths were available in 5 HFpEF RCTs. In the 3 RCTs with the highest documented CV-related mortalities (**Figure 3**, top), SD was the predominant CV-related mode of death (~40%), followed by worsening HF (~20% to 30%). MI and stroke accounted for a minority of CV deaths (each ~5% to 15%). The DIG-Ancillary and TIME-CHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) studies provided more variable estimates of cause-specific mortality, with death due to worsening HF representing 40% and 82% of total CV deaths, respectively.

Figure 4 displays representative epidemiological studies (17–19) that provide comprehensive and interpretable mode-of-death data for CV-specific mortality. SCD or SD was estimated at ~20% to 28%, whereas death due to worsening HF accounted for widely variable proportions of CV deaths, ranging from 17% to 60%. The causes of 55% of CV deaths was assigned as "other" in the Minnesota Heart Study (17).

When expressed as a proportion of total deaths (Online Table 1), SD accounted for 27% to 29% and 11% to 12% of representative trials and epidemiological studies, respectively. Worsening HF accounted for 14% to 28% of total mortality in trials, but this proportion was more variable in epidemiological studies (6.6% in 1 study and 40.4% in another).

CAUSE-SPECIFIC NON-CV MORTALITY. Detailed information about non-CV causes of death was available in 3 HFpEF trials (**Figure 3**, bottom). Cancer was the most frequently reported non-CV mode of death (30% to 40% of non-CV deaths), followed by infection/sepsis, which accounted for roughly one-quarter of non-CV deaths. Other specific non-CV causes of mortality, such as pulmonary/respiratory, gastrointestinal, and renal, were less common (<10% to 15%).

Two epidemiological studies (19,20) reported in-depth and comprehensive data on non-CV causes of mortality (**Figure 4**). Similar to the RCTs, the JCARE-CARD (Japanese Cardiac Registry of Heart Failure in Cardiology) registry (19) reported high proportions of non-CV deaths due to cancer (in 33%) and infection/sepsis (in 29%). Respiratory causes of non-CV mortality were reported in ~15% to 30%, whereas other causes, including those involving the renal and central nervous systems, were less common (19,20). Specific infectious etiologies or sources of sepsis were not reported across selected trials and epidemiological studies.

Cancer and infection/sepsis accounted for 10% to 13% and 7% to 10% of total mortality in representative studies, respectively (Online Table 1).

MODE OF DEATH IN HFpEF: WHERE DO WE STAND?

In this rigorous and comprehensive systematic review, only 8 major RCTs and 24 epidemiological studies collected information on mode of death in HFpEF over a 30-year period. Our systematic review highlights 4 major points: 1) the majority of patients with HFpEF die of CV-related causes, but there is significant variability between RCTs and epidemiological studies; 2) specific CV causes of death (i.e., SD and death due to worsening HF) are infrequently adjudicated and poorly defined; 3) SD, as currently reported, accounts for up to 30% to 40% of CV-related deaths in HFpEF; and 4) non-CV modes of death may be an important competing risk, accounting for up to 20% to 30% of deaths in HFpEF studies.

CHALLENGES IN ASCERTAINING CAUSE-SPECIFIC EVENTS. Relatively little has been written about mode of death in HFpEF (6). Our study substantially advances our current understanding as it:

1) systematically summarizes up-to-date published studies on the topic; 2) explores cause-specific event rates beyond CV versus non-CV distinctions; and 3) highlights variability in mode-of-death estimates across study designs.

As our understanding of this clinical syndrome matures, trials and registries have become increasingly larger in size and scope, and thus are capturing a greater number of mortal events. Few, however, have detailed specific modes of CV and non-CV deaths. There are distinct challenges in ascribing causes of death in HFpEF. First, despite attempts by guideline committees (21), the HF community has yet to reach a consensus regarding a uniform, standardized definition of HFpEF to allow more accurate profiling of the clinical course of these patients. Second, many RCTs and epidemiological studies do not include mortality as a major endpoint, but rather rely on surrogate (e.g., echocardiographic parameters, natriuretic peptides, among others) and intermediate endpoints (e.g., symptom scores, functional class). Third, many patients die outside of the hospital, and thus are beyond the bounds of immediate medical observation. Finally, and perhaps most importantly, there is no accepted, standardized reporting of mode-of-death information that is unique and tailored to HFpEF.

