Death in Heart Failure
A Community Perspective

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Background—Mortality in patients with heart failure (HF) remains high, but causes of death are incompletely defined. As HF is a heterogeneous syndrome categorized according to the ejection fraction (EF), the association between EF and causes of death is important, yet elusive.

Methods and Results—Community subjects with HF were classified according to the preserved (≥50%) and the reduced EF (<50%). Deaths were classified as due to coronary heart disease and other cardiovascular and noncardiovascular diseases. Among 1063 persons with HF, 45% had preserved EF with fewer cardiovascular risk factors and less coronary disease than those with reduced EF. At 5 years, survival was 45% (95% CI, 43% to 49%), and 43% of the deaths were noncardiovascular. The leading cause of death in subjects with preserved EF was noncardiovascular disease (49%) versus coronary heart disease (43%) for subjects with reduced EF. The proportion of cardiovascular deaths decreased from 69% in 1979–1984 to 40% in 1997–2002 (P=0.007) among subjects with preserved EF, which is in contrast to a modest change among those with reduced EF (77% to 64%, P=0.08). Advanced age, male sex, diabetes, smoking, and kidney disease were associated with an increased risk of all-cause and cardiovascular deaths. After adjustment, preserved EF was associated with a lower risk of cardiovascular death but not all-cause death.

Conclusions—Community subjects with HF experience a persistently high mortality, and a large proportion of deaths is noncardiovascular. Cardiovascular disease before death is less in subjects with preserved EF, and they are less likely to experience cardiovascular deaths compared with those with reduced EF. In those with preserved EF, the proportion of cardiovascular deaths declined over time. (Circ Heart Fail. 2008;1:91-97.)

Key Words: heart failure ■ ejection fraction ■ epidemiology ■ mortality
Methods

Study Setting
This study was conducted in Olmsted County, Minn. Epidemiological studies in Olmsted County are possible because the county is relatively isolated, and only a few providers deliver nearly all health care to local residents. Healthcare providers in Olmsted County include Mayo Clinic, Olmsted Medical Center, and a handful of private practitioners. Each provider uses a comprehensive medical record system in which the details of every encounter are entered and can be easily retrieved. Medical records are reviewed under the auspices of the Rochester Epidemiology Project, a record-linkage system that allows the indexing of all medical records of Olmsted County residents according to the clinical and pathological diagnoses, surgical procedures, and billing information. This indexing system enables the retrieval of all medical records for use in the epidemiological studies and ensures the complete capture of all healthcare-related events occurring in Olmsted County for local residents. This centralized system encompasses the medical records of a population representing an estimated 3 600 000 person-years of health care. The potential of this data source has been described elsewhere.19 The appropriate institutional review boards approved all aspects of the study.

HF Incidence Cohort
The validated incident HF cohort was assembled from a random sample of all potential HF cases in Olmsted County between 1979 and 2002 and thus does not include all cases of HF in the community within the study period. Cases were identified by screening the medical records of all Olmsted County patients from 1979 to 2002 using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 428. Focus on code 428 was based on the previously reported yields of all codes relating to HF.4 Nurse abstractors then reviewed the random sample of 2072 cases and validated HF diagnosis according to the Framingham Criteria.4 Persons who had a clinical diagnosis of HF in their medical record before 1979 or who were not residents of Olmsted County were excluded. After validation, 1063 cases of HF met Framingham criteria and were included in this study. Clinical characteristics, including a detailed assessment of comorbidity, were collected from the medical record.

Clinical Characteristics
Hypertension was defined by the criteria of the 6th report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (6th report, 97). Persons were considered hypertensive if 2 or more ambulatory blood pressure readings were greater than or equal to 140 mm Hg systolic and/or 90 mm Hg diastolic. Physician’s diagnosis of hypertension and treatment with antihypertensive drugs were also considered. Persons who met the standardized criteria of two consecutive fasting glucose levels greater than or equal to 140 mg/dL or 1- to 2-hour levels greater than or equal to 200 mg/dL obtained using a standard glucose tolerance test before HF were diagnosed with diabetes mellitus according to the National Diabetes Data Group recommendations (Anonymous, classification, 1979). Smoking status was categorized as never or ever (past or current).

