

ORIGINAL ARTICLE

## Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

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### ABSTRACT

#### BACKGROUND

The prevalence of heart failure with preserved ejection fraction may be changing as a result of changes in population demographics and in the prevalence and treatment of risk factors for heart failure. Changes in the prevalence of heart failure with preserved ejection fraction may contribute to changes in the natural history of heart failure. We performed a study to define secular trends in the prevalence of heart failure with preserved ejection fraction among patients at a single institution over a 15-year period.

#### METHODS

We studied all consecutive patients hospitalized with decompensated heart failure at Mayo Clinic Hospitals in Olmsted County, Minnesota, from 1987 through 2001. We classified patients as having either preserved or reduced ejection fraction. The patients were also classified as community patients (Olmsted County residents) or referral patients. Secular trends in the type of heart failure, associated cardiovascular disease, and survival were defined.

#### RESULTS

A total of 6076 patients with heart failure were discharged over the 15-year period; data on ejection fraction were available for 4596 of these patients (76 percent). Of these, 53 percent had a reduced ejection fraction and 47 percent had a preserved ejection fraction. The proportion of patients with the diagnosis of heart failure with preserved ejection fraction increased over time and was significantly higher among community patients than among referral patients (55 percent vs. 45 percent). The prevalence rates of hypertension, atrial fibrillation, and diabetes among patients with heart failure increased significantly over time. Survival was slightly better among patients with preserved ejection fraction (adjusted hazard ratio for death, 0.96;  $P=0.01$ ). Survival improved over time for those with reduced ejection fraction but not for those with preserved ejection fraction.

#### CONCLUSIONS

The prevalence of heart failure with preserved ejection fraction increased over a 15-year period, while the rate of death from this disorder remained unchanged. These trends underscore the importance of this growing public health problem.

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**A**LTHOUGH THE INCIDENCE OF HEART failure has remained stable in recent decades, the likelihood of survival after a diagnosis of heart failure has increased,<sup>1,2</sup> suggesting that the profile of heart failure may be changing. Such changes may be due to shifts in population demographics, changes in the prevalence of risk factors for heart failure, and the evolution of therapeutic strategies for heart failure.<sup>3</sup> The overall profile of heart failure may also be influenced by changes in the prevalence of heart failure with preserved ejection fraction.

We performed a study to define secular trends in the prevalence of heart failure with preserved ejection fraction among patients admitted for decompensated heart failure at a single institution over a 15-year period. We hypothesized that the prevalence of heart failure with preserved ejection fraction has increased over time. We also investigated whether patterns of the prevalence of heart failure were associated with changes in the types of cardiovascular disease among patients with heart failure. Finally, we examined whether changes in survival rate over the 15-year period differed between patients with preserved ejection fraction and those with reduced ejection fraction.

## METHODS

### STUDY SETTING

The Mayo Clinic hospitals are located in Olmsted County, Minnesota, and serve patients from the community and those referred from other sites. The institution maintains an integrated medical-record system of all encounters that identifies each patient with a unique number.<sup>4</sup> This system served as the basis for our retrospective analysis of data on patients hospitalized for heart failure. Study funding was provided by the Miami Heart Research Institute and the National Institutes of Health. The study was approved by the institutional review board of the Mayo Foundation; because the study involved only the review of records obtained as a part of routine medical care, no patient consent was required.

### IDENTIFICATION OF PATIENTS

The Mayo Integrated Computer System identified all consecutive patients admitted to Mayo Clinic hospitals in Rochester, Minnesota, between January 1, 1987, and December 31, 2001, who were discharged with a code 428 diagnosis according

to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).<sup>2</sup> The list of patients with this diagnosis was matched with the list of patients discharged with a diagnosis-related-group (DRG) code 127 diagnosis. Only patients discharged with both ICD code 428 and DRG code 127 were considered for inclusion in the study. If a patient was admitted more than once for heart failure during the study period, only the data from the first admission were analyzed. We validated the frequency with which such patients met the modified Framingham criteria for heart failure<sup>5</sup> or the clinical criterion (diagnosis of heart failure recorded on the chart by the attending physician) during the index hospitalization by manually abstracting data from the charts of a random sample of 135 patients.