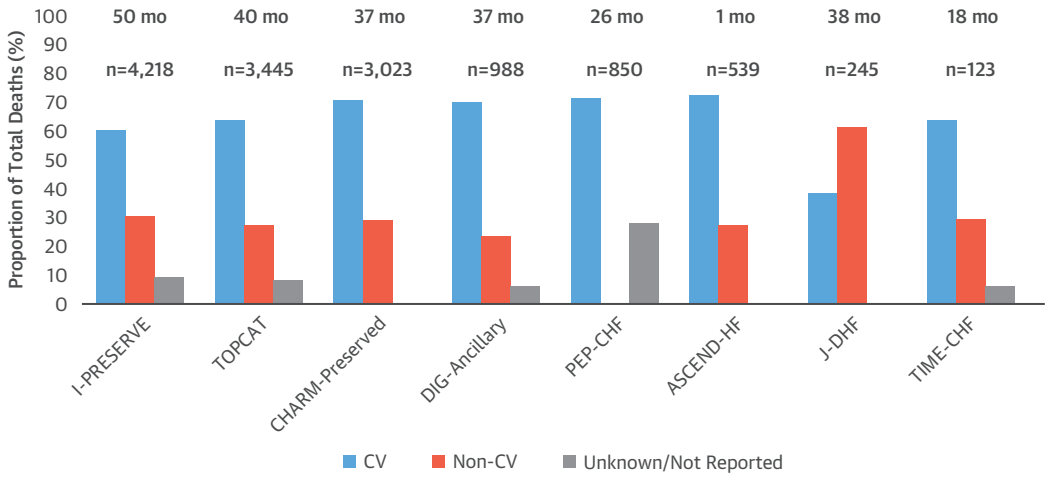
DETERMINING MODE OF DEATH ACROSS STUDY TYPES AND SETTINGS. Study design may shape the extent and accuracy of event ascertainment in HFpEF. Overall mortality tends to be higher in epidemiological studies compared with RCTs, which we confirmed in a recent broad-scale systematic review of 5 RCTs, 12 community-based observational studies, and 30 registry studies (3). This variation in observed event rates may be related to a number of factors. Trials employ stringent eligibility criteria, and limit enrollment of patients at the extremes of age and those with advanced comorbidities, thus enrolling a generally lower-risk study group. Trial participants also have greater access to medical care, and undergo more frequent assessment, laboratory testing, and evaluation of medical compliance. Most importantly, many trials use clinical event committees to review and adjudicate deaths using multiple sources of information. Epidemiological studies, by contrast, study broader, less-selected samples for which this rigorous adjudication process may not be practical or available. Review of case records by a dedicated coroner or pathologist may facilitate more accurate reporting, but may only be feasible in select settings (20). Unfortunately, other means of obtaining cause-specific event data, such as examination of death certificates, have been found to be largely erroneous when compared with detailed analysis of next-of-kin accounts, medical records, and autopsy reports (22,23). Ascertainment of cause-specific deaths in elderly patients with multiple cardiac and noncardiac comorbidities in this setting is especially challenging.

MODE-OF-DEATH DISTRIBUTION IN HFpEF. The natural history and progression of HFrEF have been well described, and many patients die in a consistent fashion. Detailed mode-of-death data (24) are available most recently from PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure), the single largest HFrEF RCT conducted to date. Of the 1,546 total deaths that occurred during the 27-month average follow-up period, 81% were deemed to be CV in etiology. Of these CV-related deaths, 45% were attributed to SCD and 26% to HF. Thus, SCD and HF alone account for nearly 60% of all deaths in this well-phenotyped population.

Despite heterogeneity in study populations, selection criteria, settings of enrollment, and study designs, common threads can be extracted regarding the overall landscape of mortal events in HFpEF. Similar to their HFrEF counterparts, CV causes are the predominant mode of death in HFpEF, with modest variability in proportional estimates across a spectrum of clinical studies. HFpEF RCTs suggest that 60% to 70% of deaths are CV-related, whereas epidemiological studies report lower proportions (~50% to 60%).