Height and weight measurements reported in the last outpatient visit before meeting criteria for HF were abstracted. Body mass index was calculated as weight (in kilograms) divided by height (in meters squared). Documented coronary disease was defined as the occurrence of a myocardial infarction validated with epidemiological criteria,20 a history of coronary surgery, or the presence of significant coronary disease at angiography, occurring before the index date of HF.

Creatinine clearance was calculated using the last outpatient serum creatinine value before the diagnosis of HF by Cockcroft and Gault equation: \([140–\text{age}] \times \text{(weight in kilograms)} \times (0.85 \text{ for women}) \div (72 \times \text{creatinine}) \text{(mg/dL)}\) and was used as an estimate of glomerular filtration rate after adjustment for body surface area.21 Chronic kidney disease was deemed severe when the glomerular filtration rate was less than or equal to 29 mL/min per 1.73 m², whereas moderate kidney disease was defined by the glomerular filtration rate of 30 to 59 mL/min per 1.73 m².22,23

Left ventricular EF (%) was determined using the values collected from any echocardiogram, radionuclide ventriculogram, or left ventricular angiogram performed within 90 days of HF diagnosis. The value closest in time to HF diagnosis was used when multiple values were available. When multiple values were measured as part of one test on the same day, the average value was used. EF greater than or equal to 50% defined HF with preserved EF, whereas reduced EF was defined as EF less than or equal to 50%.24

Comorbid conditions were categorized as peripheral vascular/cerebrovascular disease, chronic obstructive pulmonary disease, gastrointestinal or liver disease, cancer, or rheumatologic disease on the basis of ICD-9 and ICD-10 code groupings defined with the Centers for Disease Control and Prevention ICD code finder (http://wonder.cdc.gov/wonder/cgi-bin/asp/ICDFinder.asp). In addition, the Charlson Index25 was used to measure the global burden of comorbidity.

Ascertainment of Death and Cause of Death Classification
Follow-up was performed by using all inpatient and outpatient medical records. The ascertainment of death included several procedures. In addition to the deaths noted during clinical care, all death certificates for Olmsted County residents are obtained each year from the county office. The Mayo Clinic registration office records the obituaries and notices of death in the local newspapers. Finally, data on all Minnesota deaths are obtained from the State of Minnesota every year.

Assignment of the cause of death relied on the underlying cause of death listed on the death certificate and was classified into 3 categories, including coronary heart disease and other cardiovascular and noncardiovascular cause of death, based on ICD-9 and ICD-10 codes. The categories of cardiovascular deaths, including ischemic heart diseases and other cardiovascular diseases, were adapted from the classification used by the American Heart Association.26 The procedures in place in Olmsted County to complete death certificates differ from the procedures in most other locations.27 The coroner (chief medical examiner) or a pathologist member of the staff of the Mayo Clinic completes the death certificates of more than 75% of Olmsted County residents, irrespective of whether an autopsy is performed. The entire medical record is reviewed before assigning the cause of death. Death certificates for in-hospital deaths were not verified manually. However, it is less subject to misclassification than outpatient events because of the availability of the medical record.28 When an autopsy is performed, its findings are taken into account to complete the death certificate and take precedent over the clinical information. Infrequently, the oncologist assigns the cause of death for hospice patients and an internist for nursing home patients. Death certificates for patients under the care of physicians not affiliated with the Mayo Clinic are completed by their physicians.