### DATA EXTRACTION

All data were extracted electronically. Data were collected on the age, date of birth, sex, home address, admission date, body weight, and height of the patients. During the study, the proportion of patients for whom data on height and weight were electronically available increased from 9 percent in the first five years to 31 percent in the second five years to 83 percent in the last five years. Data on coexisting cardiovascular conditions in each patient were also extracted with the use of all relevant ICD codes. Data on serum creatinine and blood hemoglobin levels were extracted from the Mayo Laboratory Information System. Data on ejection fraction and the presence of valve disease that was more than moderate (aortic or mitral stenosis or regurgitation) were extracted from the Mayo echocardiographic database.<sup>6</sup> The final study cohort consisted of patients meeting the above criteria who had undergone echocardiography within 30 days before or after hospitalization.

### DEFINITION OF COVARIATES

Patients with an ejection fraction of 50 percent or higher were classified as having heart failure with preserved ejection fraction, whereas those with an ejection fraction of less than 50 percent were classified as having heart failure with reduced ejection fraction.<sup>7-9</sup> Obesity was defined by a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more. The patients were classified as community patients (residents of Olmsted County) or referral patients on the basis of their ZIP Code of residence.

**MORTALITY DATA**

Survival status was initially determined from the Mayo Clinic registration database, as previously described.<sup>2</sup> For patients with no record of death in the registration database, information on vital status and mortality was queried with the use of ACCURINT, an institutionally approved Web-based resource and location service.

**STATISTICAL ANALYSIS**

To identify changes over time, we constructed simple linear regression models with the year of admission as the independent variable. We report Pearson's correlation coefficients and P values. Differences between groups were tested by the two-sample t-test for continuous variables and the chi-square test for categorical variables. We used a regression model to adjust for the effect of age on the differences in baseline characteristics between patients with preserved ejection fraction and those with reduced ejection fraction. We estimated the overall survival by the Kaplan–Meier method and tested for differences in survival between groups or times by the log-rank test. Cox proportional-hazards regression was used to ad-

just for the effect of differences in baseline characteristics on survival. We did not adjust for body-mass index in this analysis because complete data on this variable were not available.

**RESULTS**

A total of 6076 patients with ICD code 428 and DRG code 127 were discharged from 1987 through 2001. Echocardiographic assessment of ejection fraction within 30 days was available for 4596 patients (76 percent), who constituted the study population. The proportion of patients undergoing echocardiography did not change significantly over time ( $P=0.10$ ). Ninety-five percent of the charts sampled for validation of the diagnosis of heart failure met the Framingham criteria, and 99 percent met either the clinical or the Framingham criteria. More than 97 percent of the patients were white.

**PATIENT CHARACTERISTICS AND EJECTION FRACTION**

Patients with preserved ejection fraction were older, were more likely to be female, had a higher mean body-mass index, were more likely to be

**Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.\***

Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

\* Continuous variables are expressed as means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4.

† The P values are adjusted for age. NA denotes not applicable.

‡ Data on height and weight were not consistently accessible by electronic means over the course of the study; during the three consecutive five-year periods of the study, the data were available for 9 percent, 31 percent, and 83 percent of the study population, respectively. The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Obesity was defined by a body-mass index of 30 or more.

obese, and had lower hemoglobin than those with reduced ejection fraction (Table 1). Overall, the prevalence of preserved ejection fraction among all patients with a discharge diagnosis of heart failure was 49 percent among patients 65 years of age or older and 40 percent among those under 65 years of age ( $P=0.004$ ).

The prevalence rates of hypertension and atrial fibrillation were higher and the prevalence rates of coronary artery disease and valve disease were lower among patients with preserved ejection fraction than among those with reduced ejection fraction. These differences remained significant after adjustment for the age difference between the two groups (Table 1). The serum creatinine level on admission and the prevalence of diabetes were similar in the two groups of patients.

