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Characteristics, Treatments, and Outcomes of Patients With Preserved Systolic Function Hospitalized for Heart Failure

A Report From the OPTIMIZE-HF Registry

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Objectives We sought to evaluate the characteristics, treatments, and outcomes of patients with preserved and reduced systolic function heart failure (HF).

Background Heart failure with preserved systolic function (PSF) is common but not well understood.

Methods This analysis of the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry compared 20,118 patients with left ventricular systolic dysfunction (LVSD) and 21,149 patients with PSF (left ventricular ejection fraction [EF] ≥40%). Sixty- to 90-day follow-up was obtained in a pre-specified 10% sample of patients. Analyses of patients with PSF defined as EF >50% were also performed for comparison.

Results Patients with PSF (EF ≥40%) were more likely to be older, female, and Caucasian and to have a nonischemic etiology. Although length of hospital stay was the same in both groups, risk of in-hospital mortality was lower in patients with PSF (EF ≥40%) (2.9% vs. 3.9%; $p < 0.0001$). During 60- to 90-day post-discharge follow-up, patients with PSF (EF ≥40%) had a similar mortality risk (9.5% vs. 9.8%; $p = 0.459$) and rehospitalization rates (29.2% vs. 29.9%; $p = 0.591$) compared with patients with LVSD. Findings were comparable with those with PSF defined as EF >50%. In a risk- and propensity-adjusted model, there were no significant relationships between discharge use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or beta-blocker and 60- to 90-day mortality and rehospitalization rates in patients with PSF.

Conclusions Data from the OPTIMIZE-HF registry reveal a high prevalence of HF with PSF, and these patients have a similar post-discharge mortality risk and equally high rates of rehospitalization as patients with HF and LVSD. Despite the burden to patients and health care systems, data are lacking on effective management strategies for patients with HF and PSF. (Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure [OPTIMIZE-HF]); http://www.clinicaltrials.gov/ct/show/NCT00344513?order=1; NCT00344513) (J Am Coll Cardiol 2007;50:768–77) © 2007 by the American College of Cardiology Foundation

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A substantial portion of patients with heart failure (HF) have relatively normal or preserved systolic function (PSF). Heart failure with PSF has been defined as the presence of HF symptoms in patients with a documented left ventricular ejection fraction (EF) of >40% or >50%, depending on the study (1,2). Clinical trials of HF therapies have typically required patients to have left ventricular systolic dysfunction (LVSD) with reduced EF (3–7). Consequently, few data are available in patients with HF and PSF that describe outcomes or guide management strategies; this lack of evidence is problematic, because these patients are frequently hospitalized for HF (2,3,5). Earlier studies suggest that patients with HF and PSF differ from those with HF and LVSD in both their characteristics and clinical outcomes, but these studies are limited by small and/or selective populations (8–10).

The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) is a large national registry and performance-improvement program for patients hospitalized for HF (11). The OPTIMIZE-HF registry included patients with and without reduced EF; thus, it presents an opportunity to evaluate the characteristics, treatments, and outcomes of a large unselected population of patients with PSF who require hospitalization to manage their HF. The present report describes the characteristics, hospital course, and post-discharge outcomes of patients with LVSD and patients with PSF at the time of hospitalization for HF.

Methods

The OPTIMIZE-HF design and methods have been published previously (11,12). Briefly, eligible patients were those hospitalized with new-onset or worsening pre-existing HF as the primary cause of admission or those with significant HF symptoms that developed during the hospitalization where HF was the primary discharge diagnosis. Patients were considered to have PSF if EF was documented as ≥40% or, if not quantified, qualitatively normal or mildly impaired. Because variable definitions of PSF have been used in earlier studies, additional analyses for patients with PSF and a documented EF between 40% and 50% as well as patients with a documented EF >50% were also considered for comparison. Patients considered to have LVSD were those with EF <40% or moderate/severe left ventricular dysfunction by qualitative assessment.

