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

Running Title: Lee et al: Causes of Death in Heart Failure

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Abstract

Background—The high mortality 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 vs. 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 1971-2004, 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%CI 1.73-5.78) in men and 2.39 (95%CI 1.39-4.08) in women. Prior myocardial infarction was associated with increased cardiovascular death in women with HF (odds ratio 1.87, 95%CI 1.10-3.16), but not in men. The risk of cardiovascular disease death decreased in women (odds ratio post-1980 0.41, 95%CI 0.24-0.69) and men (odds ratio 0.66, 95%CI 0.41-1.07, 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.

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 rates.\(^5\) Thus, pharmacologic 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.

Both cardiovascular and noncardiovascular conditions may contribute to HF mortality,\(^8-11\) with approximately 30% noncardiovascular deaths in clinical trials (DIG, CHARM-PRESERVED) to over 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 to 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. 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 1971-2004. 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 (CVD) 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. We determined LV ejection fraction (LVEF) in the subsample who had echocardiogram or radionuclide ventriculogram performed at HF onset. Assessments of LVEF were eligible if performed after HF onset (e.g., during hospital admission), or within one year before HF onset provided no intervening MI occurred. HFREF and HFPEF were defined based on a priori cutoff value: LVEF ≤ vs. >45%.
Data Sources Collected for Death Review. Death reviews were conducted after collection of information from: (a) hospitalization and emergency department records, (b) imaging and laboratory reports, (c) physicians’ notes, (d) death certificates, and (e) 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 three 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 employed.

Death Review and Classification. The underlying cause of death is defined as the disease or injury which initiated the train of events leading directly to death, with only one 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 six mutually exclusive categories: 1) coronary heart disease, 2) stroke, 3) other cardiovascular disease, 4) cancer, 5) other (noncardiovascular/non-cancer 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 one event could have contributed to death, the degree to which the conditions contributed (based on the judgment of the review panel upon examination of all available data) established the primacy of the final cause of death. At least two 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 two 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18-20} For each decedent, there was one underlying and one immediate cause of death, but potentially multiple contributing causes of death. Thus, a HF patient with prior MI and chronic obstructive pulmonary disease (COPD), 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 COPD 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 re-grouped into the 6 category framework noted above for underlying causes of death to facilitate analyses.

\textit{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 vs. HFPEF (for the subset with available LVEF data), or the time period of death (before versus after 1980) were associated with underlying cardiovascular vs. 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 the: (i) entire sample, and (ii) LVEF subsample. We used regression analyses to estimate the predicted probabilities of death due to CVD versus non-CVD underlying cause according to age at death (categorized into 3 strata: <65, 65-79, or ≥80 years), sex, and prior MI overall, and according to HFREF vs. HFPEF in the subsample with LVEF.\textsuperscript{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 non-cardiovascular immediate causes of death were performed paralleling the analyses of underlying cause of death noted above.

All analyses were performed using SAS Statistical Software, Release 8.2, SAS Institute (Cary, NC). A p-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% (1980-1989, n=555), 92.6% (1990-1999, 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 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, since more than one contributing condition could be attributed to each participant. Over 60% of deaths occurred in a hospital setting.

**Classification of Cause of Death.** The categorization of underlying and immediate causes of death into cardiovascular (e.g., 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 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 died from 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 due to 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% CI 1.10, 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 (post-1980) compared to earlier (pre-1980) time period, with an odds ratio of 0.41 (95% CI 0.24, 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 post-1980 than pre-1980 (81.7±9.6 vs. 70.3±9.5 years), this did not fully explain the trend, since 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 more than a 3-fold risk in men and greater than 2-fold risk 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 cardiovascular (Table 4). Instead, presence of HFREF was the most significant predictor of an immediate cause of death that was cardiovascular with a nearly 5-fold risk in men and greater than 2-fold risk 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 contributors 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 and women overall, those with prior MI or LV systolic dysfunction, and in younger individuals. HFREF increased the odds of cardiovascular death more than three-fold in men and two-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 vs. 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 setting. In the SOLVD treatment and prevention trials, 89% and 87% of deaths, respectively, were cardiovascular. In the DIG study, 90% of deaths were cardiovascular in those with severe LV systolic dysfunction (e.g., LVEF ≤15%), but cardiovascular deaths were less pronounced with preserved LV function (LVEF >55%). 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 (e.g., HF or sudden death) differed from the predictors of all-cause mortality. 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.

