A Systematic Assessment of Causes of Death After Heart Failure Onset in the Community
Impact of Age at Death, Time Period, and Left Ventricular Systolic Dysfunction

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Background—The high mortality rate in patients with heart failure (HF) is influenced by presence of multiple comorbidities. Data are limited on the relative contributions of cardiovascular versus noncardiovascular diseases to death in individuals with HF in the community.

Methods and Results—We examined the incidence and predictors of cardiovascular versus noncardiovascular death in participants with HF in the Framingham Heart Study. Underlying, immediate, and contributing causes of death (3 key elements of the World Health Organization classification) were adjudicated by a 3-physician review panel. During 1971 to 2004, 1025 participants with HF died (499 men, mean [SD] age at death 79 [11] years), including 463 participants with left ventricular ejection fraction (LVEF) data. Cardiovascular disease was the cause of death in 66.1% overall. Stratified by LVEF, cardiovascular deaths occurred in 44.5% and 69.9% of those with preserved and reduced LVEF, respectively. Presence of reduced LVEF increased the risk of cardiovascular death, with odds ratios of 3.16 (95% confidence interval [CI], 1.73 to 5.78) in men and 2.39 (95% CI, 1.39 to 4.08) in women. Prior myocardial infarction was associated with increased cardiovascular death in women with HF (odds ratio, 1.87; 95% CI, 1.10 to 3.16) but not in men. The risk of cardiovascular disease death decreased in women (odds ratio after 1980, 0.41; 95% CI, 0.24 to 0.69) and men (odds ratio, 0.66; 95% CI, 0.41 to 1.07, $P=0.095$) with HF over time. Infections and kidney disease emerged as key immediate and contributing causes of death, respectively.

Conclusions—Individuals with HF in the community often experience cardiovascular death, but noncardiovascular disease also contributes significantly especially among those with preserved LVEF. (*Circ Heart Fail*. 2011;4:36-43.)

Key Words: heart failure ■ death ■ cause of death ■ cardiovascular diseases ■ epidemiology

Community-based studies have ubiquitously documented the high mortality rate in patients with heart failure (HF),[1,2] which is contributed by the lethality of HF as well as noncardiac disease burden.[3] Noncardiac comorbidities may also contribute to the observed disparity in HF mortality rates between randomized controlled trial enrollees and observational study cohorts.[4] Cardiovascular therapies that increase survival in HF patients do so primarily by decreasing cardiovascular mortality.[5] Thus, pharmacological treatments and cardiac device therapies, such as implantable cardioverter-defibrillators, largely act by reducing the probability of cardiovascular death.[6] Yet, patients with HF have substantial residual mortality risk on optimal medical treatment.[7] An improved understanding of the causes and factors leading to death may potentially facilitate efforts to improve HF survival, including mitigating the residual mortality risk.

Clinical Perspective on p 43

Both cardiovascular and noncardiovascular conditions may contribute to HF mortality,[8–11] with approximately 30% noncardiovascular deaths in clinical trials (DIG, CHARM-PRESERVED) to more than 50% in community-based studies.[9] These new insights notwithstanding, several gaps remain in our understanding of how patients with HF die.[12] First, none of the prior studies evaluated causes of HF death using the standard World Health Organization (WHO) reporting format, with the 3

key elements of underlying, immediate, and contributing causes of death. As detailed below (see Methods), each of these elements conveys critical information that could help improve survival in HF patients. Second, prior studies used information obtained from death certificates despite their limitations (compared with information obtained from a physician review panel).[13] Third, information on temporal trends in the relative contributions of cardiovascular versus noncardiovascular disease to HF death is limited,[9] as are data on the impact of heart failure with preserved (HFPEF) versus reduced left ventricular (LV) ejection fraction (HFREF).[14]

The Framingham Heart Study is a prospective, community-based study that has collected detailed information on underlying causes of death using a physician-review, panel-based adjudication process. In this approach, deaths are adjudicated after comprehensive review of all available medical records. In the present investigation, we examined the causes of death in participants with HF. We hypothesized that the relative contributions of cardiovascular versus noncardiovascular disease to HF death would vary with age, sex, prior myocardial infarction (MI), LV systolic dysfunction, and decade of death. We postulated that older age, HFPEF, and death in recent decades would be associated with greater proportion of noncardiovascular causes of death.