Misdiagnosis of HFpEF and lack of precision of inclusion criteria in these studies may introduce increased competing risks of death, and perhaps bias estimates towards the causes of death in general populations of older adults. Exercise intolerance and dyspnea represent hallmark symptoms of HFpEF, but also are major presenting symptoms of other non-HF disease states including obesity, chronic obstructive pulmonary disease, and sleep-disordered breathing. These non-CV comorbidities often coexist and may be difficult to definitively discern from HFpEF (25). Indeed, in the TOPCAT trial, substantial regional variation existed in enrolled populations, clinical outcomes, and response to spironolactone (26). The TOPCAT experience highlights the inherent difficulties in defining this syndrome, even in well-conducted global RCTs. Compared with RCTs and populations of HFrEF, HFpEF epidemiological studies have included older patients with higher rates of non-CV comorbidities (3). Life-limiting or advanced non-CV disease states (e.g., patients with an estimated glomerular filtration rate below 30 ml/min/1.73 m^2, active malignancy, advanced pulmonary

FIGURE 2 Proportion of CV vs. Non-CV Deaths in RCTs of HFpEF



The average duration of follow-up and total number of HFpEF patients enrolled in each trial are provided. ASCEND-HF = Acute Studies of Nesiritide in Decompensated Heart Failure; CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CV = cardiovascular; DIG = Digitalis Investigation Group; HFpEF = heart failure with preserved ejection fraction; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction Study; J-DHF = Japanese Diastolic Heart Failure; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; RCT = randomized controlled study; TIME-CHF = Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

disease, among others) represent key exclusion criteria across HFpEF trials, which may bias the overall mode-of-death distribution in these RCTs towards CV-predominant causes compared with that of unselected populations.

DO PATIENTS DIE OF OR WITH HFpEF? Although worsening HF accounts for roughly similar proportions (~20% to 30%) of total CV deaths in recent HFpEF and HFrEF trials, this mode of death is variably and poorly defined, often only necessitating the exclusion of other major causes of death. Unlike in HFrEF, the mechanism of worsening HF as a primary etiology of mortality in HFpEF is also conceptually challenging. Advanced cardiogenic shock and low output states are less frequently observed in HFpEF, especially in the absence of overt right HF and/or restrictive cardiomyopathy. Worsening chronic HF has been recognized as an important endpoint in contemporary HFrEF clinical trials (27), but ascribing death to worsening HF is challenging and fraught with misclassification issues in HFpEF patients who tend to have dysfunction of multiple organ systems (**Central Illustration**).

SUDDEN DEATH IN HFpEF. SD accounts for up to 25% of all-cause mortality and 40% of CV mortality in HFpEF, as currently reported in recent trials. Although the proportion of SD in HFpEF is modestly less than in HFrEF, where it constitutes 35% to 40% of all mortal events, SD remains an attractive target for therapeutic intervention. However, important variation in the definitions of SD across the range of HFpEF RCTs (**Table 1**) may pose difficulties in providing accurate SD incidence estimates and characterizing the subset of patients who are at risk for SD.

Unfortunately, none of the contemporary HFpEF trials provide sufficient detail to distinguish SCD from the broader syndrome of SD. Earlier trials of HFpEF, such as CHARM-Preserved (9), did not require detailed information regarding timing and presence of antecedent CV symptoms when defining SD. According to a recent consensus statement from the Heart Rhythm Society and the National Heart, Lung, and Blood Institute regarding SCD prevention (28), the timing of death in relation to symptom onset (usually within 1 h) is, in fact, the hallmark of SCD. Indeed, more recent trials of HFpEF, including TOPCAT (11) have adopted this more stringent definition of SD, which is also in line with more contemporary HFrEF trial definitions (24). The rapidity of death is also crucial in defining SCD, as noted in the definition of "arrhythmic death" in the MADIT (Multicenter Automatic Defibrillator Implantation Trial) (7), which is described as the loss of pulse before circulatory collapse and is derived from Hinkle and Thaler's seminal work (29) regarding classification of CV

