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Outcomes in Heart Failure Patients With Preserved Ejection Fraction

Mortality, Readmission, and Functional Decline

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OBJECTIVES We evaluated the six-month clinical trajectory of patients hospitalized for heart failure (HF) with preserved ejection fraction (EF), as the natural history of this condition has not been well established. We compared mortality, hospital readmission, and changes in functional status in patients with preserved versus depressed EF.

BACKGROUND Although the poor prognosis of HF with depressed EF has been extensively documented, there are only limited and conflicting data concerning clinical outcomes for patients with preserved EF.

METHODS We prospectively evaluated 413 patients hospitalized for HF to determine whether EF ≥40% was an independent predictor of mortality, readmission, and the combined outcome of functional decline or death.

RESULTS After six months, 13% of patients with preserved EF died, compared with 21% of patients with depressed EF ($p = 0.02$). However, the rates of functional decline were similar among those with preserved and depressed EF (30% vs. 23%, respectively; $p = 0.14$). After adjusting for demographic and clinical covariates, preserved EF was associated with a lower risk of death (hazard ratio [HR] 0.49, 95% confidence interval [CI] 0.26 to 0.90; $p = 0.02$), but there was no difference in the risk of readmission (HR 1.01, 95% CI 0.72 to 1.43; $p = 0.96$) or the odds of functional decline or death (OR 1.01, 95% CI 0.59 to 1.72; $p = 0.97$).

CONCLUSIONS Heart failure with preserved EF confers a considerable burden on patients, with the risk of readmission, disability, and symptoms subsequent to hospital discharge, comparable to that of HF patients with depressed EF. (J Am Coll Cardiol 2003;41:1510–8) © 2003 by the American College of Cardiology Foundation

An estimated half of all patients with heart failure (HF) have a preserved ejection fraction (EF) (1,2). Studies report lower mortality rates of 8% in these patients, compared with 19% to over 50% annual mortality in patients with depressed EF (3,4). These and other studies are often considered evidence that the prognosis for patients with preserved EF

See page 1519

is more benign (1,3,5–8), although some studies report no difference in the risk of death (2,9–15). Thus, it is unclear whether HF patients with preserved EF have a prognosis similar to patients with depressed EF (16). Few comparative studies have addressed hospital readmission rates in these patients, and examinations of functional outcomes in these patients are virtually non-existent.

Accordingly, we sought to compare a range of clinical outcomes in a prospective cohort of hospitalized HF patients with preserved versus depressed EF. We comprehensively assessed the risks of mortality, all-cause and HF hospital readmissions, and decline in functional status, as measured by a loss in activities of daily living (ADL) during follow-up.

METHODS

Study sample. We screened consecutive patients admitted to Yale–New Haven Hospital between March 1996 and September 1998, who were ≥50 years old and met clinical criteria for the presence of HF on admission. To identify eligible patients, admissions were screened daily in two phases. First, patients were identified with an admission diagnosis or radiologic signs of HF on the admission chest X-ray. Second, patients who met the aforementioned conditions had their medical records reviewed within three days of admission to verify the presence of HF, based on modified National Health and Nutrition Examination Survey-I study criteria and criteria by Schocken et al. (17) and Harlan et al. (18). Details are published elsewhere (19).

Patients excluded were those admitted without evidence of HF, those transferred from other hospitals or admitted

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ADL = activities of daily living
CI = confidence interval
EF = ejection fraction
HF = heart failure
HR = hazard ratio
OR = odds ratio
V-HeFT = Veterans Administration Heart Failure Trial

from nursing homes, those having a non-cardiovascular terminal illness such as cancer with less than six months of expected survival (for follow-up), or those having HF secondary to high-output states or non-cardiac diseases (for homogeneity of sample). Of 1,151 patients screened, 648 met eligibility criteria. Of these, 126 were already enrolled in our study and were re-screened during a subsequent readmission, 45 died or were discharged before an interview, 45 refused or were unable to participate in an interview, and six lived in another state (Table 1). We excluded five patients due to missing baseline interview or medical record and eight patients due to missing EF data, yielding a total sample of 413 patients.

All patients were followed up for six months. Of the 342 patients who survived, 316 provided complete functional status data at six-month follow-up (92%). Rates of loss to follow-up were not significantly different among patients with preserved versus depressed EF (n = 8 vs. 12; p = 0.44).