Methods

Participants

The study sample was obtained from the original and offspring cohorts of the Framingham Heart Study, which have been previously described.[15] Both original and offspring cohort participants are examined approximately every 2 or 4 years, respectively. In this investigation, we included participants with HF in both cohorts who died and underwent a death review at the Heart Study during the time period 1971 to 2004. The study protocol was approved by the Boston University Medical Center Institutional Review Board, and all participants provided written informed consent.

HF Definition

The original cohort and offspring cohort participants are under ongoing surveillance for HF and other cardiovascular disease events (including death), through physician interviews and retrieval of medical records from hospitals and physicians' offices. All HF events were adjudicated by a 3-member physician panel according to the previously published Framingham criteria.[16] We determined LV ejection fraction (LVEF) in the subsample who had an echocardiogram or radionuclide ventriculogram performed at HF onset. Assessments of LVEF were eligible if performed after HF onset (eg, during hospital admission), or within 1 year before HF onset provided no intervening MI occurred.[17] HFREF and HFPEF were defined based on an a priori cutoff value: LVEF ≤45% versus >45%.[17]

Data Sources Collected for Death Review

Death reviews were conducted after collection of information from (1) hospitalization and emergency department records, (2) imaging and laboratory reports, (3) physicians' notes, (4) death certificates, and (5) autopsy/medical examiners' reports. In selected cases, family members, eyewitnesses, or other caregivers who were present at the time of death were interviewed to gather additional details. Death reviews were conducted by a panel of 3 experienced physicians who had access to all information above and who adjudicated the cause of death based on the totality of data collected. Adjudicated causes of death may differ from death certificates,[13] and therefore conditions recorded in the death certificate were not used.

Death Review and Classification

The underlying cause of death is defined as the disease or injury that initiated the train of events leading directly to death, with only 1 underlying cause of death assigned to each decedent.[18,19] Knowledge of the underlying cause of death is critical condition because it identifies the condition, which, if prevented, would have the greatest impact on outcome from a public health perspective. Based on a detailed evaluation of all available data sources, the review panel adjudicated an underlying cause of death from the following 6 mutually exclusive categories: (1) coronary heart disease, (2) stroke, (3) other cardiovascular disease, (4) cancer, (5) other (noncardiovascular/noncancer causes), or (6) unknown. When an underlying cause of death could not be identified because of insufficient information, deaths were classified as due to an "unknown" cause. When more than 1 event could have contributed to death, the degree to which the conditions contributed (based on the judgment of the review panel on examination of all available data) established the primacy of the final cause of death. At least 2 of the three members of the review panel were required to concur on the cause of death. The process for review of deaths and the categorization schema for the underlying cause (of death) have not changed over the last 4 decades.

Over the last 2 decades (after 1981), adjudication of both immediate and contributing causes of death was implemented at the Framingham Heart Study, consistent with the WHO reporting framework. The immediate cause of death is the disease or condition directly leading to death, usually a condition occurring closest to the time of death, and is distinct from the mode of death.[18–20] The immediate cause of death reflects how patients died and thus provides insights into potential interventions to prevent terminal events and prolong survival.[21] Contributing causes of death included other diseases or conditions believed to have unfavorably influenced the course of the morbid process and thereby contributed to the fatal outcome but were not related to the disease or condition directly causing death.[18–20] For each decedent, there was 1 underlying and 1 immediate cause of death but potentially multiple contributing causes of death. Thus, an HF patient with prior MI and chronic obstructive pulmonary disease, who is hospitalized with decompensated HF and concomitant pneumonia and dies of pneumonia, would have an underlying cause of death of atherosclerotic coronary heart disease, pneumonia as an immediate cause of death, and chronic obstructive pulmonary disease and worsening HF as contributing causes. For the present investigation, the specific immediate and contributing causes of death were codified using the *International Classification of Diseases,* 9th edition (*ICD-9*) coding system, with modifications to accommodate all potential diagnoses (see supplemental material). Immediate and contributing causes of death were then regrouped into the 6 category framework noted above for underlying causes of death to facilitate analyses.