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. 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]. 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. We found higher rates of cardiovascular death in a sex-specific analysis, and greater impact of HFREF on cardiovascular 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. 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. 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 vs. 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 largely New England, and white and generalizability to other regions or ethnicities/races is uncertain. Finally, in the very elderly, the primacy of one underlying cause over another may not be easily established, when based solely upon records review.

**Implications**

In the community, the majority of HF deaths remain cardiovascular in nature. Deaths due to cancer and other noncardiovascular conditions comprised a minority in HFREF, but were substantial with HFPEF. Deaths due to cardiovascular disease were somewhat reduced post-1980 (especially in women), which may be attributable to pharmacologic therapies (e.g., ACE inhibitors, beta-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 since 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 due to cardiovascular causes may result in a shift towards noncardiovascular death, without a change in lifespan itself. Therefore, the proportion of cardiovascular disease versus non-cardiovascular underlying causes of death may mirror advances in treatment. Thus, increasing non-cardiovascular...
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 (e.g., 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. 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. Our findings suggest that all-cause mortality is due in large part to underlying cardiovascular conditions, and re-affirms 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 deaths 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.
Acknowledgement

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Disclosures

None.
References


Table 1. Description of Decedents With HF

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<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total deaths</strong></td>
<td>499</td>
<td>526</td>
</tr>
<tr>
<td>Age at death, mean (SD)</td>
<td>75.3 (10.9)</td>
<td>81.4 (9.9)</td>
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<tr>
<td>Prior MI, %</td>
<td>21.2%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Valve disease, %</td>
<td>4.6%</td>
<td>3.2%</td>
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<tr>
<td><strong>Individuals with Prior MI</strong></td>
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<td></td>
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<tr>
<td>Cardiovascular deaths (all causes)</td>
<td>71 (67.0%)</td>
<td>61 (72.6%)</td>
</tr>
<tr>
<td>Noncardiovascular deaths</td>
<td>35 (33.0%)</td>
<td>23 (27.4%)</td>
</tr>
<tr>
<td><strong>Individuals with no Prior MI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular deaths (all causes)</td>
<td>277 (70.5%)</td>
<td>269 (60.9%)</td>
</tr>
<tr>
<td>Noncardiovascular deaths</td>
<td>116 (29.5%)</td>
<td>173 (39.1%)</td>
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<tr>
<td><strong>Place of Death</strong></td>
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<tr>
<td>In-Hospital, %</td>
<td>67.7%</td>
<td>60.7%</td>
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<tr>
<td>Out-of-Hospital, %</td>
<td>32.3%</td>
<td>39.3%</td>
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Table 2. Characteristics of Decedents With or Without LVEF Measured

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<th>EF Measured</th>
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<td><strong>Total deaths</strong></td>
<td>581</td>
<td>444</td>
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<tr>
<td>Age at death, mean(SD)</td>
<td>82.4 (9.7)</td>
<td>73.3 (10.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Prior MI, n(%)</td>
<td>119 (20.5)</td>
<td>71 (16.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Valve disease, %</td>
<td>16 (3.8)</td>
<td>-</td>
<td></td>
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<tr>
<td>Individuals with Prior MI, n*</td>
<td>102</td>
<td>62</td>
<td></td>
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<tr>
<td>Cardiovascular deaths (all causes) n(%)</td>
<td>60 (58.8)</td>
<td>46 (74.2)</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular deaths</td>
<td>42 (41.2)</td>
<td>16 (25.8)</td>
<td>0.046</td>
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<tr>
<td>Individuals with no Prior MI, n*</td>
<td>318</td>
<td>240</td>
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<tr>
<td>Cardiovascular deaths (all causes)</td>
<td>130 (40.9)</td>
<td>139 (57.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>Noncardiovascular deaths</td>
<td>188 (59.1)</td>
<td>101 (42.1)</td>
<td></td>
</tr>
<tr>
<td>Place of Death, n*</td>
<td>455</td>
<td>437</td>
<td></td>
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<tr>
<td>In-Hospital, %</td>
<td>251 (55.2)</td>
<td>321 (73.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Out-of Hospital, %</td>
<td>204 (44.8)</td>
<td>116 (26.5)</td>
<td></td>
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</table>

* For patients with identifiable causes/places of death by physician review.
Table 3. Predictors of Cardiovascular (vs. Noncardiovascular) Underlying Cause of Death