Study measures and outcomes. Patients were interviewed within three days of admission for demographic information and baseline functional status. Clinical information, assessed through medical records abstraction, included cardiac and non-cardiac history, EF, discharge systolic and diastolic blood pressure, and discharge medications. Ejection fraction was determined from quantitative or qualitative assessments from multi-gated acquisition/radionuclide ventriculography, cardiac catheterization, or echocardiography performed during the index admission or within one year before the hospital stay. In cases with multiple assessments, priority was given to the most recent and quantitative assessment. If quantitative results were unavailable (n = 41), then the following values were assigned: severely depressed function = 20%; moderate to severely depressed function = 25%; moderately depressed function = 35%; mild to moderately depressed function = 40%; mildly depressed function = 45%; and normal function = 50%. Of 413 patients, 71% had EF assessed during the index admission, 13% had a value within the previous six months, and 17% had a value obtained between six months and one year before admission. Preserved EF was defined as ≥40%, based on clinical observations that EFs below this value are associated with systolic dysfunction. This definition has been used in previous studies comparing patients with preserved versus depressed systolic function (2,20). Other studies indicate that higher cutoff values ranging from ≥45% to ≥50% reflect preserved systolic function. Subsidiary analyses detailed subsequently address this issue.

Dyspnea and functional limitations were assessed at baseline and six-month follow-up. Limitations in activity due to dyspnea were assessed using the Dyspnea Index, which measures the degree of functional impairment and the magnitude and effort of tasks that precipitate breathlessness (21,22). Dyspnea was dichotomized as "severe" or "not severe," based on whether patients experienced shortness of breath with mild activities or at rest.

Limitations in ADL were assessed using the Katz ADL scale (23), where patients reported whether they needed help in performing basic ADLs in the month before admission. Disability was coded as needing help with or not being able to perform at least one of the following: walking across a small room, bathing, dressing, eating, moving from bed to chair, and using the toilet. This instrument measures functional status with high validity and reliability and is appropriate for use in an acutely ill population. Versions of this instrument have been used in other studies of HF patients (24–26). The Minnesota Living with Heart Failure Questionnaire, a disease-specific instrument (27), was not used, as it is more suitable for use with outpatients. The Kansas City Cardiomyopathy Questionnaire (28) was not available at the initiation of this study.

Clinical outcomes included time to death, time to first all-cause and first HF hospital readmission, and functional decline. Follow-up was calculated from the date of discharge. Deaths were ascertained through next-of-kin, hospital records, and active monitoring of obituaries. Comprehensive assessment of hospital readmissions was conducted using hospital administrative data bases for case finding and discharge summaries for case review. Validation in a subsample of patients (21%) indicated that 95% of readmissions occurred at Yale–New Haven Hospital. Functional decline, or decline in ADL during follow-up, was calculated by subtracting the number of ADL limitations at baseline from the number of limitations at follow-up. This outcome was

Table 1. Demographic Characteristics in a Subset of Screened Patients Not Enrolled

Outcome	Total Sample (n = 413)	Patients Who Died or Were Discharged Before Interview (n = 45)	Patients Who Died Before Interview (n = 14)
White race	77%	74%	64%
Men	52%	55%	29%
Mean age ± SD (yrs)	72 ± 11	70 ± 11	75 ± 10

Table 2. Baseline Differences in Preserved Versus Depressed Ejection Fraction

Characteristics	Preserved EF (n = 200)	Depressed EF (n = 213)	p Value
Demographic			
Age (yrs)	73 ± 11	70 ± 11	0.004
Male gender	74 (37%)	139 (65%)	0.001
White race	158 (79%)	159 (75%)	0.30
Cardiac history			
EF	60 ± 8	28 ± 10	0.0001
HF	128 (64%)	169 (79%)	0.001
Any previous hospitalizations for HF	60 (30%)	94 (45%)	0.002
Years of HF	2.4 ± 5.4	3.3 ± 5.5	0.002
Hypertension	160 (80%)	139 (65%)	0.001
Arrhythmia	77 (39%)	112 (53%)	0.004
Pacemaker placement	20 (10%)	40 (19%)	0.01
Chronic, stable angina	66 (33%)	91 (43%)	0.04
Myocardial infarction	78 (39%)	118 (55%)	0.001
Cardiac catheterization	75 (38%)	123 (58%)	0.001
CABG	39 (20%)	67 (31%)	0.006
PCI	19 (10%)	32 (15%)	0.09
Coronary artery disease	56 (24%)	176 (76%)	0.0001
Aortic stenosis	9 (9%)	14 (9%)	0.86
Non-cardiac history			
Renal insufficiency	72 (36%)	74 (35%)	0.79
Respiratory disease	61 (31%)	56 (26%)	0.34
CVA/stroke	30 (15%)	33 (15%)	0.89
Diabetes	95 (48%)	102 (48%)	0.94
Discharge characteristics			
Systolic blood pressure (mm Hg)	132 ± 20	120 ± 21	0.0001
Diastolic blood pressure (mm Hg)	70 ± 11	67 ± 10	0.02
Pulse (beats/min)	77 ± 15	80 ± 13	0.07
Laboratory values			
Creatinine >1.5 mg/dl	99 (50%)	110 (52%)	0.66
Discharge medications			
Diuretics	151 (79%)	183 (89%)	0.004
ACE inhibitors	66 (34%)	144 (70%)	0.001
Nitrates	67 (35%)	89 (43%)	0.07
Calcium channel blockers	97 (50%)	35 (17%)	0.001
Vasodilators	28 (14%)	42 (20%)	0.11
Beta-blockers	77 (40%)	70 (34%)	0.22
Digoxin	59 (30%)	153 (75%)	0.001
Beta-agonists	37 (19%)	27 (13%)	0.11
Aspirin	85 (44%)	91 (44%)	0.91
Warfarin	59 (30%)	88 (43%)	0.01
Functional status and quality of life			
No. of limitations in ADL	0.7 ± 1.4	0.4 ± 1.0	0.08
Dyspnea (severe)	40 (20%)	69 (32%)	0.004
Health status (excellent)	86 (44%)	76 (36%)	0.10