Statistical Analysis
The data are presented as frequency or mean ± standard deviation. Associations between patient characteristics and EF category were examined with logistic regression. Survival was analyzed with the Kaplan-Meier method. Trends in the cause of death over time were analyzed with logistic regression with a 4-level categorical year variable as the predictor variable, with levels representing 1979–1984, 1985–1990, 1991–1996, and 1997–2002. Trends in baseline characteristics over time were analyzed with linear regression for continuous variables and with the Mantel-Haenszel χ² test for categorical variables. Proportional hazards regression was used to examine the association between death and baseline characteristics. First-order interactions between EF and baseline characteristics were examined and reported when present. Missing values did not exceed 5% for any variable used in the regression analyses except for EF, which was missing in 39% of the cases. Multiple imputation was
used to impute missing values using the Markov Chain Monte Carlo method and assuming that the missing data mechanism was missing at random. This means that the probability of missingness may depend on data that are observed but not on values that are missing. The model used to impute EF included demographic variables, cardiovascular risk factors, and comorbidities. Five complete data sets were created for the analyses. The relative efficiency from using 5 imputed data sets is 93%, which is desirable for estimating model parameters. Each of the complete data sets was analyzed using standard statistical analyses. Results were combined, with standard errors obtained using the rules given by Rubin.29 A probability value of 0.05 was selected for the threshold of statistical significance, except when testing for interactions when a probability value of 0.10 was used. Analyses were performed using SAS statistical software, version 8 (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Clinical Characteristics

One thousand sixty-three persons with incident HF diagnosed between 1979 and 2002 were included in the study. Their mean age was 76±12 years, and 46% were men. Most subjects had a prior diagnosis of hypertension or were smokers. Comorbid conditions were common (Table 1). Mean age increased over time (P=0.04) as did the number of comorbidities (P<0.001).

Forty-five percent of subjects had HF with preserved EF. These subjects were older and more often women. Subjects with preserved EF had a lesser global burden of cardiovascular risk factors, as they were equally likely to be overweight and hypertensive but less likely to have diabetes mellitus or to have a smoking history compared with their counterparts with reduced EF.

Congruent with the prevalence of cardiovascular risk factors, the antemortem prevalence of documented coronary disease was markedly lower among subjects with preserved EF. This was particularly noticeable for myocardial infarction, which was recorded among 16% of patients with preserved EF compared with 28% among persons with reduced EF (P<0.001). The total comorbidity burden, as measured by the Charlson Index, did not differ according to EF. Among subjects with preserved EF, 52% had a Charlson Index of 2 or more, whereas 56% of subjects with reduced EF had a Charlson Index of 2 or more (P=0.34).

All-Cause and Cardiovascular Deaths

After a median follow-up of 4.3 years (minimum=0 years, maximum=27.7 years), 917 deaths were noted, corresponding to a 5-year survival of 45% (95% CI, 43% to 49%). Overall, 525 (57%) deaths were categorized as cardiovascular. A total of 330 coronary heart disease deaths occurred, which represented 36% of all deaths and 63% of cardiovascular deaths.

Of the 392 (43%) noncardiovascular deaths, the most common causes of death were pulmonary disease (28%) and cancer (25%), followed by central nervous system disease (12%), gastrointestinal disease or genitourinary disease (12%), and diabetes mellitus or endocrine disorders (9%).

Over time, a shift in the distribution of causes of death occurred. The proportion of deaths occurring within 5 years of incident HF that were categorized as cardiovascular decreased from 74% in 1979–1984 to 51% in 1997–2002 (P<0.001).
Advanced age, male sex, diabetes mellitus, history of smoking, and chronic kidney disease were associated with the increased risk of all-cause mortality and cardiovascular mortality (Table 2). In particular, severe chronic kidney disease was associated with more than a 2-fold increase in the risk of overall and cardiovascular death adjusting for other clinical characteristics.

Death in HF According to EF
Among subjects with preserved EF, death was most commonly attributed to noncardiovascular causes (49% of all deaths; Figure). Noncardiovascular deaths included deaths most commonly due to pulmonary disease (29%) and cancer (23%), followed by central nervous system disease (14%), gastrointestinal or genitourinary disease (11%), and diabetes mellitus or endocrine disorders (7%). Coronary heart disease and other cardiovascular deaths occurred in 29% and 22% of cases, respectively.

In contrast, among subjects with reduced EF, the leading cause of death was coronary heart disease (43%), whereas 36% of deaths were attributed to noncardiac causes. These included deaths most commonly due to cancer (28%) and pulmonary disease (27%), followed by gastrointestinal or genitourinary disease (14%), central nervous system disease (10%), and diabetes mellitus or endocrine disorders (10%).