<table>
<thead>
<tr>
<th>UNDERLYING CAUSE OF DEATH*</th>
<th>OR for CV Death (95% CI)</th>
<th>p-value</th>
<th>OR for CV Death (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Entire Sample</td>
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</tr>
<tr>
<td>Number of deaths</td>
<td>499</td>
<td>0.003</td>
<td>526</td>
<td>0.14</td>
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<tr>
<td>Logistic Regression Model:</td>
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<tr>
<td>Age at death, per 10 yrs</td>
<td>0.74 (0.60 - 0.90)</td>
<td>0.003</td>
<td>0.86 (0.69 - 1.05)</td>
<td>0.14</td>
</tr>
<tr>
<td>Time period, post-1980</td>
<td>0.66 (0.41 - 1.07)</td>
<td>0.10</td>
<td>0.41 (0.24 - 0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.88 (0.55 - 1.41)</td>
<td>0.60</td>
<td>1.87 (1.10 - 3.16)</td>
<td>0.020</td>
</tr>
<tr>
<td>c-statistic (95%CI)</td>
<td>0.621 (0.569-0.674)</td>
<td>0.93</td>
<td>0.616 (0.569-0.663)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hosmer-and-Lemeshow statistic</td>
<td></td>
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<td></td>
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<tr>
<td>II. Sample with LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths</td>
<td>224</td>
<td>0.26</td>
<td>239</td>
<td>0.54</td>
</tr>
<tr>
<td>Logistic Regression Model:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at death, per 10 yrs</td>
<td>0.84 (0.62 - 1.14)</td>
<td>0.26</td>
<td>0.91 (0.68 - 1.23)</td>
<td>0.54</td>
</tr>
<tr>
<td>Prior MI†</td>
<td>0.74 (0.38 - 1.42)</td>
<td>0.36</td>
<td>1.36 (0.67 - 2.78)</td>
<td>0.40</td>
</tr>
<tr>
<td>HFREF†</td>
<td>3.16 (1.73 - 5.78)</td>
<td>&lt;0.001</td>
<td>2.39 (1.39 - 4.08)</td>
<td>0.002</td>
</tr>
<tr>
<td>c-statistic (95%CI)</td>
<td>0.648 (0.575-0.725)</td>
<td>0.87</td>
<td>0.622 (0.552-0.692)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hosmer-and-Lemeshow statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR = odds ratio
* Noncardiovascular death is referent group for OR calculation
† Analysis limited to post-1980
Table 4. Predictors of Cardiovascular (vs. Noncardiovascular) 'Immediate' Cause of Death

<table>
<thead>
<tr>
<th>IMMEDIATE CAUSE OF DEATH*</th>
<th>Men OR for Cardiovascular Disease Death (95% CI)</th>
<th>p-value</th>
<th>Women OR for Cardiovascular Disease Death (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=125</td>
<td></td>
<td>N=192</td>
<td></td>
</tr>
<tr>
<td>Age at death, per 10 yrs</td>
<td>0.69 (0.40 - 1.18)</td>
<td>0.17</td>
<td>1.15 (0.72 - 1.84)</td>
<td>0.55</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.87 (0.37 - 2.02)</td>
<td>0.74</td>
<td>2.03 (0.95 - 4.35)</td>
<td>0.07</td>
</tr>
<tr>
<td>c-statistic (95% CI)</td>
<td>0.567 (0.468-0.665)</td>
<td>0.74</td>
<td>0.582 (0.506-0.659)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hosmer-and-Lemeshow statistic</td>
<td>1.97</td>
<td>0.74</td>
<td>6.13</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>IV. Sample with LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>102</td>
<td></td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Age at death, per 10 yrs</td>
<td>0.71 (0.38 - 1.34)</td>
<td>0.29</td>
<td>1.05 (0.62 - 1.75)</td>
<td>0.87</td>
</tr>
<tr>
<td>Prior MI†</td>
<td>0.65 (0.25 - 1.66)</td>
<td>0.36</td>
<td>1.51 (0.65 - 3.51)</td>
<td>0.34</td>
</tr>
<tr>
<td>HFREF†</td>
<td>4.90 (2.02 - 11.91)</td>
<td>&lt;0.001</td>
<td>2.12 (1.09 - 4.10)</td>
<td>0.027</td>
</tr>
<tr>
<td>c-statistic (95% CI)</td>
<td>0.716 (0.616-0.816)</td>
<td>0.98</td>
<td>0.621 (0.533-0.710)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hosmer-and-Lemeshow statistic</td>
<td>0.67</td>
<td>0.98</td>
<td>0.98</td>
<td>0.96</td>
</tr>
</tbody>
</table>

OR = odds ratio
* Noncardiovascular death is referent group for OR calculation
† Analysis limited to post-1980
Table 5. Leading conditions contributing to death in HF