TABLE 2 Cause-Specific Mortality Rates in Major Epidemiological Studies of HFpEF

Epidemiological Study (Ref. #)	Yr of Publication	HFpEF Patients	Average Follow-Up (months)	Sudden Death	HF Death	Other CV Death	Total CV Deaths	Total Non-CV Deaths	Total Deaths	% CV of Total Deaths
CHART-2 (41)	2015	2,316	36	–	–	–	139*	162*	301*	46.2
Shinken Database (42)	2013	1,121	37.8	–	9	–	19	31	50	38.0
Minnesota Heart Survey (17)	2012	787	60	44	27	88	159	252	411	38.7
SCDB-HF (43)	2015	751	24	–	–	–	100	100	200	50.0
Liu et al. (44)	2012	576	12	–	–	–	72		134	53.7
ODIN (45)	2014	575	19	–	–	–	79	54	133	59.4
Olmstead County (20)	2008	478	51.6	–	–	–	–	–	–	51.0
CHART-1 (41)	2015	463	36	–	–	–	79*	27*	106*	74.5
LURIC (46)	2014	459	116	–	–	–	117	67	184	64.0
Grigorian-Shamagian et al. (18)	2008	443	44.4	–	–	–	–	–	–	82.0
JCARE-CARD (19)	2012	429	25.2	18	59	6	98	48	169	58.0
IN-HF (47)	2014	377	12	–	27	–	53	16	74	72.0
Tribouilloy et al. (48)	2008	368	60	–	–	–	–	–	158	59.0
Yan et al. (49)	2013	224	30	–	–	–	36	21	57	63.0
Framingham Heart Study (50)	2011	191	–	7*	14*	15*	36*	70*	106	34.0
Cardiovascular Health Study (51)	2002	170	76.8	–	–	–	40.9 per 1,000 patient-yrs	–	87 per 1,000 patient-yrs	47.0
Zafrir et al. (52)	2011	164	24	10	9	–	19	33	53	35.8
Zotter-Tufaro et al. (53)	2015	142	14	–	–	–	6	3	9	67.0
Miyagishima et al. (54)	2009	129	28.8	6	18	–	–	–	39	77.0
Cenkerova et al. (55)	2015	54	12	–	–	–	4	3	7	57.1
Setaro et al. (56)	1992	52	53.7	–	–	–	24	5	30	80.0
Brogan et al. (57)	1992	51	68	–	–	–	1	6	7	14.0
Helsinki Aging Study (58)	1997	28	48	–	–	–	10	2	12	83.0

*Number of cause-specific events estimated on the basis of reported proportions of total deaths.

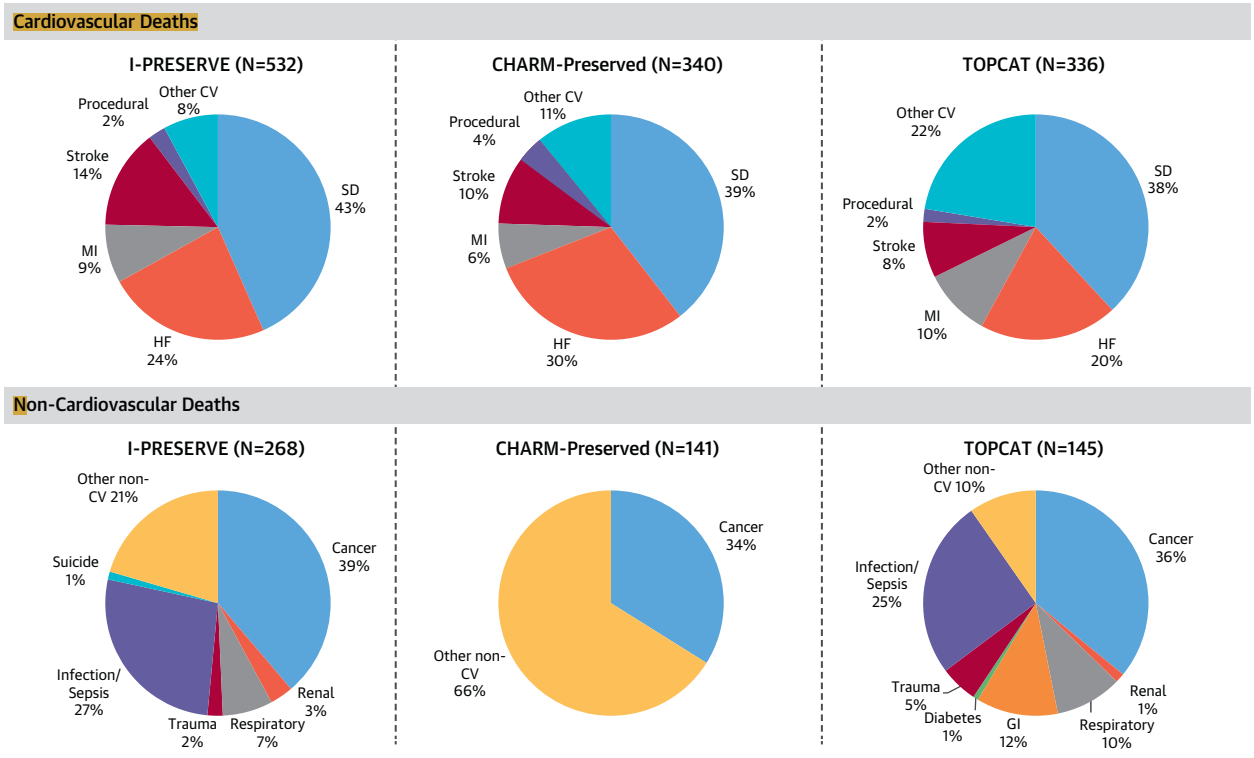
CHART = Chronic Heart Failure Analysis and Registry in the Tohoku District; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; IN-HF = Italian Network on Heart Failure; JCARE-CARD = Japanese Cardiac Registry of Heart Failure in Cardiology; LURIC = Ludwigshafen Risk and Cardiovascular Health; ODIN = Observatoire de l'insuffisance cardiaque; SCDB-HF = Singapore Cardiac Databank Heart Failure; SCD = sudden cardiac death.