Statistical Analysis

All HF deaths were studied in both sex-specific and combined analyses. The entire sample of participants with incident HF from 1971 to 2004 (inclusive) contributed to the analyses of underlying causes of death. We determined if age at death, sex, prior MI, HFREF versus HFPEF (for the subset with available LVEF data), or the time period of death (before versus after 1980) were associated with underlying cardiovascular versus noncardiovascular death using multiple logistic regression. For these multivariable analyses we combined other, cancer and unknown underlying causes as noncardiovascular deaths. Two sets of analyses were conducted on (1) the entire sample and (2) the LVEF subsample. We used logistic regression analyses to estimate the predicted probabilities of death caused by cardiovascular disease versus non–cardiovascular disease underlying cause according to age at death (categorized into 3 strata: <65, 65 to 79, or ≥80 years), sex, and prior MI overall and according to HFREF versus HFPEF in the subsample with LVEF.[22] Immediate and contributing causes of death could be analyzed on a subset of individuals who died between 1981 and 2004. Multivariable analyses for cardiovascular versus noncardiovascular immediate causes of death were performed paralleling the analyses of underlying cause of death noted above.

Table 1. Description of Decedents With HF

	Men	Women
Total deaths, n	499	526
Age at death, mean (SD)	75.3 (10.9)	81.4 (9.9)
Prior MI, %	21.2%	16.0%
Valve disease, %	4.6%	3.2%
Individuals with prior MI	106	84
Cardiovascular deaths, all causes	71 (67.0%)	61 (72.6%)
Noncardiovascular deaths	35 (33.0%)	23 (27.4%)
Individuals with no prior MI	393	442
Cardiovascular deaths, all causes	277 (70.5%)	269 (60.9%)
Noncardiovascular deaths	116 (29.5%)	173 (39.1%)
Place of death		
In-hospital, %	67.7%	60.7%
Out-of-hospital, %	32.3%	39.3%

All analyses were performed using SAS Statistical Software, Release 8.2, SAS Institute (Cary, NC). A probability value <0.05 was considered statistically significant.

Results

Participants

A total of 1025 decedents (mean age, 79±11 years, 526 women) with HF were examined, of whom 900 were original cohort and 125 were offspring cohort participants. Examination of participant characteristics (shown in Table 1) revealed that cardiovascular deaths were of high prevalence with or without prior MI. An underlying cause of death was identified (or deemed unknown) in all decedents. Characteristics of participants with or without LVEF assessment are shown in Table 2. Although those without LVEF assessment were younger, they were also more likely to die of cardiovascular causes. LVEF measurements were performed increasingly over time, with 24.9% (1980 to 1989, n=555), 92.6% (1990 to 1999, n=349), and 99.2% (2000-, n=121) of patients undergoing the study. Of the subsample with detailed death review, 463 decedents (mean age, 82.2±9.3

Table 2. Characteristics of Decedents With or Without LVEF Measured

	LVEF Measured	No LVEF	P Value
Total deaths, n	581	444	
Age at death, mean (SD)	82.4 (9.7)	73.3 (10.2)	<0.001
Prior MI, n (%)	119 (20.5)	71 (16.0)	0.07
Valve disease, n (%)	16 (3.8)	...	
Individuals with prior MI, n*	102	62	
Cardiovascular deaths, all causes, n (%)	60 (58.8)	46 (74.2)	
Noncardiovascular deaths, n (%)	42 (41.2)	16 (25.8)	0.046
Individuals with no prior MI, n*	318	240	
Cardiovascular deaths, all causes, n (%)	130 (40.9)	139 (57.9)	
Noncardiovascular deaths, n (%)	188 (59.1)	101 (42.1)	<0.001
Place of death, n*	455	437	
In-hospital, n (%)	251 (55.2)	321 (73.5)	
Out-of-hospital, n (%)	204 (44.8)	116 (26.5)	<0.001

*For patients with identifiable causes/places of death by physician review.
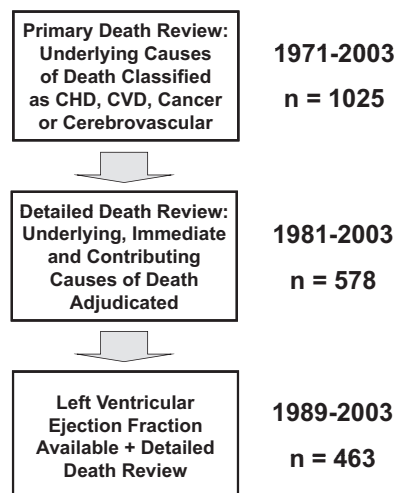

Figure 1. Study cohorts available for death review. Primary death reviews for underlying cause of death were conducted in the largest HF cohort (n=1025). Detailed death reviews for underlying, immediate, and contributing causes of death were conducted in those with (n=463) and without (n=578) LVEF data available.

years, 239 [52%] women) had LVEF assessed, of which 369 were original cohort and 94 were offspring participants, and 272 (59%) had HFREF. Evaluation of LVEF was performed temporally close to the HF onset date: 0.08±0.59 days for those evaluated after (n=399, 86.2%) and 0.36±0.70 days for those evaluated before HF onset date (n=64, 13.8%). A detailed diagram of the study cohort is shown in Figure 1. A total of 1144 contributing causes were identified in 317 participants, with 2 to 7 contributing factors (mean, 3.6) per participant, because more than 1 contributing condition could be attributed to each participant. More than 60% of deaths occurred in a hospital setting.