Study components included a web-based registry, which collected detailed patient data including demographics, medical history, signs and symptoms, medications, laboratories, diagnostic testing, procedures, discharge status, and adherence to performance indicators. Sites could view and analyze their adherence to benchmarked performance measures in real time. The registry coordinating center was Outcome Sciences (Cambridge, Massachusetts). The process-of-care improvement program provided participating hospitals with a comprehensive tool kit including evidence-based best-practice algorithms, standing orders, and discharge checklists. These tools were based on published HF guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) and the Heart Failure Society of America (HFSA) (13,14). Algorithms focused on patients with LVSD, because no evidence-based therapies were available for PSF. Recommendations for PSF included complete discharge instructions, smoking-cessation counseling, anticoagulation and ventricular rate control for atrial fibrillation, hypertension control, and diuretics for volume control.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
EF = ejection fraction
HF = heart failure
LVSD = left ventricular systolic dysfunction
PSF = preserved systolic function

The incidence of death or rehospitalization within 60 to 90 days was prospectively collected on a pre-specified 10% subset of the total OPTIMIZE-HF population (11,12). The protocol was approved by each participating center's institutional review board or by a central institutional review board. Written informed consent was obtained from patients who participated in the follow-up data collection before enrollment.

All statistical analyses were conducted independently by the Duke Clinical Research Institute, Durham, North Carolina. Data are reported as mean and standard deviation for continuous variables or percentages of nonmissing values for categoric variables. Patient characteristics and treatments were compared using the Pearson chi-square test for categoric variables and the Wilcoxon test for continuous variables. Performance measures were constructed among eligible patients without specific contraindications, intolerance, or other physician-documented reasons, as previously described (15). The unadjusted relationships between presence of PSF and outcomes were tested using Pearson chi-square test for categoric variables and the Wilcoxon test for continuous variables. Previously developed models of in-hospital mortality, mortality from hospital discharge to 90 days, and post-discharge mortality or rehospitalization were used to adjust for significant covariates (12). Logistic regression modeling was used for in-hospital mortality. Cox proportional hazard modeling was applied to all-cause mortality in the follow-up period, and logistic regression modeling was used for the composite end point. The assumption of linearity was evaluated for the continuous measures using restricted cubic splines, and, when violated appropriate linear spline transformations were applied (Appendix). For the Cox model, the proportional hazard assumption was assessed. Variable selection techniques included backward, forward-stepwise, and bootstrapping the backward selection process of 100 replicated samples to obtain the percentage of time each variable was retained in the model and the variation in parameter estimates across the bootstrapped samples. A p value of 0.05 was used for

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both entry and retention in the model during the selection process. The variables that were common in each and chosen in at least 75% of the replicated samples were retained. The final model for each end point was also bootstrapped to obtain an estimate of the C-statistic after accounting for the overfitting of testing and creating the model on the same population. All the variables retained in the final models are used as adjusted variables (Appendix). Propensity score analysis was used to account for medication selection bias when looking at the association between the medication and outcome. The variables selected for the score were applied to a logistic regression model with the probability of receiving the medication generated as the score. Generalized estimating equations were used to account for the correlation of the data within the same hospital in the adjusted models. For all statistical analyses, SAS version 8.2 (SAS Institute, Cary, North Carolina) was used.

Results

Baseline characteristics. Of the 48,612 patients hospitalized for HF at 259 hospitals, 41,267 (84.9%) had data for EF or a qualitative assessment of left ventricular function and were included in this analysis. Overall, patients enrolled in the OPTIMIZE-HF registry displayed a wide distribution of EF values (Fig. 1). Of the patients with left ventricular function assessed, 21,149 (51.2%) had EF ≥40% or a qualitatively normal/mildly impaired EF and were classified as having HF with PSF. Among those patients with PSF and a quantitative EF of ≥40%, 7,321 patients had a documented EF ≥40% and ≤50% and 10,072 patients had a documented EF >50%. The baseline characteristics, history, and HF characteristics on admission for all patients included in this analysis are summarized in Table 1. Compared with LVSD patients, those with PSF were significantly older and were more often women; this group also included significantly fewer African Americans. Patients with PSF were also more likely to have a history of hypertension and a higher systolic blood pressure on admission. As expected, the mean EF was in the normal range for patients with PSF, but it was 24.3 ± 7.7 in those with LVSD, a lower value than that typically observed in HF clinical trials (3). The etiology of HF was ischemic in a higher percentage of patients with LVSD, whereas a hypertensive etiology was more common in those with PSF. The HF symptoms and routine laboratory measurements were similar in both groups on admission. B-type natriuretic peptide levels, though significantly lower in patients with PSF, were markedly elevated in both groups, consistent with acutely decompensated HF. On admission, a smaller percentage of patients with PSF were receiving angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, aldosterone antagonists, digoxin, and loop diuretics, but more PSF patients were receiving amlodipine and angiotensin receptor blockers (ARB). There were significant differences in characteristics seen within the PSF group in patients with EF between 40% and 50% and those with EF >50% (Table 1). The magnitude of these differences was generally smaller than those observed between patients with PSF and LVSD.