Data are presented as the mean value ± SD or number (%) of subjects.
ACE = angiotensin-converting enzyme; ADL = activities of daily living; CABG = coronary artery bypass graft surgery; CVA = cerebrovascular accident; EF = ejection fraction; HF = heart failure; PCI = percutaneous coronary intervention.

coded dichotomously, with any increase in the number of disabilities considered as a decline in functional status.

Statistical analysis. BASELINE CHARACTERISTICS. Demographic and clinical characteristics and medications were candidate covariates. These were compared between patients with preserved and depressed EF using the Pearson chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Associations between selected outcomes and ordinal categories of EF (≤20%, 21% to 40%, 41% to 54%, and ≥55%) were tested using the chi-square test for trend.

PREDICTORS OF MORTALITY AND READMISSION. Multivariable Cox proportional hazards regression tested whether EF was an independent predictor of time to death and time to readmission (all-cause and HF). Multivariable analyses included covariates identified in previous studies of readmission (29) and mortality (2,9,30) or those associated with outcomes in bivariate analyses with $p < 0.25$. In these models, the number of baseline ADL and years of HF were entered as continuous independent variables. A history of coronary artery disease was a composite variable defined as any history of myocardial infarction, coronary artery bypass

Table 3. Unadjusted Outcomes at Six-Month Follow-Up

Clinical Outcomes	Preserved EF (n = 200)	Depressed EF (n = 213)	p Value
Mortality			
Death during follow-up	25 (13%)	45 (21%)	0.02
Death during index admission	4 (2%)	3 (1%)	0.61
Days to death	167 ± 46	158 ± 52	0.01
Readmissions			
Readmissions (any)	92 (46%)	98 (46%)	0.99
Readmissions (HF)	31 (16%)	46 (22%)	0.11
Median no. of readmissions per patient (IQR)	1 (1–2)	1 (1–2)	0.88
Days to all-cause readmission	119 ± 72	113 ± 74	0.62
Days to HF readmission	71 ± 57	57 ± 48	0.24
Functional decline and dyspnea (% of survivors)			
Decline in ADL	50 (30%)	34 (23%)	0.14
No. of limitations in ADL	1.0 ± 1.7	0.7 ± 1.4	0.02
Dyspnea (severe) at follow-up	41 (25%)	32 (20%)	0.34

Data are presented as the number (%) of subjects or mean value ± SD.
IQR = interquartile range; other abbreviations as in Table 2.

graft, or percutaneous coronary intervention. Models for readmission were censored for deaths. Proportionality assumptions were tested using time-interaction terms in models, which were excluded if not significant.

Predictors of functional decline. Multivariable logistic regression analysis was used to determine the independent association between EF and the combined outcome of decline in ADL or death, adjusting for baseline ADL, demographic characteristics, and clinical history. As previous studies have not established clear correlates of functional decline in HF patients, variables identified in bivariate analyses ($p < 0.25$) and those considered clinically important were included in the multivariable model and retained at $p < 0.25$. Logistic regression analysis was conducted for the outcome of functional decline alone, limited to survivors (n = 316).

For all models, continuous covariates were tested for linearity, and those without a linear relationship with outcomes were recoded categorically. Diagnostic plots tested model fit.

Subsidiary analyses. Subsidiary analyses were performed that included only the 305 patients with a definitive diagnosis of HF on the chest radiograph during the index admission to reduce misclassification of HF. Additionally, analyses were performed that included only the 295 patients with EF assessed during the index admission, the 274 patients with quantitative EF assessed during the index admission, and the 390 patients without aortic stenosis to reduce misclassification of preserved EF. Finally, models were performed with preserved EF defined as ≥50%, which is a more restrictive categorization. This alternative definition was tested, as published studies have used a variety of definitions for preserved EF.

All tests for significance were two-tailed with an alpha level of 0.05. Statistical analyses were conducted using SAS version 6.12 (Cary, North Carolina).