Classification of Cause of Death

The categorization of underlying and immediate causes of death into cardiovascular (eg, CHD, stroke) or noncardiovascular disease categories is shown in Figure 2. Overall, 62% of underlying causes of death were cardiovascular, with a large proportion (25%) of underlying causes attributable to CHD. Progressive pump failure was the major non-CHD cause of cardiovascular death (16% of all underlying causes). Respiratory disease (infectious and noninfectious) was the leading underlying cause of noncardiovascular death (10%), followed by cancer (9%).

Overall, 46% of immediate causes of death were cardiovascular, with the majority attributable to non-CHD cardiovascular disease. The leading immediate cardiovascular causes of death overall were progressive pump failure (24%) and arrhythmia or sudden cardiac death (15%). The leading noncardiovascular causes of death were infectious/noninfectious respiratory disease (17%), and other systemic infections (8%).

Underlying Causes of Death by LV Systolic Function

For the subset with available LVEF, the underlying causes of death for those with systolic dysfunction or preserved systolic function are shown in Figure 3. Cardiovascular death was the predominant underlying cause of death in those with HFREF, representing 76% of deaths in men and 70% in women. In contrast, cardiovascular conditions represented a smaller

Underlying Causes of Death
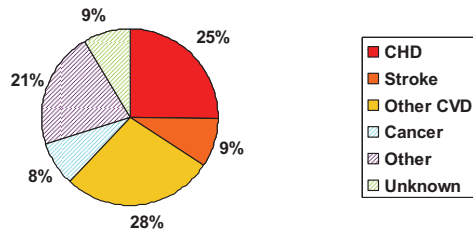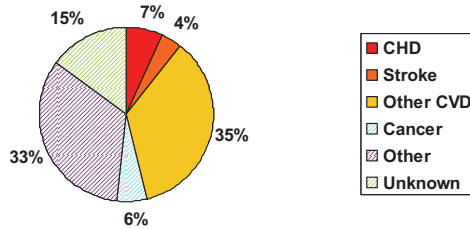

Immediate Causes of Death

Figure 2. Underlying and immediate causes of death by subcategories. Nearly two-thirds of underlying causes (total, n=317 deaths) and nearly one-half of immediate causes (total, n=313 deaths) were cardiovascular in nature.

proportion of the underlying causes of death in those with HFPEF, with 39% of deaths in men and 49% in women attributed to a cardiovascular cause.

Classification of Immediate Causes of Death by LV Systolic Function

Classification of immediate causes of death according to LVEF status is shown in Figure 4. Although most with HFREF had cardiovascular death (55%), other cardiovascular disease etiologies were the most important reasons for cardiovascular death. In those with HFPEF, cardiovascular causes were responsible

for only 34% of immediate causes of death. Among the "other cardiovascular disease" etiologies, progressive HF and arrhythmia or sudden cardiac death were the predominant factors leading immediately to death. In those with HFREF, cardiovascular deaths accounted for 20.4% and 18.5% of all deaths in men and women, respectively. In HFPEF, 23.2% of men and 11.7% of women died of immediate cardiovascular causes.

Predictors of Cardiovascular Disease as the Underlying Cause of Death

Results of sex-specific adjusted analyses are shown in Table 3. Increased age at death was associated with greater odds of noncardiovascular death in both sexes. In men, prior MI was not associated with cardiovascular versus noncardiovascular death. In women, however, prior MI was associated with increased risk of cardiovascular disease as the underlying cause of death, with an odds ratio of 1.87 (95% confidence interval [CI], 1.10 to 3.16).

In women, there was a significant decrease in the odds of cardiovascular disease as the underlying cause of death in those with HF in the latter (after 1980) compared with the earlier (before 1980) time period, with an odds ratio of 0.41 (95% CI, 0.24 to 0.69). In men, the decline in the odds of cardiovascular disease as the underlying cause of death was of borderline statistical significance. Although mean age at death was higher after 1980 than before 1980 (81.7±9.6 versus 70.3±9.5 years), this did not fully explain the trend because the aforementioned odds ratios were age-adjusted. The presence of LV systolic dysfunction was a strong predictor of cardiovascular disease as an underlying cause of death, conferring a more than 3-fold odds in men and 2-fold odds in women with HFREF (see Table 3).