Over time, a shift in the distribution of causes of death occurred among those with preserved EF. The proportion of deaths occurring within 5 years of incident HF that were categorized as cardiovascular decreased from 69% in 1979–1984 to 40% in 1997–2002 (P<0.007). In contrast, among subjects with reduced EF, the temporal decrease in the proportion of cardiovascular deaths was modest and not statistically significant (77% in 1979–1984 to 64% in 1997–2002, P=0.08).

EF was not associated with all-cause death (hazard ratio for preserved versus reduced EF, 0.95; 95% CI, 0.81 to 1.11; P=0.52). Adjustment for age, sex, diabetes mellitus, smoking, documented coronary disease, and chronic kidney disease did not unmask any significant association between EF and death (Table 2). Conversely, preserved EF was univariately associated with a markedly lower risk of cardiovascular death (hazard ratio, 0.76; 95% CI, 0.61 to 0.94; P=0.014). This association remained after the adjustment for age, sex, diabetes mellitus, smoking, documented coronary disease, and chronic kidney disease.

**Discussion**
In the community, all subjects with HF experienced high mortality, irrespective of EF, and the frequency of noncardiovascular deaths is high. Subjects with preserved EF had less documented coronary disease. Accordingly, cardiovas-
cular deaths were less frequent among subjects with preserved EF. Age, male sex, diabetes, smoking, and kidney disease were important indicators of an increased risk of overall and cardiovascular death, whereas reduced EF was associated with an increased risk of cardiovascular death but not all-cause death.

Few studies have reported on cause-specific deaths in HF. Results of such studies underscored that noncardiac causes of death were frequent in HF. In a cohort of hospitalized patients from Canada, this was estimated at nearly one-third.30

The present community-based findings support and extend previous findings by demonstrating that patients with HF have a poor survival and that the frequency of noncardiovascular deaths in this cohort, including both outpatients and hospitalized subjects, is higher than previously reported,30 accounting for nearly half of all deaths. Factors associated with worse survival include advanced age, male sex, preexisting diabetes, smoking history, and chronic kidney disease.16,31,32 In our cohort, patients with HF were becoming older and had increasing comorbidity over the study period. This underscores the importance of the identification and management of comorbid diseases among all patients with HF. Indeed, as noncardiac comorbidities are highly prevalent in patients with HF in the community, further improvement in the survival of patients with HF may be hindered by comorbid conditions, which interfere with HF management strategies and adversely affect outcomes.33

HF is a disease of the elderly, typically with a similar distribution across sexes or a slight female preponderance. Community studies have consistently indicated a high prevalence, even predominance, of preserved EF among subjects with HF.7 As HF is a syndrome, its pathogenesis differs by EF,34 and the mechanisms of HF with preserved EF, although remaining controversial, are likely related to impaired myocardial relaxation and reduced left ventricular compliance, leading to impaired left ventricular filling.34-36 Within this context, examining the cause of death in HF can enhance our understanding of the pathophysiology of the disease.7

Herein, patients with preserved EF were less likely to have a history of diabetes, smoking, or documented coronary disease compared with those with reduced EF. During a long follow-up period, EF was not associated with mortality. These data extend a prior report from our group showing no difference in short-term mortality according to EF.18 Additionally, the SENIORS study of older adults with HF showed no difference in all-cause mortality between patients with preserved or reduced EF.37 Other studies, however, indicated that preserved EF was associated with better survival.7,8,14,15 These conflicting results likely reflect differences in study design, sample size, and cause of death ascertainment and distributions. These methodological considerations are important as they determine the applicability of these results to different populations and thus the clinical usefulness of such data.