Table 4. Multivariate Model: Patients With Preserved Versus Depressed Ejection Fraction

Clinical Outcomes	HR or OR	95% CI	p Value
Mortality*	0.51	0.27,0.96	0.04
All-cause readmission†	1.01	0.72,1.43	0.96
HF readmission†	0.77	0.38,1.56	0.46
Functional decline or death‡	0.98	0.57,1.69	0.63
Functional decline only (survivors: n = 316)‡	1.59	0.83,3.04	0.33

*Adjusted for age, gender, systolic blood pressure, creatinine, years of heart failure (HF), diabetes, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and baseline functional status. †Adjusted for age, gender, history of HF, years of HF, creatinine, ACE inhibitors, diuretics, digoxin, and baseline functional status. ‡Adjusted for gender, race, systolic blood pressure, angina, ACE inhibitors, diuretics, digoxin, dyspnea, and baseline functional status.
CI = confidence interval; HR = hazard ratio; OR = odds ratio.

RESULTS

Study sample. Of 413 patients, 200 (48%) had preserved EF (≥40%). Patients were elderly; about half of the sample were men; and the majority of patients were white. The majority (72%) of patients had a history of HF, and many patients had renal insufficiency (35%), diabetes (48%), and previous hospitalization for HF (38%).

Baseline differences. Patients with preserved EF tended to be older and female and were more likely to have a history of hypertension, whereas patients with depressed EF were more likely to have a longer history of HF, arrhythmia, and clinically manifest coronary artery disease. Differences existed in quality-of-life measures, with patients with preserved EF having significantly greater functional limitations at baseline, but having a trend toward a lower frequency of severe dyspnea and better general health status (Table 2).

Outcomes. MORTALITY. A total of 70 patients (17%) died. Patients with depressed EF had a higher death rate during follow-up, as compared with patients with preserved EF (21% vs. 13%; p = 0.02) (Table 3). The proportion of patients who died decreased with greater EF: EF ≤20% (30%; n = 26), EF 21% to 40% (16%; n = 25), EF 41% to 54% (11%; n = 6), and EF ≥55% (11%; n = 13) (p = 0.001

Table 5. Subsidary Multivariate Analyses

Outcome	HR or OR	95% CI	p Value
Adjusting for patients with CAD (n = 413)			
Mortality	0.51	0.27–0.96	0.04
Readmission (all-cause)	1.03	0.73–1.45	0.86
Readmission (HF only)	0.73	0.35–1.52	0.40
Functional decline	1.60	0.84–3.07	0.15
Including only patients with current EF (measured during index admission; n = 295)			
Mortality	0.40	0.18–0.88	0.02
Readmission (all-cause)	0.93	0.60–1.44	0.75
Readmission (HF only)	1.07	0.39–2.97	0.90
Functional decline	1.49	0.67–3.31	0.42
Including only patients with current and quantitative EF assessments (n = 274)			
Mortality	0.51	0.27–0.96	0.04
Readmission (all-cause)	0.96	0.67–1.39	0.84
Readmission (HF only)	0.74	0.35–1.55	0.43
Functional decline	1.60	0.81–3.17	0.40
Including only patients without aortic stenosis (n = 390)			
Mortality	0.40	0.20–0.79	0.009
Readmission (all-cause)	0.97	0.68–1.40	0.87
Readmission (HF only)	0.77	0.38–1.56	0.46
Functional decline	1.47	0.76–2.86	0.40
Preserved EF defined as ≥50% (n = 413)			
Mortality	0.42	0.20–0.89	0.02
Readmission (all-cause)	0.98	0.68–1.41	0.90
Readmission (HF only)	1.26	0.57–2.78	0.57
Functional decline	1.13	0.69–2.17	0.72

CAD = coronary artery disease; other abbreviations as in Tables 2 and 4.

for trend). After adjusting for age, gender, systolic blood pressure, serum creatinine, diabetes, baseline ADL, and discharge medications (angiotensin-converting enzyme [ACE] inhibitors and diuretics), preserved EF was significantly associated with better survival (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.27 to 0.96; p = 0.04) (Table 4). Adjusting for coronary artery disease did not change the results (Table 5). Survival curves are presented in Figure 1.

READMISSION. A total of 190 patients (46%) were readmitted for any cause, with 77 (19%) readmitted for HF; the total number of readmissions during follow-up was 346. After adjusting for age, gender, history of HF, years of HF, baseline creatinine, baseline ADL, and discharge medications (ACE inhibitors, diuretics, and digoxin), preserved EF was not associated with an increased risk of all-cause readmission (HR 1.01, 95% CI 0.72 to 1.43; p = 0.96) or HF readmission (HR 0.77, 95% CI 0.38 to 1.56; p = 0.46) (Table 4). For all models, proportionality assumptions were met, and residual plots indicated adequate fit and no outliers.

FUNCTIONAL STATUS AND DYSPNEA. Baseline functional status and dyspnea reflected the patients' limitations and symptoms in the month before hospitalization. Although there was a trend toward more functional limitations at baseline for patients with preserved EF, this difference was not significant (Table 2). Among those with limitations, the distribution of the number of disabilities was similar in both groups, and distributions indicated that floor effects were minimal. The most commonly indicated limitations for all patients were an inability to bathe (n = 69; 17%) or dress (n = 57; 14%) without help.