Predictors of Cardiovascular Disease as the Immediate Cause of Death

Sex-specific adjusted analyses demonstrated that prior MI did not predict an immediate cause of death that was cardiovas-
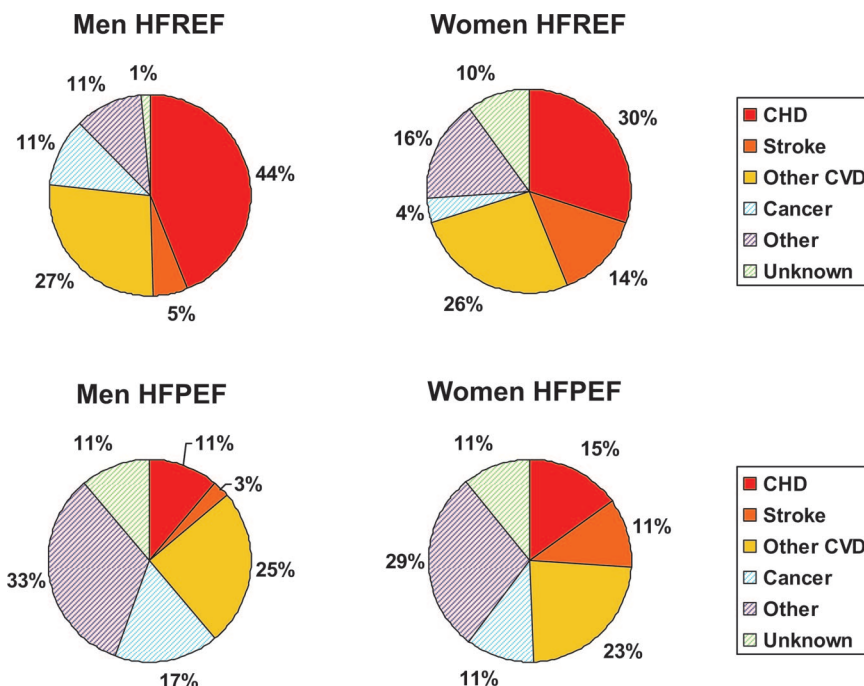

Figure 3. Causes of death by sex and LVEF status. Deaths that were cardiovascular in nature occurred in approximately one-half of those with HFPEF (total, n=109 deaths) and in nearly three-fourths of those with HFREF (total, n=153 deaths) and were consistent between men and women.
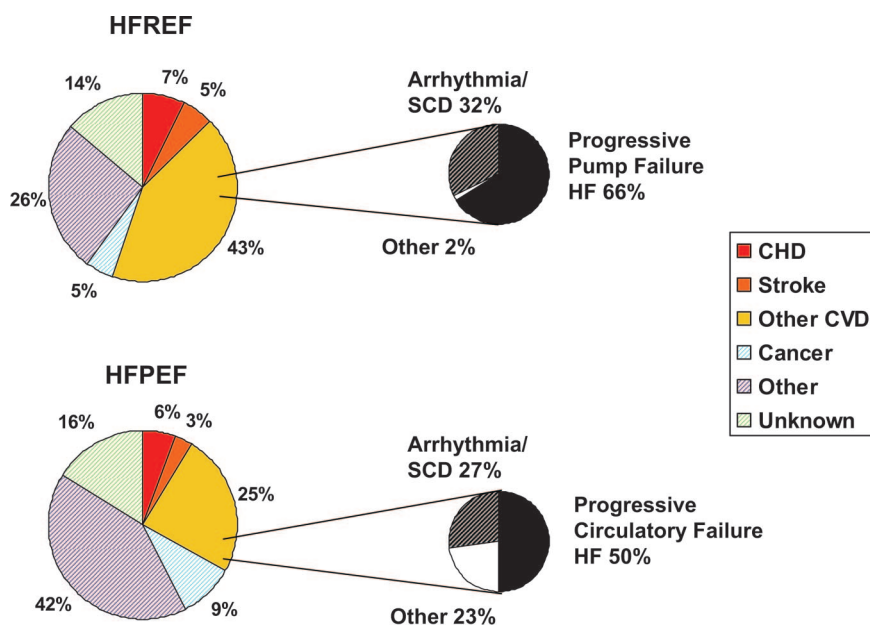
Figure 4. Immediate causes of death by LVEF status. The majority of other cardiovascular deaths were contributed by arrhythmia, progressive pump failure (HFREF, n=152 deaths), and circulatory failure (HFPEF, n=106 deaths).