death. The recently convened Clinical Data Interchange Standards Consortium (CDISC), formed by a multidisciplinary team including members of the Food and Drug Administration, have drafted a comprehensive, but infrequently used, definition of SCD, which leverages available data regarding timing of the event, presence of a witness, antecedent symptoms, and corroboration with electrical monitoring (30).

In order to determine the cohort of patients with HFpEF who succumb to SCD, cohesive efforts from trial and registry committees are required to improve the event ascertainment process. Such efforts include routinely obtaining next-of-kin accounts of death, autopsy reports, and medical records, which will assist in determining the circumstances surrounding death, and possibly the presenting rhythm. This detailed information will not only aid in isolating "true" SCD, but will be integral in determining mechanisms of SD in the HFpEF population.

When detailed information regarding the surrounding events before and after a patient's death is not available at the time of adjudication, SCD has often been considered the default mode of death, thus potentially inflating reported incidence rates. The current estimates of SD in HFpEF may not all represent true ventricular tachyarrhythmic events, and thus may not be expected to uniformly respond to attempts at SCD prevention with implantable cardioverter-defibrillator (ICD) therapy. Terminal arrhythmic events may be nonshockable rhythms (e.g., pulseless electrical activity or asystole) or may represent significant bradyarrhythmias, which may be especially common in older HFpEF patients. Even beyond this, a proportion of SD may actually be nonarrhythmic in origin, caused by other major systemic events, including massive pulmonary embolism, catastrophic stroke, aortic dissection, or ruptured aortic aneurysm. Furthermore, dissecting major causes and contributors to SCD (including MI) and SCD itself may be challenging in clinical practice. Indeed, given high rates of comorbid coronary artery disease in HFpEF and the older overall population, the contribution of ischemia and microinfarctions to

FIGURE 3 Cause-Specific Mortality in RCTs of HFpEF



Mode of death was stratified into CV **(top)** and non-CV deaths **(bottom)**. The N reported refers to the total number of CV or non-CV deaths in each individual trial. GI = gastrointestinal; HF = heart failure; MI = myocardial infarction; SD = sudden death; other abbreviations as in Figure 2.

SCD requires further study. Careful attention to standardized definitions and increased adjudication efforts will be necessary to differentiate these potentially important sudden events.