At baseline, significantly fewer patients with preserved EF reported severe, function-limiting dyspnea, compared with patients with depressed EF (odds ratio [OR] 0.62, 95% CI 0.44 to 0.86; p = 0.004). When EF was categorized ordinally, the proportion of patients experiencing dyspnea at baseline decreased with increasing EF, at 39% (n = 34), 27% (n = 42), 26% (n = 14), and 16% (n = 19) (p = 0.001 for trend).

DECLINE IN FUNCTIONAL STATUS. Of the 316 surviving patients, 84 (27%) experienced a decline in ADL at six months. For patients with preserved EF, 30% experienced a decline in ADL, compared with 23% of patients with depressed EF (unadjusted OR 1.46, 95% CI 0.90 to 2.48; p = 0.14) (Table 3, Fig. 2). The proportion of survivors experiencing a functional decline increased with increasing EF: ≤20% (20%; n = 11), 21% to 40% (24%; n = 28), 41% to 54% (28%; n = 12), and ≥55% (33%; n = 33) (p = 0.04 for trend). Patients with preserved EF had a significantly higher number of functional limitations at follow-up (p = 0.02) (Table 3).

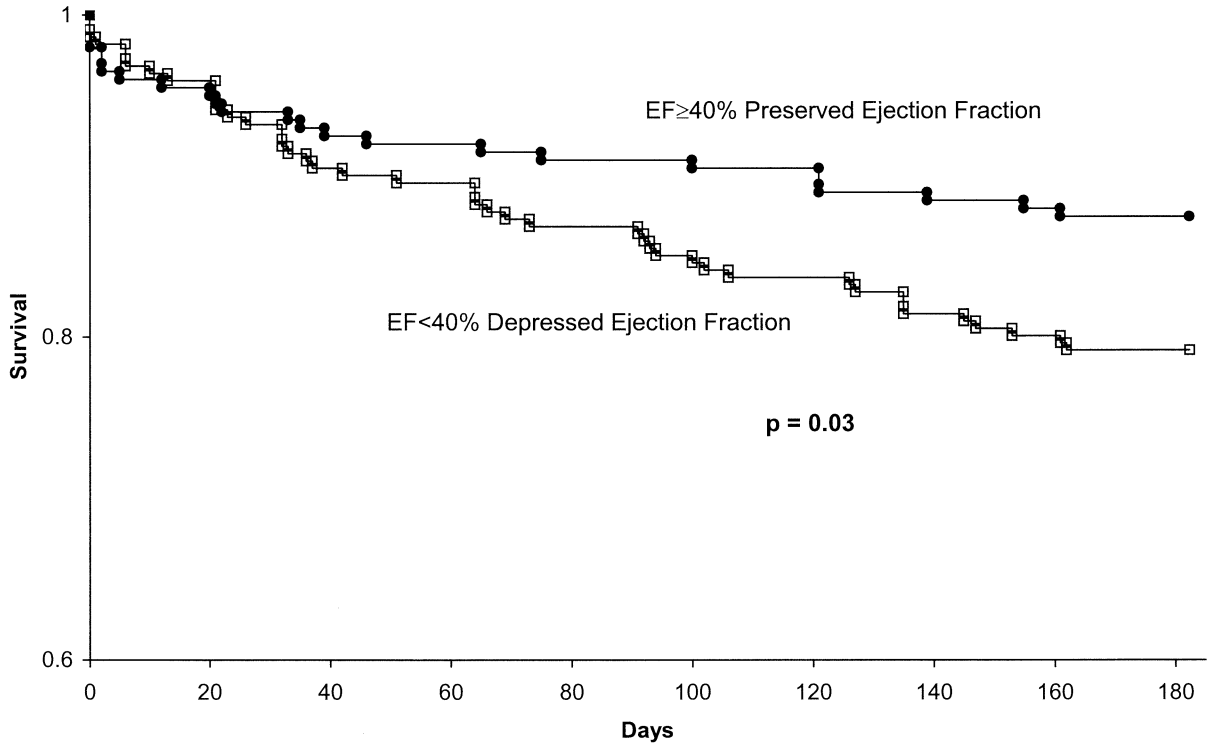

Figure 1. Proportional hazards model of adjusted overall survival. EF = ejection fraction.

For the combined outcome of functional decline or death, after adjusting for age, gender, race, systolic blood pressure, history of chronic stable angina, baseline ADL, baseline dyspnea, and discharge medications (ACE inhibitors, diuretics, and digoxin), patients with preserved EF showed no difference in the odds of a decline in ADL or death (OR 0.98, 95% CI 0.57 to 1.69; p = 0.63), and survivors showed no difference in the odds of a decline in ADL (Table 4). In this model, the likelihood ratio test for the overall effect of cardiac history variables was marginally significant (p = 0.07). The Hosmer-Lemeshow goodness-of-fit test indicated a satisfactory model fit, and the *c* statistic for this model was 0.65.