**SECULAR TRENDS IN THE PREVALENCE OF HEART FAILURE WITH PRESERVED EJECTION FRACTION**

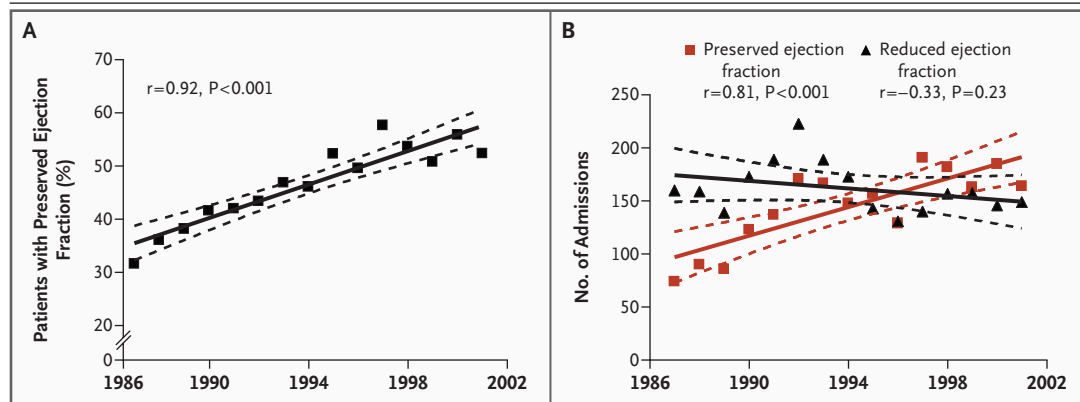
The prevalence of preserved ejection fraction among patients with a discharge diagnosis of heart failure increased over time (Fig. 1A). The average prevalence increased from 38 percent to 47 percent to 54 percent in the three consecutive five-year periods included in the study. The increase in the prevalence of preserved ejection fraction was due to an increase in the number of patients admitted with preserved ejection fraction, with no significant change in the number of patients admitted

with reduced ejection fraction (Fig. 1B). After adjustment for age, there was no substantive change in these secular trends. The increase in the prevalence of preserved ejection fraction over time was also observed when it was defined as an ejection fraction greater than 60 percent.

The proportion of patients with preserved ejection fraction was higher among community patients (599 of 1093, 55 percent) than among referral patients (1568 of 3503, 45 percent;  $P<0.001$ ). The prevalence of heart failure with preserved ejection fraction increased over time in both community patients ( $r=0.62$ ,  $P=0.01$ ) and referral patients ( $r=0.66$ ,  $P=0.006$ ).

**SECULAR TRENDS IN THE PREVALENCE OF CARDIOVASCULAR DISEASES AMONG PATIENTS WITH HEART FAILURE**

The proportion of patients with hypertension increased over time ( $r=0.98$ ,  $P<0.001$ ) from 48 percent to 53 percent to 63 percent in the three consecutive five-year periods included in the study. During these periods, the proportion of patients with atrial fibrillation increased from 29 percent to 33 percent to 41 percent ( $r=0.90$ ,  $P<0.001$ ) and the proportion with diabetes mellitus increased from 32 percent to 33 percent to 36 percent ( $r=0.65$ ,  $P=0.008$ ), whereas the prevalence of coronary artery disease was stable at 59 percent, 58 percent, and 59 percent ( $r=0.10$ ,  $P=0.73$ ).



**Figure 1. Secular Trends in the Prevalence of Heart Failure with Preserved Ejection Fraction.**

Panel A shows the increase during the study in the percentage of patients with heart failure who had preserved ejection fraction. Panel B shows that the number of admissions for heart failure with preserved ejection fraction increased during the study period, whereas the number of admissions for heart failure with reduced ejection fraction did not change. The solid lines represent the regression lines for the relation between the year of admission and the percentage of patients with heart failure who had preserved ejection fraction (Panel A) and the number of admissions for heart failure with preserved or reduced ejection fraction (Panel B). The dashed lines indicate 95 percent confidence intervals.