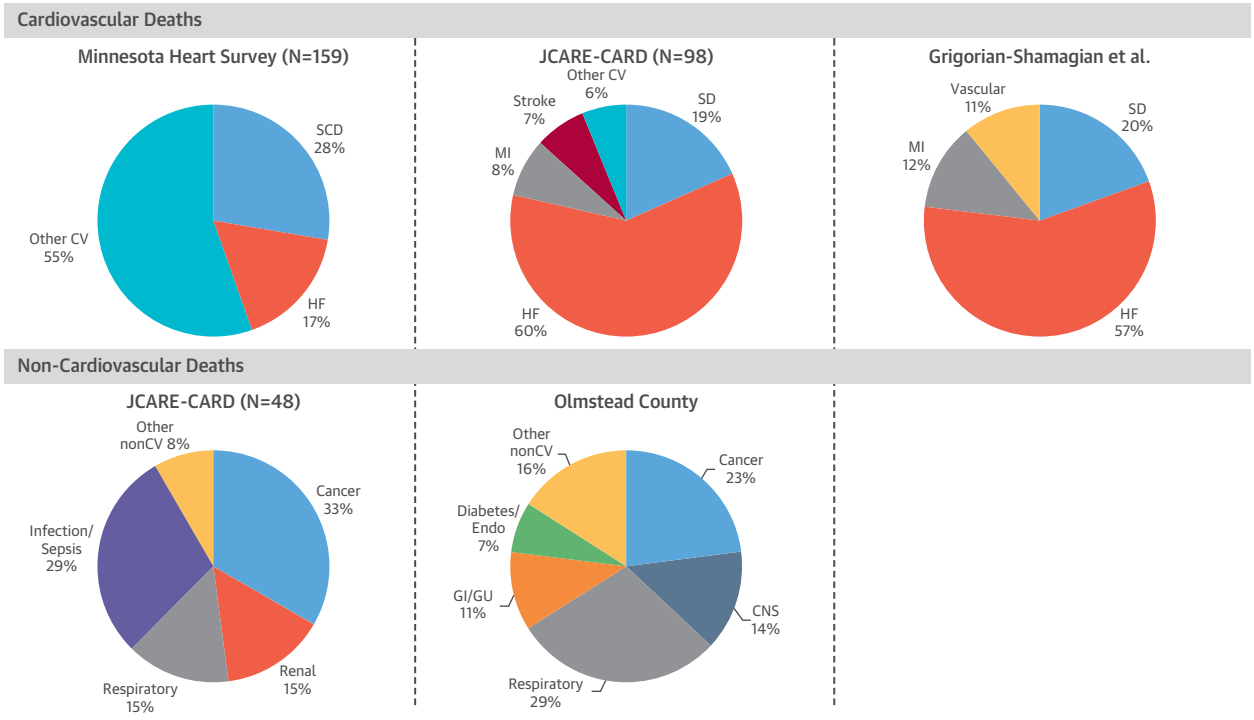
There has been a recent call for definitive trials of ICD therapies in patients with HFpEF. The MISTIC (MIBG Scintigraphy as a Tool for Selecting Patients Requiring Implantable Cardioverter Defibrillator; NCT01185756) study is currently evaluating the role of excess sympathetic activity in identifying appropriate ICD placement in HFrEF. The ADMIRE-ICD (International Study to Determine if AdreView Heart Function Scan Can be Used to Identify Patients With Mild or Moderate Heart Failure That Benefit From Implanted Medical Device; NCT02656329) trial is studying the utility of a novel scintigraphy-based imaging modality in guiding ICD implantation in patients with HF and EF between 30% and 35%. There has been interest in expanding these approaches to HFpEF. However, compared with estimates in HFrEF (24), the rates of SCD in HFpEF are lower, and may be overestimated. As such, insufficient data are available to support testing a routine strategy of ICD therapy in broad, unselected patients with HFpEF. Enriched subsets of HFpEF with enhanced arrhythmic risk may respond favorably to SCD preventative approaches. Novel machine learning-based phenomapping (31), cardiac magnetic resonance imaging (32), and certain clinical/biomarker risk scores (33) may assist in profiling and identifying these at-risk cohorts.

NEXT STEPS IN CHARACTERIZING CAUSE-SPECIFIC MORTALITY

Data-driven approaches to understanding the clinical profiles and cause-specific events in HFpEF are necessary to inform the natural history of this disease and future design of targeted studies.

STANDARDIZED MODE-OF-DEATH REPORTING SCHEMES. There is a lack of uniformity of definitions, with large variability across classification schema. Standardized reporting is paramount to accruing and synthesizing sufficient mode of death information in this population. Recent broad-scale efforts (30,34)

FIGURE 4 **Cause-Specific Mortality in Representative Epidemiological Studies of HFpEF**