Subsidiary analyses. Multivariable analyses that included the 305 patients with HF definitively diagnosed by chest radiograph were similar to those for the entire sample. Analyses restricted to the 295 patients with EF assessment during the index admission, the 274 patients with quantitative EF assessment during the index admission, and the 390 patients without aortic stenosis also showed no substantial differences.

A total of 8% (n = 31) of patients had EF between 40% and 50%. When preserved EF was defined as ≥50%, the results for all models remained similar. Preserved EF was significantly associated with better survival (HR 0.42, 95% CI 0.20 to 0.89; p = 0.02) and was not associated with an increased risk of all-cause readmission, HF readmission, or odds of functional decline (Table 5).

DISCUSSION

Heart failure with preserved EF confers a considerable burden on patients and portends a prognosis similar to that of patients with depressed EF. Patients with EF ≥40% have a substantial risk of adverse clinical outcomes, disability, and symptoms after hospital discharge, at least as great as morbidity the risk experienced by patients with depressed EF. Our results showed that although survival was better in patients with preserved EF, the absolute rate of death was still high: 13% of patients died by six months. Patients with preserved EF did not have a lower risk of hospital readmission or functional decline, compared with patients with depressed EF, and experienced comparable levels of dyspnea after discharge.

In a review of HF, Gaasch (5) notes the poor outcomes of patients with depressed EF, but also states that the prognosis of patients with preserved EF is "not as ominous," a conclusion that numerous other investigators have supported (3,7,31). In contrast to this conventional wisdom, Senni and Redfield (16) recently challenged this conclusion in another review comparing mortality rates in HF. We have demonstrated that both groups of patients experience poor trajectories after hospitalization for an episode of HF.

Natural history of HF with preserved EF. Several studies indicate better survival in patients with preserved EF. Annual mortality in the Veterans Administration Heart Failure (clinical) Trial (V-HeFT) was 8% for preserved EF, versus 19% for patients with depressed EF (3). In the

JACC Vol. 41, No. 9, 2003
May 7, 2003:1510–8

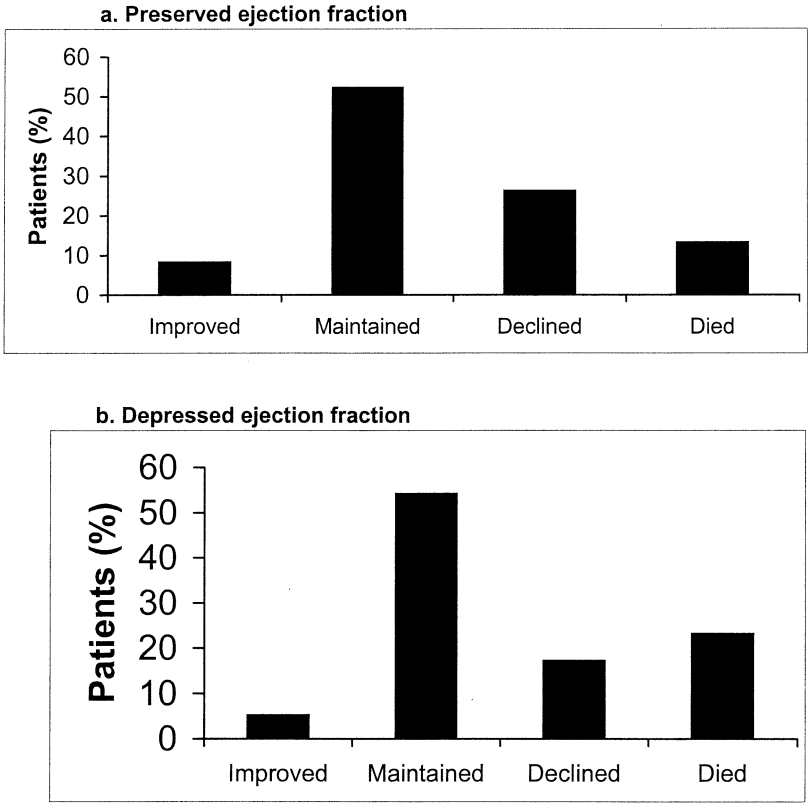

Figure 2. Death and functional status changes at follow-up.