cular (Table 4). Instead, the presence of HFREF was the most significant predictor of an immediate cause of death that was cardiovascular, with a nearly 5-fold odds in men and more than 2-fold odds in women. Predicted probabilities of total cardiovascular death are shown in the Supplemental Table, demonstrating higher probabilities of cardiovascular death in younger patients, with prior MI, and HFREF.

Contributing Causes of Death
The most frequent contributing causes of death stratified by LVEF are shown in Table 5. After pump failure, ischemic and valvular heart diseases were the most important cardiac contrib-

utors to death irrespective of LV systolic function status. Renal disease, diabetes, and noninfectious respiratory conditions were the most common noncardiovascular contributors.

Discussion

Principal Findings
Epidemiologically, HF is characterized by an older age at onset than MI, and with rising prevalence of age-related comorbidities, investigators have underscored the contributions of noncardiovascular conditions to death.[9,10,23] We observed that cardiovascular disease was the major underlying cause of death in men

Table 3. Predictors of Cardiovascular (Versus Noncardiovascular) Underlying Cause of Death

	Men		Women	
	OR for Cardiovascular		OR for Cardiovascular	
Underlying Cause of Death*	Death (95% CI)	P Value	Death (95% CI)	P Value
Entire sample				
No. of deaths	499		526	
Logistic regression model				
Age at death, per 10 y	0.74 (0.60–0.90)	0.003	0.86 (0.69–1.05)	0.14
Time period, after 1980	0.66 (0.41–1.07)	0.10	0.41 (0.24–0.69)	<0.001
Prior MI	0.88 (0.55–1.41)	0.60	1.87 (1.10–3.16)	0.020
C-statistic (95% CI)	0.621 (0.569–0.674)		0.616 (0.569–0.663)	
Hosmer-Lemeshow statistic	1.87	0.93	4.47	0.48
Sample with LVEF				
No. of deaths	224		239	
Logistic regression model				
Age at death, per 10 y	0.84 (0.62–1.14)	0.26	0.91 (0.68–1.23)	0.54
Prior MI†	0.74 (0.38–1.42)	0.36	1.36 (0.67–2.78)	0.40
HFREF†	3.16 (1.73–5.78)	<0.001	2.39 (1.39–4.08)	0.002
C-statistic (95% CI)	0.648 (0.575–0.725)		0.622 (0.552–0.692)	
Hosmer-Lemeshow statistic	3.19	0.87	9.98	0.08

OR indicates odds ratio.

*Noncardiovascular death is referent group for OR calculation.

†Analysis limited to HF events occurring after 1980.

Table 4.   Predictors of Cardiovascular (Versus Noncardiovascular) "Immediate" Cause of Death

Immediate Cause of Death*	Men		Women	
	OR for Cardiovascular Disease Death (95% CI)	P Value	OR for Cardiovascular Disease Death (95% CI)	P Value
Entire sample				
n	125		192	
Age at death, per 10 y	0.69 (0.40–1.18)	0.17	1.15 (0.72–1.84)	0.55
Prior MI	0.87 (0.37–2.02)	0.74	2.03 (0.95–4.35)	0.07
C-statistic (95% CI)	0.567 (0.468–0.665)		0.582 (0.506–0.659)	
Hosmer-Lemeshow statistic	1.97	0.74	6.13	0.11
Sample with LVEF				
n	102		153	
Age at death, per 10 y	0.71 (0.38–1.34)	0.29	1.05 (0.62–1.75)	0.87
Prior MI†	0.65 (0.25–1.66)	0.36	1.51 (0.65–3.51)	0.34
HFREF†	4.90 (2.02–11.91)	<0.001	2.12 (1.09–4.10)	0.027
C-statistic (95% CI)	0.716 (0.616–0.816)		0.621 (0.533–0.710)	
Hosmer-Lemeshow statistic	0.67	0.98	0.98	0.96

OR indicates odds ratio.

*Noncardiovascular death is referent group for OR calculation.

†Analysis limited to HF events occurring after 1980.

and women overall, those with prior MI or LV systolic dysfunction, and in younger individuals. HFREF increased the odds of cardiovascular death more than 3-fold in men and 2-fold in women. However, noncardiovascular underlying causes of death predominated in those with HFPEF, especially in those aged 65 years or more at death.