To this end, in the Digitalis Investigation Group trial, EF was associated with increased mortality.32 These data present some striking differences compared with the present community study. Indeed, participants in the Digitalis Investigation Group trial were more than 10 years younger than the present community population and included one fourth of women as compared with half in the present study, and 63% of trial enrollees had a history of myocardial infarction compared with 23% herein. Accordingly, 78% of deaths were due to cardiovascular diseases in the Digitalis Investigation Group trial compared with 57% in the present study. Similarly, participants in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity trial38 were younger and more likely to be male, with a preponderance of coronary disease and most deaths (85%) of cardiovascular cause. Thus, in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity trial, as in the Digitalis Investigation Group, the association between EF and overall mortality reflects the characteristics and outcomes of selected clinical trial participants that differ markedly from that of community populations. The discrepancies between the clinical trial findings and the present community-based data illustrate the limitations of extrapolating the observations made in clinical trials to the community.39 Among hospitalized patients in Ontario, no association between EF and survival was detected.40 This study, however, included only subjects who underwent an assessment of EF, which represented only 42% of all patients with HF hospitalized during the time period. Thus, this by design led to a substantial selection bias, which may have impact on the external validity of these results amplified by the fact that outpatient subjects with HF were excluded. This underscores in turn the importance and relevance of the present data to the community practice. These findings contribute to resolving the aforementioned controversy on the impact of EF on death in HF by indicating that preserved EF carries a lower risk of cardiovascular, but not overall, death. Patients with preserved EF have fewer comorbid cardiovascular conditions than do their counterparts with reduced EF; thus, deaths from noncardiac causes predominate among subjects with preserved EF. Further, the present study indicates that the proportion of cardiovascular deaths has decreased over time among subjects with HF and preserved EF, a finding previously not reported, which should be interpreted in light of a previous report from our group indicating that the prevalence of HF with preserved EF increased over time, with no improvement in survival among these patients.8 This may help to explain findings such as those in the Perindopril in Elderly People with Chronic Heart Failure study, in which older patients with preserved EF had no 1-year mortality benefit with use of perindopril therapy.41 Indeed, the present findings extend data by indicating that within the context of stable overall survival, the distribution of the causes of death is shifting toward less cardiovascular causes, which has important implications for the understanding of secular trends in HF and for therapeutic trials for this condition.

Limitations and Strengths

As no study will be generalizable to the entire US population, the racial and ethnic composition of the present population may impact the extrapolation of the data to under-represented populations. Although the population of the present study consists mainly of white subjects, the value of Olmsted County studies lies in the ability to measure in one population
the occurrence of disease and subsequent outcomes and provide benchmarks for needed comparisons to other populations. Ascertainment of the cause of death relied on death certificates. The procedure for death certificate completion, as indicated in the Methods section, is standardized. The validity of a death certificate to diagnose deaths due to coronary disease in the outpatient setting is robust. Although we cannot exclude that some deaths could be misclassified, it seems unlikely, however, that misclassification would differ appreciably according to EF such that it should not affect the primary findings of the study. Further, misclassification tends to be less problematic for broad categories of death causes, such as were used herein. We acknowledge that there are limitations to the Framingham criteria for the diagnosis of HF.

Our community-based study has notable strengths. The HF cohort, validated using standardized criteria, includes both inpatient and outpatient data. Our findings address the stated need for more data on the cause of death among subjects with inpatient and outpatient data. Our findings address the stated need for more data on the cause of death among subjects with preserved EF in a community cohort, which optimizes its applicability to clinical practice. EF was directly measured in a larger proportion of subjects than most previous reports. Further, multiple imputation was used to impute EF values when EF was not directly measured, thereby enabling to report on the entire experience of all subjects with HF in the community. This methodology provides unbiased estimates and, therefore, is a better approach to handling missing data than using an indicator variable to represent missing EF that has known biases.

Conclusions

Community subjects with HF experience high mortality whether EF is preserved or reduced, and the frequency of noncardiovascular deaths is high. Subjects with preserved EF have a lower burden of cardiovascular comorbidity before death and experience fewer cardiovascular deaths than do subjects with reduced EF. Among subjects with preserved EF, the proportion of noncardiovascular deaths increases over time. These findings underscore the heterogeneity of HF and have implications for the design and interpretation of interventions aiming at reducing mortality in HF.

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Disclosures

None.

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