Digitalis Intervention Group study, mortality was 23% for preserved EF, versus 35% for depressed EF, over a mean follow-up of about three years (32). A recent study based on consecutive hospital admissions for HF found a 17% six-month mortality rate in patients with preserved EF, versus 23% for depressed EF (33). Our study similarly exhibited six-month mortality rates of 13% and 21%, respectively. Other studies report no differences in survival (2,9–15); however, in contrast to those cohorts, our sample was selected from consecutive hospital admissions and adjusted for numerous clinical cofactors. Although data from the Rochester Epidemiology Project show no significant survival difference, there appears to be a trend over time toward better survival in patients with preserved EF (10). Vasan et al. (9) showed no statistically significant difference in the risk of death after adjustment for gender, but the they acknowledged this result could be due to the small sample size. Additionally, our results show that although mortality for patients with preserved EF may be lower, the absolute burden of mortality is still substantial, particularly compared with the annual mortality rate of 3% for a gender- and age-matched population, based on national survey data (34).

Several studies reporting lower rates of HF readmissions for patients with preserved EF (2,11) did not control for a history of HF and comorbidities. Our analysis provides a more detailed picture of the comparable risk of all-cause and HF readmissions after considering other clinical features. Moreover, independent of EF, the absolute burden of readmission is considerable, with nearly half of both groups experiencing at least one hospital readmission within six months. The readmission rates in our cohort are higher than those in some clinical trials and cohort studies (10,32), as those studies recruited stable outpatients or patients with new-onset HF. The rates in our study, however, are similar to the rates of readmission in other studies of hospitalized HF patients (29,35).

A functional decline in HF patients surviving with preserved EF has not been examined in previous studies. In our study, a functional decline occurred in over a quarter of survivors. Patients with preserved EF presented with more functional limitations on hospital admission and follow-up, and their risk of death or functional decline after discharge was not better than that of patients with depressed EF. These results underscore the need to define optimal management strategies for patients with preserved EF to reduce symptoms and morbidity, especially as preventing a decline in quality of life becomes an increasingly important goal of therapy.

Although a functional decline alone is an important outcome that has not yet been addressed in previous studies, it is difficult to assess during follow-up because of the competing risk of death. Using a combined end point may obscure the distinct risks for these different adverse outcomes. Both suggest a poor prognosis, although better survival with poorer functional status suggests a chronic, costly, and burdensome outcome. Although a major goal of

therapy is to prolong life, improvement in the quality of life and a decrease in the risk of disability must also be considered.

Although six-month follow-up is shorter than that for population-based cohorts, a significant difference was detected for survival. Other studies have shown that substantial numbers of events, including readmission and functional decline, occur within this period for HF patients (29,35,36).

Study limitations. There are several issues to consider in our study. A retrospective chart review and variation in method and time of EF determination could cause misclassification of EF. Noise in measurements would likely be non-differential with respect to outcomes and could have biased the result toward null, particularly considering the results for readmission and functional decline. Analyses limited to patients with current EF assessments and with current quantitative EF assessments addressing this potential misclassification showed no impact on the findings. There is no consensus in the published data supporting one most appropriate definition of preserved EF. However, even analyses with the most restrictive definition showed similar findings. Additionally, a clinical event precipitating an admission could also have changed the EF. The evidence suggests, however, that transient systolic dysfunction among hospitalized HF patients with normal EF is rare (37).

Also, because our study was not population-based and patients were recruited over the period of 1996 to 1998, the absolute rates of mortality, hospital admission, and functional decline may not be generalizable to all HF patients. However, medical therapy for patients with preserved EF has not changed significantly over this period, and thus the time lag would likely not affect the effect size of our findings. Strikingly, the mortality rates in the majority of studies are similar to our results, with about half the risk of death for patients with preserved EF, despite differences in study sample sources and absolute rates of events. Furthermore, although we screened consecutive hospital admissions, we did not likely capture the full spectrum of HF patients, particularly those with less severe symptoms, which may impact the generalizability of our findings. Readmissions may have occurred at other institutions, although subsample analysis suggests that 95% of readmissions occurred at our institution.

Conclusions. The clinical trajectory for HF with preserved EF may not be as relatively benign as previously described. Our study shows that patients with relatively normal EF still experience substantial mortality, readmission, disability, and symptoms after hospitalization. Previous studies tend to ignore that the referent for comparisons (HF with depressed EF) is a particularly morbid and lethal condition and obscures the absolute impact of HF with preserved EF. Our data provide a wider spectrum of the burden of this disease, especially illuminating patterns of high rates of hospital readmission and functional decline after discharge. Trials of HF treatments have generally excluded HF patients with preserved EF, and to many clinicians, HF is almost synonymous with systolic dysfunction. These data indicate the need to better define disease management strategies for patients with preserved EF. Our results challenge the present characterization of this disease, highlighting the significant burdens attributed to death, readmission, and functional decline.