Immediate causes of death were primarily cardiovascular among those with HFREF, with a large proportion of deaths attributable to progressive HF, sudden cardiac death, or arrhythmia. Although most immediate causes of death in those with HFPEF were noncardiovascular, progressive HF and arrhythmia were also significant contributors. The effects of noncardiovascular conditions also differed when analyzed by underlying versus immediate causes of death. Whereas neoplastic, respiratory, and gastrointestinal diseases were the

most prevalent noncardiovascular underlying causes of death, pneumonia, infections, and other respiratory diseases were the most important noncardiovascular immediate causes of death. Noncardiovascular conditions that commonly contributed to death were renal disease and diabetes.

Comparison With Published Literature

The mode of HF death has been evaluated in the randomized clinical trial settings. In the SOLVD treatment and prevention trials, 89% and 87% of deaths, respectively, were cardiovascular.[5] In the DIG study, 90% of deaths were cardiovascular in those with severe LV systolic dysfunction (eg, LVEF ≤15%), but cardiovascular deaths were less pronounced with preserved LV function (LVEF >55%).[24] The ATLAS trial found that risk factors for all-cause death and cardiovascular mortality were largely similar, but the correlates of specific causes of death (eg, HF or sudden death) differed from the predictors of all-cause mortality.[25] However, it is widely appreciated that there are differences in HF patients in the community compared with randomized trials, which have largely examined patients with LV systolic dysfunction.[26]

There are few community-based studies that have analyzed the causes of HF death in detail. In a study of HF patients with CHD, most deaths in patients with HFPEF (35 of 38 deaths) were cardiac, whereas all (83 of 83) deaths were cardiac in those with HFREF.[27] In the Cardiovascular Health Study, which examined 269 HF patients without valvular disease, cardiovascular and all-cause mortality rates were lower in those with HFPEF relative to HFREF. However, this report was limited by a relatively small number of total deaths (approximately 130).[28] An analysis of HF deaths from Olmstead county reported that 43% of deaths were noncardiovascular, and preserved EF was associated with a marginally lower risk of cardiovascular death, with hazard ratio 0.76, in both sexes combined.[9] We found higher rates of cardiovascular death in a sex-specific analysis and greater impact of HFREF on cardio-

Table 5.   Leading Conditions Contributing to Death in HF

Contributing Cause of Death	HFREF (n=199) n (%)	HFPEF (n=137) n (%)
HF/myopathic	81 (40.7)	56 (40.9)
Ischemic cardiovascular disease	66 (33.2)	30 (21.9)
Renal disease/genitourinary/electrolyte	56 (28.1)	29 (21.2)
Diabetes/endocrine	22 (11.1)	12 (8.8)
Valvular heart disease	18 (9.0)	15 (10.9)
Noninfectious respiratory conditions	17 (8.5)	15 (10.9)
Gastrointestinal disease	19 (9.5)	9 (6.6)
Arrhythmia (tachycardia or bradycardia)	15 (7.5)	9 (6.6)
Dementia/neurologic conditions	10 (5.0)	11 (8.0)
Infection	29 (14.6)	12 (8.8)
Hematologic/neoplasm	16 (8.0)	8 (5.8)
Other cardiovascular disease death (eg, pulmonary vascular, congenital, endocardial/pericardial)	5 (2.5)	6 (4.4)
Trauma/musculoskeletal/integument	6 (3.0)	5 (3.6)

vascular causes of death. In another tertiary center referral sample, renal dysfunction was noted to be an important antecedent of death in patients with severe LV systolic dysfunction.[29] We also observed that renal dysfunction was an important contributor to noncardiovascular death, and we extended these observations further by demonstrating the differential contributions of cardiovascular and noncardiovascular etiologies to the underlying and immediate causes of death.

Strengths and Limitations

Our study extends the literature on causes of HF death by examining a large cohort of decedents who were closely followed throughout their lifetime. This study is particularly unique because all deaths were reviewed by a panel of physicians who had access to medical records, the hospitalization record when death occurred, autopsy reports, office physicians' records, and accounts of family members or eyewitnesses who were present at the time of death. It has been suggested that a death review panel is the preferred approach for determining the cause of death.[30] Furthermore, all deaths were systematically and consistently reviewed in this manner throughout the duration of the Heart Study.