**MORTALITY**

Survival data were available for 4594 of the 4596 patients, with a mean ( $\pm$ SD) follow-up of 10.0  $\pm$ 4.2 years. A total of 3691 deaths occurred during follow-up, 120 of them during the index hospitalization.

The survival rate was higher among patients with preserved ejection fraction than among those with reduced ejection fraction, although the difference was small (Fig. 2). The respective mortality rates were 29 percent and 32 percent at one year and 65 percent and 68 percent at five years. The unadjusted hazard ratio for death in the group with preserved ejection fraction as compared with the group with reduced ejection fraction was 0.96 (95 percent confidence interval, 0.93 to 1.00;  $P=0.03$ ). After adjustment for differences in baseline characteristics and the year of admission, the likelihood of survival was still slightly higher among patients with preserved ejection fraction than among those with reduced ejection fraction (hazard ratio for death, 0.96; 95 percent confidence interval, 0.92 to 1.00) (Table 2). Among patients with reduced ejection fraction, the likelihood of survival increased during the study period (Fig. 3A), with an unadjusted hazard ratio for death of 0.98 per year (95 percent confidence interval, 0.97 to 1.00;  $P=0.005$ ). The survival rate among patients with preserved ejection fraction did not change significantly over time (Fig. 3B). After adjustment for differences in baseline characteristics, the survival rate increased over time among those with reduced ejection fraction but not among those with preserved ejection fraction (Table 2). Secular trends in survival were similar when preserved ejection fraction was defined as an ejection fraction greater than 60 percent and reduced ejection fraction was defined as an ejection fraction less than 40 percent.

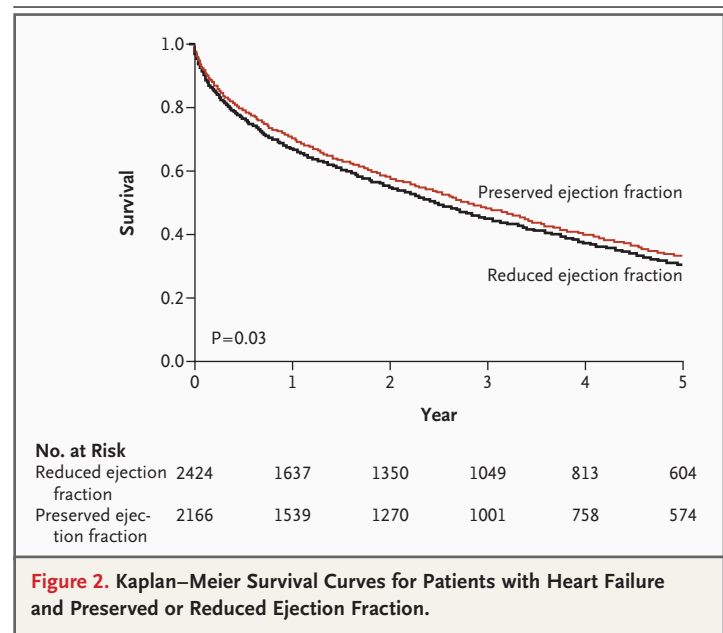
In Kaplan–Meier survival analysis, the difference in survival between patients with reduced ejection fraction and those with preserved ejection fraction appeared less dramatic in the group of patients who were 65 years of age or older (hazard ratio, 0.97;  $P=0.06$ ) than in the group of patients who were younger than 65 (hazard ratio, 0.87;  $P=0.003$ ). In Cox proportional-hazards analysis, the interaction between the effects of age group and type of heart failure on survival was significant ( $P=0.03$ ).