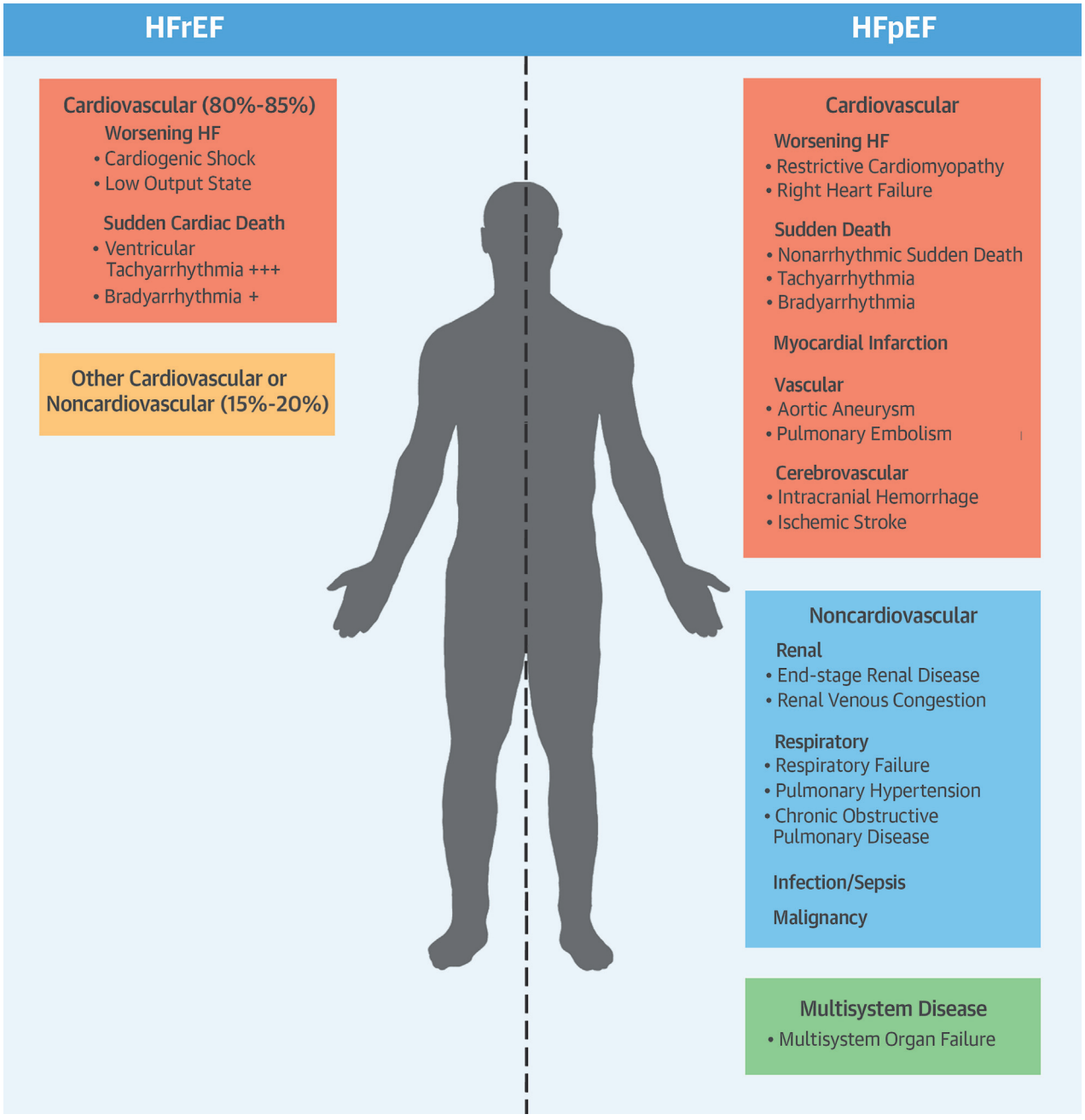
The N reported refers to the number of CV **(top)** and non-CV deaths **(bottom)** in each registry. Two studies only reported proportions of each mode of death, and as such, absolute numbers of events were not available. CNS = central nervous system; GU = genitourinary; other abbreviations as in Figures 2 and 3.

have made substantial progress in developing uniform reporting standards and event definitions for emerging cardiovascular clinical trials. Unfortunately, these data elements are not unique to HF, and may not be suitable for the complex, contemporary HFpEF population. Prior HF-specific working groups (35) have proposed a framework for classification of mode of death, calling for detailed information to be collected on the activity, cause, mode, and event for each coded death. Narang et al. (35) distinguish cause of death (e.g., contributing conditions to mortality, such as pneumonia) from mode of death (e.g., the final pathway leading to mortality, such as hypoxemic respiratory failure). Although this generic HF classification scheme is exhaustive, and would almost certainly expand our knowledge of these mortal events, collection of this information in a systematic fashion would be tedious and resource intensive.

FORGING NEW EVENT DEFINITIONS TAILORED TO HFpEF. In clinical practice, HFpEF patients often experience terminal events related to progressive right ventricular failure, pulmonary hypertension, end-stage renal disease, and multiorgan failure. Simply applying event definitions from prior HFrEF trials is insufficient, and may collectively characterize these as "HF deaths," introducing the potential for misclassification. In a patient with HFrEF, death due to worsening HF may be presumed related to progressive systolic dysfunction, cardiogenic shock, and low-output state, leading to multiorgan dysfunction/failure. Similar mechanisms do not readily apply to the HFpEF population. Similarly, SD in a previously stable HFrEF patient may be presumed to be a SCD related to a ventricular tachyarrhythmia. This linear pathway may not be true for many patients with HFpEF, due to the complexity of the disease process and high rates of non-CV comorbidities.