<table>
<thead>
<tr>
<th>Contributing Cause of Death</th>
<th>HFREF (n=199)</th>
<th>HFPEF (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Heart failure / myopathic</td>
<td>81 (40.7)</td>
<td>56 (40.9)</td>
</tr>
<tr>
<td>Ischemic cardiovascular disease</td>
<td>66 (33.2)</td>
<td>30 (21.9)</td>
</tr>
<tr>
<td>Renal disease / Genitourinary / Electrolyte</td>
<td>56 (28.1)</td>
<td>29 (21.2)</td>
</tr>
<tr>
<td>Diabetes / Endocrine</td>
<td>22 (11.1)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>18 (9.0)</td>
<td>15 (10.9)</td>
</tr>
<tr>
<td>Noninfectious respiratory conditions</td>
<td>17 (8.5)</td>
<td>15 (10.9)</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>19 (9.5)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>Arrhythmia (tachy- or bradycardia)</td>
<td>15 (7.5)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>Dementia / neurologic conditions</td>
<td>10 (5.0)</td>
<td>11 (8.0)</td>
</tr>
<tr>
<td>Infection</td>
<td>29 (14.6)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Hematologic / Neoplasm</td>
<td>16 (8.0)</td>
<td>8 (5.8)</td>
</tr>
<tr>
<td>Other CVD death (e.g., pulm vasc., congenital, endo/pericardial)</td>
<td>5 (2.5)</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>Trauma / MSK / Integument</td>
<td>6 (3.0)</td>
<td>5 (3.6)</td>
</tr>
</tbody>
</table>
Figure Legends

**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) LV ejection fraction data available.

**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.

**Figure 3.** Causes of death by sex and LV ejection fraction 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 LV ejection fraction 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).
Primary Death Review: Underlying Causes of Death Classified as CHD, CVD, Cancer or Cerebrovascular

1971-2003
n = 1025

Detailed Death Review: Underlying, Immediate and Contributing Causes of Death Adjudicated

1981-2003
n = 578

Left Ventricular Ejection Fraction Available + Detailed Death Review

1989-2003
n = 463
Cause of Death in Overall Cohort

Underlying Causes of Death

Immediate Causes of Death
Underlying Causes of Death in HFREF vs. HFPEF

Men HFREF
- CHD: 11%
- Stroke: 1%
- Other CVD: 27%
- Cancer: 5%
- Other: 1%
- Unknown: 14%

Women HFREF
- CHD: 10%
- Stroke: 16%
- Other CVD: 26%
- Cancer: 4%
- Other: 11%
- Unknown: 30%

Men HFPEF
- CHD: 11%
- Stroke: 11%
- Other CVD: 33%
- Cancer: 25%
- Other: 17%
- Unknown: 3%

Women HFPEF
- CHD: 11%
- Stroke: 29%
- Other CVD: 23%
- Cancer: 11%
- Other: 15%
- Unknown: 11%
Immediate Causes of Death in HFREF vs. HFPEF

**HFREF**

- Progressive Pump Failure: HF 66%
- Arrhythmia/SCD: 32%
- Other: 2%

**HFPEF**

- Progressive Circulatory Failure: HF 50%
- Arrhythmia/SCD: 27%
- Other: 23%

Legend:
- CHD
- Stroke
- Other CVD
- Cancer
- Other
- Unknown
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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Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2010/11/11/CIRCHEARTFAILURE.110.957480.DC1

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SUPPLEMENTAL MATERIAL
Categorization of Causes of Death

**CHD death:**
410-414.9 = Ischemic heart disease

**Noncoronary cardiovascular death:**
390-398.99 = Rheumatic heart disease
401-405.99 = Hypertensive disease
415-417.9 = Pulmonary vascular disease
420-423.9 = Pericardial, endocardial, myocarditis
424-424.99 or V43.3-V43.31 = Valvular heart disease
425-425.9 = Cardiomyopathy
426-427.99 = Arrhythmia (brady or tachy)
428-428.9 or 514 or 518.4 = Heart failure / pulmonary edema
429-429.9 or 458-458.9 = Other cardiovascular disease death
430-438.9 = Cerebrovascular
440-457.8 or 459-459.9 or 785.4-785.41 or 998.1-998.13 = Vascular disease (aortic, peripheral; arterial, venous)
745-747.9 = Congenital heart or vascular disease
785.5-785.59 = Shock
798.1 = Sudden death