**DISCUSSION**

We found that the prevalence of heart failure with preserved ejection fraction among patients with a discharge diagnosis of heart failure increased significantly from 1987 to 2001. The prevalence of hypertension, atrial fibrillation, and diabetes increased during the study period, while the prevalence of coronary disease remained stable. Patients with preserved ejection fraction fared slightly better than patients with reduced ejection fraction. However, although survival improved during the study period among patients with reduced ejection fraction, it did not improve among patients with preserved ejection fraction.

Heart failure has been classified as “diastolic” (preserved ejection fraction) or “systolic” (reduced ejection fraction), but this nomenclature has become the subject of controversy.<sup>10,11</sup> Because the recently revised American College of Cardiology–American Heart Association guidelines for the diagnosis and management of heart failure<sup>12</sup> use the term “heart failure with preserved ejection fraction” rather than “diastolic heart failure,” this terminology has been adopted here.

The increase in the prevalence of heart failure with preserved ejection fraction over time noted in our analysis has also been suggested by previous studies. A review of 31 studies of patients



**Figure 2.** Kaplan–Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction.

**Table 2. Multivariate Analysis of the Association of Clinical Characteristic, Year of Admission, and Type of Heart Failure with Mortality.\***

Variable	All Patients		Preserved Ejection Fraction		Reduced Ejection Fraction	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.03 (1.02–1.03)	<0.001	1.03 (1.03–1.04)	<0.001	1.03 (1.02–1.03)	<0.001
Female sex	0.96 (0.92–0.99)	0.01	0.93 (0.89–0.98)	0.009	0.98 (0.93–1.03)	0.37
Serum creatinine on admission	1.13 (1.10–1.16)	<0.001	1.12 (1.08–1.17)	<0.001	1.15 (1.10–1.19)	<0.001
Hemoglobin on admission	0.95 (0.94–1.00)	<0.001	0.93 (0.91–0.95)	<0.001	0.97 (0.95–1.00)	0.03
Hypertension	0.90 (0.89–0.93)	<0.001	0.88 (0.84–0.93)	<0.001	0.91 (0.87–0.96)	<0.001
Coronary artery disease	1.05 (1.01–1.08)	0.01	1.03 (0.98–1.09)	0.24	1.07 (1.02–1.12)	0.01
Atrial fibrillation	1.01 (0.98–1.05)	0.58	1.01 (0.96–1.07)	0.61	1.01 (0.96–1.07)	0.66
Diabetes mellitus	1.09 (1.05–1.13)	<0.001	1.12 (1.06–1.18)	<0.001	1.07 (0.92–1.12)	0.01
Any significant valve disease	0.94 (0.81–1.08)	0.34	0.90 (0.75–1.06)	0.22	0.98 (0.77–1.21)	0.86
Year of admission	0.99 (0.98–1.00)	0.10	1.00 (0.99–1.02)	0.70	0.99 (0.97–1.00)	0.01
Heart failure with preserved ejection fraction	0.96 (0.92–0.99)	0.01	NA	NA	NA	NA

\* HR denotes hazard ratio, CI confidence interval, and NA not applicable.

with heart failure conducted from 1970 through 1995 noted that most studies (90 percent) involved patients who had been referred for treatment and that the prevalence of preserved ejection fraction among patients with heart failure ranged from 13 to 74 percent, with a median value of 40 percent.<sup>9</sup> Subsequently, 12 community-based studies published from 1998 through 2003 found that the prevalence of preserved ejection fraction among patients with heart failure ranged from 40 to 71 percent, with a mean of 54 percent.<sup>7,8</sup> The difference between the average prevalence rates reported in the early referral-based studies and those reported in the later community-based studies does suggest that the prevalence of preserved ejection fraction among patients with heart failure has either increased over time or differs between referral and community settings. Our findings, obtained with the use of consistent methods of patient identification at a single center serving both referral and community patients over a 15-year period, suggest that both factors are important.