Our study had several limitations that merit comment. Although this was an extensive examination of causes of HF death in a community-based setting, we did not have LVEF data on all participants over the 30-year study period. Analyses requiring LVEF data were limited to more recent decades, which limited our statistical power to detect trends in cardiovascular versus noncardiovascular deaths. Despite this, we were able to examine a large subsample of patients who underwent LV functional evaluation in whom causes of death were adjudicated for all, mitigating the potential for survival bias to have adversely influenced the analysis. It is also noteworthy that those who did not have LVEF assessed also had high rates of cardiovascular death. Preventability was not determined and is beyond the scope of the current study. Our study sample was white and largely based in New England, and generalizability to other regions or ethnicities/races is uncertain. Finally, in the very elderly, the primacy of 1 underlying cause over another may not be easily established when based solely on records review.

Implications

In the community, the majority of HF deaths remain cardiovascular in nature. Deaths caused by cancer and other noncardiovascular conditions comprised a minority in HFREF but were substantial with HFPEF. Deaths caused by cardiovascular disease were somewhat reduced after 1980 (especially in women), which may be attributable to pharmacological therapies (eg, angiotensin-converting enzyme inhibitors, β-adrenoreceptor antagonists), advances in coronary revascularization, and other secondary prevention measures. A large proportion of underlying cardiovascular deaths remained attributable to coronary heart disease, highlighting the importance of broadly screening for ischemic heart disease. Given the large proportion of immediate causes of death due to noncardiovascular disease etiologies, our data reinforce the importance of treatment for these conditions because they have significant impact on the longevity of HF patients.

It is important to note that HF is a disease of the elderly, and ultimately reduction in mortality rate due to cardiovascular causes may result in a shift toward noncardiovascular death, without a change in lifespan itself.[31] Therefore, the proportion of cardiovascular disease versus noncardiovascular underlying causes of death may mirror advances in treatment. Thus, increasing noncardiovascular causes in recent decades may be due to older patients, greater burden of HFPEF, and better prevention of cardiovascular death.

Our study may have significant implications for HF care and approaches to improve survival. First, our results suggest that all-cause mortality is represented highly by cardiovascular disease death, and therefore, to improve survival in HF, continued efforts to optimally treat such conditions are warranted. Second, infectious and respiratory conditions were common immediate causes of death, and therefore prevention (eg, vaccination), early diagnosis, and appropriate drug therapy are paramount. Third, there has been varied opinion about the importance of all-cause mortality as an outcome in HF.[5] It has been suggested that outcomes should not only be clinically important but should be related to the postulated mechanism of action of an intervention and therefore potentially sensitive to change.[5] Our findings suggest that all-cause mortality is due in large part to underlying cardiovascular conditions and reaffirms the importance of this outcome in HF. However, when translating randomized trials to the general population, the estimated effect of treatment may be attenuated, depending on the demographic characteristics of the study population and the attendant risk of noncardiovascular death.

Conclusions

In our study of a large community-based sample of individuals with HF spanning 3 decades of observation, the major underlying cause of death was cardiovascular disease. However, the relative contributions of cardiovascular versus noncardiovascular causes to death varied according to age at death, sex, prior MI, and LV systolic function status. Older individuals with HF, especially those with HFPEF, often die of noncardiovascular disease. Infections and renal disease emerged as key immediate and contributing causes of death, respectively. Overall, our data underscore the importance of targeting comorbidities, preventing infections, and maintaining renal function for reducing residual mortality risk in optimally treated patients.[10]

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CLINICAL PERSPECTIVE

We examined the incidence and predictors of cardiovascular versus noncardiovascular death in 1025 participants with heart failure (HF) in the Framingham Heart Study by analyzing underlying, immediate, and contributing causes of death (3 key elements of the World Health Organization classification of death). Cardiovascular disease was the principal underlying cause of death in two-thirds of the participants with HF. Stratified by left ventricular ejection fraction (LVEF), cardiovascular deaths occurred in 44.5% and 69.9% of those with preserved and reduced LVEF, respectively. The presence of a reduced LVEF increased the odds of cardiovascular death 2- to 3-fold. Infections and kidney disease emerged as key immediate and contributing causes of death, respectively. Overall, our data indicate that individuals with HF in the community often experience cardiovascular death, but noncardiovascular disease also contributes significantly, especially among those with a preserved LVEF. These observations underscore the importance of targeting comorbidities, preventing infections, and maintaining renal function for reducing residual mortality risk in optimally treated HF patients.