**Cancer:**
140-239.9 = Neoplasm

**Other Noncardiovascular:**
001-139.9 or 790.7-790.8 = Infection
460-466.2 or 480-487.8 or 519.5 = Respiratory infection / Pneumonia
780.6 = Fever
580-589.9 = Renal
240-246.9 or 251-259.9 = Endocrine disease
250-250.9 = Diabetes
260-279.9 = Metabolic, electrolyte
280-289.9 = Hematologic
290-290.9 or 294.1 or 320-359.9 = Dementia / neurologic
291-293.9 or 294.0 or 294.8-319 = Mental disorders
360-389.9 = Eye and ear
470-478.9 or 490-513.1 or 515-518.3 or 518.5-519.4 or 519.8-519.9 or 799.1 = Noninfectious respiratory conditions
520-579.9 or 787-787.99 or 789-789.9 or 792.1-792.11 or 799.81 = Gastrointestinal (GI)
590-608.9 or 614-629.9 = Other Genitourinary (GU)
680-709.9 = Integument
710-739.9 or 810-848.9 = Musculoskeletal (MSK) / fractures
740-744.9 or 748-759.9 = Other congenital disorders
783.7 = Failure to thrive
798.9 = Unwitnessed death
799.9 = Unknown
959.9 = Trauma
**Supplemental Table.** Predicted probabilities (standard error) of cardiovascular vs. noncardiovascular death, based on sex, age at death, myocardial infarction, and LV systolic function status.

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>No MI</th>
<th>HFREF</th>
<th>HFPEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All CVD Death</td>
<td>All CVD Death</td>
<td>All CVD Death</td>
<td>All CVD Death</td>
</tr>
<tr>
<td><strong>Total n</strong></td>
<td>97</td>
<td>350</td>
<td>190</td>
<td>85</td>
</tr>
<tr>
<td>&lt;65 Men</td>
<td>0.742 (0.061)</td>
<td>0.767 (0.050)</td>
<td>0.801 (0.077)</td>
<td>0.589 (0.118)</td>
</tr>
<tr>
<td>Women</td>
<td>0.810 (0.056)</td>
<td>0.693 (0.061)</td>
<td>0.771 (0.089)</td>
<td>0.545 (0.121)</td>
</tr>
<tr>
<td>65-79 Men</td>
<td>0.650 (0.053)</td>
<td>0.679 (0.034)</td>
<td>0.708 (0.042)</td>
<td>0.464 (0.059)</td>
</tr>
<tr>
<td>Women</td>
<td>0.732 (0.054)</td>
<td>0.592 (0.039)</td>
<td>0.670 (0.055)</td>
<td>0.420 (0.061)</td>
</tr>
<tr>
<td>80+ Men</td>
<td>0.591 (0.055)</td>
<td>0.622 (0.035)</td>
<td>0.712 (0.040)</td>
<td>0.468 (0.055)</td>
</tr>
<tr>
<td>Women</td>
<td>0.681 (0.055)</td>
<td>0.531 (0.029)</td>
<td>0.674 (0.040)</td>
<td>0.424 (0.041)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>No MI</th>
<th>HFREF</th>
<th>HFPEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non- CVD</td>
<td>Non- CVD</td>
<td>Non- CVD</td>
<td>Non- CVD</td>
</tr>
<tr>
<td><strong>Total n</strong></td>
<td>52</td>
<td>234</td>
<td>82</td>
<td>106</td>
</tr>
<tr>
<td>&lt;65 Men</td>
<td>0.258 (0.061)</td>
<td>0.233 (0.050)</td>
<td>0.199 (0.077)</td>
<td>0.411 (0.118)</td>
</tr>
<tr>
<td>Women</td>
<td>0.190 (0.056)</td>
<td>0.307 (0.061)</td>
<td>0.229 (0.089)</td>
<td>0.455 (0.121)</td>
</tr>
<tr>
<td>65-79 Men</td>
<td>0.350 (0.053)</td>
<td>0.321 (0.034)</td>
<td>0.292 (0.042)</td>
<td>0.536 (0.059)</td>
</tr>
<tr>
<td>Women</td>
<td>0.268 (0.054)</td>
<td>0.408 (0.039)</td>
<td>0.330 (0.055)</td>
<td>0.580 (0.061)</td>
</tr>
<tr>
<td>80+ Men</td>
<td>0.409 (0.055)</td>
<td>0.378 (0.035)</td>
<td>0.288 (0.040)</td>
<td>0.532 (0.055)</td>
</tr>
<tr>
<td>Women</td>
<td>0.319 (0.055)</td>
<td>0.469 (0.029)</td>
<td>0.326 (0.040)</td>
<td>0.576 (0.041)</td>
</tr>
</tbody>
</table>