A true increase in the age-specific prevalence of heart failure with preserved ejection fraction could be related to changes in associated cardiovascular disease in the population. In our analysis, the prevalence of atrial fibrillation increased over time; this dysrhythmia is a common precipitant of acute decompensation in patients with heart failure with preserved ejection fraction.<sup>13,14</sup>

The prevalence rates of hypertension and diabetes mellitus, both of which are commonly associated with heart failure with preserved ejection fraction, also increased significantly over time among patients with heart failure.

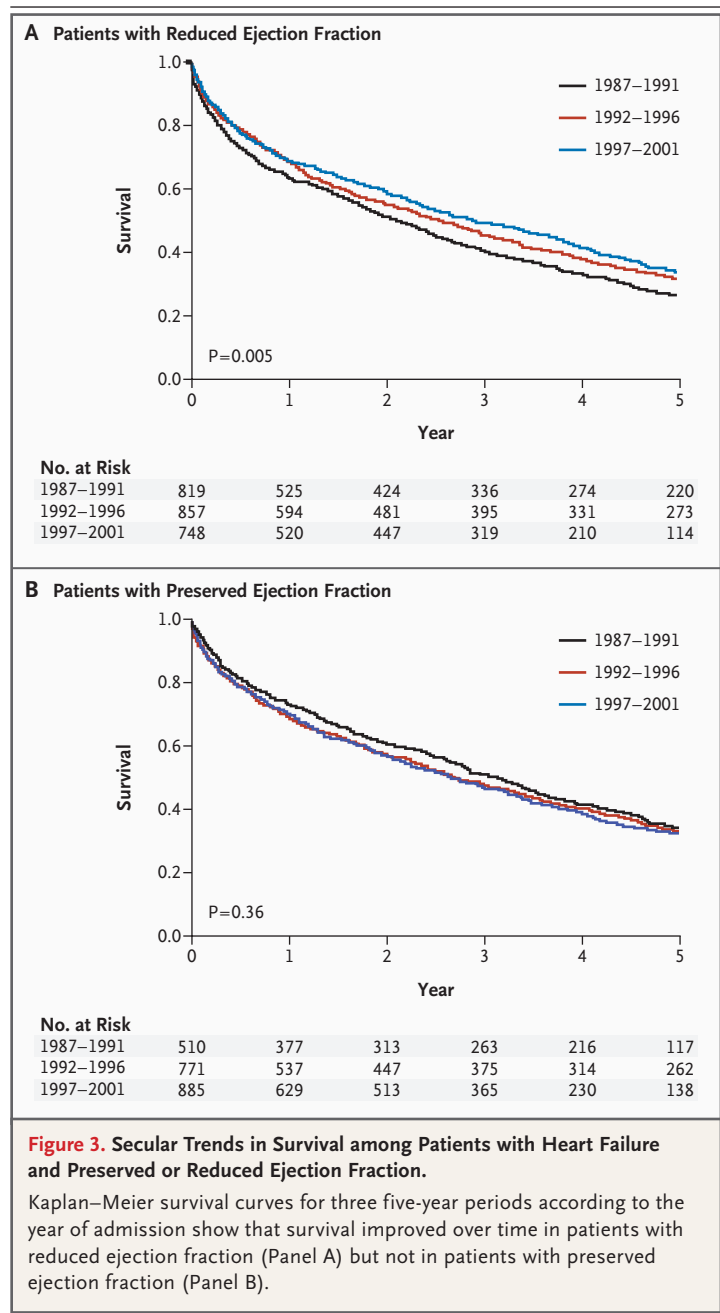
The observed increase in heart failure with preserved ejection fraction could also be a consequence of changing physician behavior over time. The concept of “diastolic dysfunction” evolved markedly during the study period, and it is likely that the propensity to diagnose heart failure with preserved ejection fraction has evolved as well. The likelihood that this diagnosis will be made also depends to some extent on the rigor with which other diagnoses are considered.<sup>15,16</sup> Some patients admitted during the early period of this study with symptoms of heart failure who were found to have preserved ejection fraction might have been assigned a different diagnosis at discharge and would therefore not be included in our data set. The prevalence of preserved ejection fraction among hospitalized patients with heart failure from Olmsted County in 1991 (45 percent) was similar to that found in a study conducted in Olmsted County in the same year that included both inpatients and outpatients (43 percent)<sup>17</sup>; however, similar reservations regarding diagnosis may apply to the outpatients in that report.