The CDISC document offers a rigorous and comprehensive approach to characterizing CV deaths; however, it does not offer direction regarding defining and delineating specific non-CV modes of death. This classification schema would need to be updated and tailored to the HFpEF population to include more robust reporting of these prevalent non-CV modes of death. Specific attention to understanding the burden and impact of major infections, including pneumonia, in this population may be

CENTRAL ILLUSTRATION **Mode of Death Distribution in HFrEF and HFpEF**



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This simplified schematic highlights that whereas patients with heart failure with reduced ejection fraction die predominantly of worsening heart failure and sudden cardiac death, patients with heart failure with preserved ejection fraction may die of more varied causes in clinical practice. HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

worthwhile as this is potentially addressable with more widespread vaccination programs and prevention efforts. When rigorous adjudication and application of these conservative event definitions are impractical, technically infeasible, or economically untenable, then use of less specific, but patient-oriented event definitions should be considered in emerging HFpEF studies. For instance, the large, ongoing, pragmatic INVESTED (INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure; NCT02787044) trial of high- versus standard-dose influenza vaccination has used definitive endpoints that require minimal adjudication (all-cause mortality and cardiopulmonary hospitalization).

IMPROVED CAPTURE AND SURVEILLANCE OF MORTAL EVENTS. In order to advance the collection of cause-specific mortality data, broad-scale community and in-hospital autopsy studies are in progress. Prospectively consenting stable outpatients with HFpEF may facilitate acquisition of routine autopsies at the time of death. Recent successful applications of this model of widespread and systematic autopsies in geographically-defined cohorts include the San Francisco, California, Postmortem Systematic Investigation of Sudden Cardiac Death study (36), the Oregon Sudden Unexpected Death Study (37), and the Olmstead County experience (20). Short of autopsy-based assessment, there is an unmet need for a longitudinal multicenter, global registry of inpatients and outpatients with HFpEF, in order to closely follow and track the natural history of this disease process. Implantable loop recorders in patients with HFpEF may better characterize the burden of ventricular tachyarrhythmias in this population, and is the subject of the ongoing VIP-HF (Ventricular Tachyarrhythmia Detection by Implantable Loop Recording in Patients with Heart Failure with Preserved Ejection Fraction; NCT01989299) phase 2 study. More broadly, explantation, interrogation, and analysis of CV implantable electronic devices at the time of autopsy (38) may provide unique information in the HFpEF population; however, rates of overall device use in this cohort are limited when compared with HFrEF.

REFINED TRIAL DESIGNS AND ENDPOINTS. Until now, all-cause mortality has been a standard single or composite endpoint in late-phase HFrEF trials. This strategy has proved to be efficacious in expeditiously bringing novel drugs and devices to the market for the chronic HFrEF population. However, given recent therapeutic failures, it is apparent that a more nuanced approach is necessary in HFpEF. Given the complexity of the syndrome, cause-specific endpoints in specific subgroups with enhanced risk may yield better therapeutic results (39). Furthermore, given that non-CV causes account for up to 30% of total mortality, advanced statistical accounting for these competing risks will be important in emerging trials (40).

EXPANDING CAUSE-SPECIFIC ANALYTICAL APPROACHES. The distribution of cause-specific mortality may not be uniform across patients with HFpEF, and may vary by setting (in-hospital vs. ambulatory), geographical region, and the presence of certain comorbidities. Beyond mortal events, characterizing cause-specific hospitalizations and other patient-centered outcomes will assist in guiding future efforts to curb the alarming clinical and economic impact of HFpEF.

CONCLUSIONS

Only a minority of contemporary HFpEF studies captures cause-specific events. Among this subset, CV causes account for the majority of mortal events, but wide variation exists between RCTs and non-randomized cohorts. Current event definitions have been directly applied from HFrEF studies. Reporting of mode of death must be revised and tailored to the HFpEF population, in order to better reflect prevalent causes of death observed in clinical practice. 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 inpatients and outpatients with HFpEF to map its natural history. Developing a deeper understanding of cause-specific patterns of mortality in HFpEF may improve our understanding of the pathophysiology of this entity, and guide near-term drug and device development. Matching available and novel therapies with specific mechanisms of death may be a more successful therapeutic strategy in HFpEF moving forward.

ACKNOWLEDGMENTS The authors thank Charlotte Cookson, DPhil, and William Gattrell, PhD, of Oxford PharmaGenesis, Oxford, United Kingdom, for their assistance in facilitating author communication and collaboration. Study selection, data analysis, and manuscript drafting were, however, performed independently by the first 2 authors.

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KEY WORDS epidemiology, mortality, outcomes

APPENDIX For a supplemental table, please see the online version of this article.