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REFERENCES

1. Vasan R, Benjamin E, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26:1565–74.
2. Pernenkil R, Vinson J, Shah A, Beckham V, Wittenberg C, Rich M. Course and prognosis in patients > or = 70 years of age with congestive heart failure and normal versus abnormal left ventricular ejection fraction. Am J Cardiol 1997;79:216–9.
3. Cohn J, Johnson G, the Veterans Administration Cooperative Study Group. Heart failure with normal ejection fraction: the V-HeFT study. Circulation 1990;81 Suppl III::III48–53.
4. Rodeheffer R, Jacobsen S, Gersh B, et al. The incidence and prevalence of congestive heart failure in Rochester, Minnesota. Mayo Clin Proc 1993;68:1143–50.
5. Gaasch W. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. JAMA 1994;271:1276–80.
6. Cohn JN, Rector TS. Prognosis of congestive heart failure and predictors of mortality. Am J Cardiol 1988;62:25A–30A.
7. Ghali J, Kadakia S, Bhatt A, Cooper R, Liao Y. Survival of heart failure patients with preserved versus impaired systolic function: the prognostic implication of blood pressure. Am Heart J 1992;123:993–7.
8. Brogan W, Hillis L, Flores E, Lange R. The natural history of isolated left ventricular diastolic dysfunction. Am J Med 1992;92:627–30.
9. Vasan R, Larson M, Benjamin E, Evans J, Reis C, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.
10. Senni M, Tribouillowy C, Rodenheffer R, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–9.
11. McGrae McDermott M, Feinglass J, Lee P, et al. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. Am Heart J 1997;134:728–36.
12. Kupari M, Lindroos M, Iivanainen AM, Heikkila J, Tilvis R. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med 1997;241:387–94.
13. McAlister FA, Teo KK, Taher M, et al. Insights into the contemporary epidemiology and outpatient management of congestive heart failure. Am Heart J 1999;138:87–94.
14. Chen H, Lainchbury H, Senni M, Redfield MM. Factors influencing survival in patients with diastolic heart failure in Olmsted County, MN, in 1996–97 (abstr). Circulation 2000;102 Suppl II:II412.
15. Ansari M, Tutar A, Bullard J, Teerlink J, Massie B. Heart failure in a veteran cohort: predictors of outcome (abstr). J Am Coll Cardiol 2001;37 Suppl:158A.
16. Senni M, Redfield MM. Heart failure with preserved systolic function: a different natural history? J Am Coll Cardiol 2001;38:1277–82.
17. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992;20:301–6.

18. Harlan WR, Oberman A, Grimm R, Rosati RA. Chronic congestive heart failure in coronary artery disease: clinical criteria. Ann Intern Med 1977;86:133–8.
19. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline and death in patients with heart failure. J Am Coll Cardiol 2001;38:199–205.
20. Pfeffer MA, Braunwald E, Moye LA, et al., the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival And Ventricular Enlargement trial. N Engl J Med 1992;327: 669–77.
21. Mahler D, Weinberg D, Wells C, Feinstein A. The measurement of dyspnea: contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;85:751–8.
22. Feinstein A, Fisher M, Pigeon J. Changes in dyspnea-fatigue ratings as indicators of quality of life in the treatment of congestive heart failure. Am J Cardiol 1989;64:50–5.
23. Katz S, Downs T, Cash H, Grotz R. Progress in development of the index of ADL. Gerontologist 1970;10:20–30.
24. Smith L, Branch L, Scherr P, et al. Short-term variability of measures of physical function in older people. J Am Geriatr Soc 1990;38:993–8.
25. Jaagosild P, Dawson NV, Thomas C, et al., the Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments (SUPPORT) Investigators. Outcomes of acute exacerbation of severe congestive heart failure: quality of life, resource use, and survival. Arch Intern Med 1998;158:1081–9.
26. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA 2001;285:2987–94.
27. Rector T, Cohn J. Assessment of patient outcome with the Minnesota Living with Heart Failure Questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimibendan. Am Heart J 1992;124:1017–25.
28. Green C, Porter C, Bersnahan D, Spertus J. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–55.
29. Krumholz H, Chen Y, Wang Y, Vaccarino B, Radford M, Horwitz R. Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J 2000;139:72–7.
30. Aronow W, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older men and women with abnormal versus normal left ventricular ejection fraction. Am J Cardiol 2000;85:1382–4.
31. Diller P, Smucker D, David B, Graham R. Congestive heart failure due to diastolic or systolic dysfunction: frequency and patient characteristics in an ambulatory setting. Arch Fam Med 1999;8:414–20.
32. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336: 525–33.
33. Philbin E, Rocco T Jr., Lindenmuth N, Ulrich K, Jenkins P. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. Am J Med 2000;109:605–13.
34. United States Life Tables, 1999. National Vital Statistics Reports. Hyattsville, MD: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS), 2002;50:1–39.
35. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch Intern Med 1997;157:99–104.
36. Vaccarino V, Gahbauer E, Kasl SV, Charpentier PA, Acampora D, Krumholz HM. Differences between African Americans and whites in the outcome of heart failure: evidence for a greater functional decline in African Americans. Am Heart J 2002;143:1058–67.
37. Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17–22.