The survival rates of patients with heart failure with reduced ejection fraction and of those

with preserved ejection fraction have been extensively studied and compared, with disparate conclusions. Previous reviews noted the variation in findings of studies performed before 2001.<sup>7-9,18</sup> More recent studies also report variable findings.<sup>19-32</sup> Six studies reported findings similar to ours, with time-specific hazard ratios within approximately 10 percent of those in our study.<sup>19,20,22-24,32</sup> These studies had a design similar to ours — that is, they were single-center or single-region studies confined to patients hospitalized for heart failure, measurements of ejection fraction were available for most of the patients, and all consecutive patients for whom measurements of ejection fraction were available were included in the study. Eight recent studies reported greater differences in survival between patients with reduced ejection fraction and those with preserved ejection fraction than we found in our study.<sup>21,25-31</sup> Most of these studies enrolled outpatients,<sup>21,29-31</sup> enrolled hospitalized patients who were not admitted specifically for heart failure,<sup>28</sup> did not include all consecutive patients admitted for heart failure,<sup>27</sup> or included a much smaller percentage of consecutive patients with heart failure than we did, because of the lack of echocardiographic data.<sup>21,26</sup>

The methodologic differences described above may have resulted in cohorts of patients with preserved ejection fraction who had much milder heart failure than did patients with reduced ejection fraction. In contrast, we enrolled patients with reasonably uniform symptom status (i.e., their symptoms were sufficiently severe that they were hospitalized for heart failure). The diagnosis of heart failure in patients with preserved ejection fraction and milder symptoms not requiring hospital admission raises concern about the possible misdiagnosis of heart failure and about comparisons between cohorts of patients with heart failure of different severity. On the other hand, our requirement that patients be hospitalized emphasized the prognosis of patients who had reached a somewhat advanced stage in their illness and did not permit us to incorporate the natural history of heart failure with preserved ejection fraction from the time of first diagnosis until the need for hospitalization.

Community-based studies suggest that overall survival among patients with heart failure is improving.<sup>1,2</sup> We found a trend toward improved overall survival that did not achieve statistical significance. However, among patients with reduced



ejection fraction, survival improved significantly over time, whereas there was no trend toward improvement among patients with preserved ejection fraction. These observations suggest that improvement over time in the survival of broader populations of patients with heart failure may be due primarily to improvement among those with reduced ejection fraction. Although several interventions known to improve survival among patients with reduced ejection fraction were in-

troduced into clinical practice during the study period, no agents have been proven to improve survival among patients with preserved ejection fraction. Thus, it is not unexpected that survival among patients with preserved ejection fraction did not change significantly over the study period.

This study is subject to the limitations inherent in retrospective studies. Restriction to patients with DRG code 127 provides a potential for bias based on coding practices. The absence of ejection-fraction data from some patients could have affected the absolute prevalence of heart failure with preserved ejection fraction as well as secular trends (although the proportion of patients who underwent echocardiography was stable during the study period). Restriction of the study to hospitalized patients might have introduced bias, since the results from this population may not reflect larger trends in disease prevalence in the community. We were not able to take into account any possible evolution of the diagnostic behavior of physicians. Our data may not reflect secular trends

among patients with different racial or ethnic, regional, or socioeconomic backgrounds.

The increase in the prevalence of heart failure with preserved ejection fraction over time and the stability in the rates of death from this condition underscore the importance of studies to determine the pathophysiology of this form of heart failure and develop therapeutic strategies against it. Indeed, should these trends be confirmed and should they continue, heart failure with preserved ejection fraction may become the most common form of heart failure. Because no proven therapy for heart failure with preserved ejection fraction currently exists, there is a need for coordinated efforts to address this growing problem.

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