Hospital course and management. Intravenous vasodilators were used in 17% of LVSD patients and 12% of PSF patients ($p < 0.0001$). Inotropes were used infrequently, with 12% and 4% of LVSD and PSF patients, respectively, receiving therapy ($p < 0.0001$). The overall use of in-hospital procedures (coronary angiography, cardioversion, mechanical ventilatory or circulatory support, and so forth) was low, although a higher proportion of LVSD patients received a procedure compared with PSF patients (29% vs.

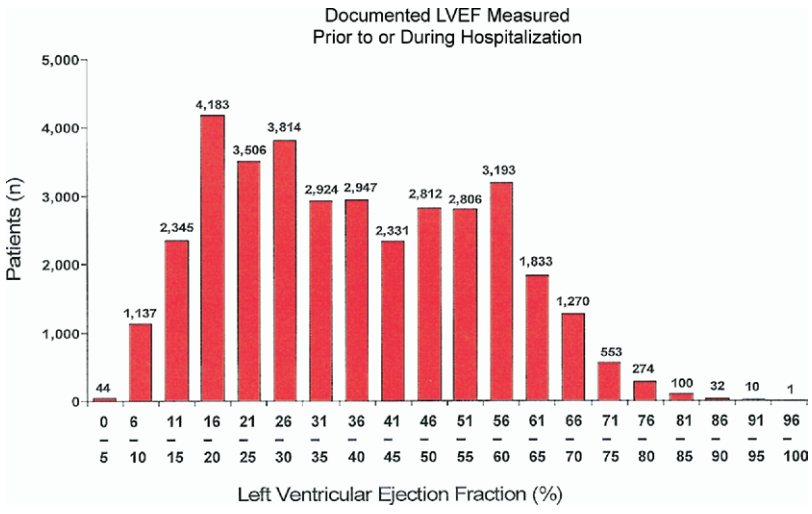

Figure 1 **Distribution of Patients' LVEFs**

Histogram of left ventricular ejection fraction (LVEF) in patients hospitalized with a primary discharge diagnosis of heart failure.

Table 1 Baseline Patient Characteristics, Heart Failure History, and Findings on Admission by Ventricular Function

Characteristics at Admission	Patients With LVSD (n = 20,118)	Patients With PSF (n = 21,149)	p Value (LVSD vs. PSF)	Patients With 40% ≤ EF ≤ 50% (n = 7,321)	Patients With EF >50% (n = 10,072)	p Value (40% ≤ EF ≤ 50% vs. EF >50%)
Demographics						
Mean age (yrs)	70.4 ± 14.3	75.1 ± 13.1	<0.0001	74.3 ± 13.0	75.6 ± 13.1	<0.0001
Male (%)	62	38	<0.0001	48	32	<0.0001
Caucasian (%)	71	77	<0.0001	78	77	0.086
African American (%)	21	15	<0.0001	15	15	0.880
Medical history (%)						
Diabetes, insulin-treated	15	17	<0.0001	18	16	0.013
Diabetes, noninsulin-treated	24	26	0.009	26	25	0.418
Hypertension	66	76	<0.0001	74	77	<0.0001
Hyperlipidemia	34	32	<0.0001	35	31	<0.0001
Atrial arrhythmia	28	33	<0.0001	33	32	0.179
Vital signs on admission						
Median body weight (kg [25th, 75th percentile])	78.5 [65.8, 94.0]	78.9 [64.0, 97.5]	0.019	79.4 [65.0, 97.5]	78.0 [63.5, 97.1]	0.002
Mean heart rate (beats/min)	89 ± 22	85 ± 21	<0.0001	86 ± 21	84 ± 21	<0.0001
Mean SBP (mm Hg)	135 ± 31	149 ± 33	<0.0001	147 ± 33	150 ± 33	<0.0001
Mean DBP (mm Hg)	77 ± 19	76 ± 19	<0.0001	77 ± 19	75 ± 19	<0.0001
Etiology (%)						
Ischemic	54	38	<0.0001	49	32	<0.0001
Hypertensive	17	28	<0.0001	22	31	<0.0001
Idiopathic	18	21	<0.0001	18	23	<0.0001
Findings on admission (%)						
Acute pulmonary edema	3	2	0.270	2	3	0.362
Chest pain	23	24	0.512	24	24	0.618
Uncontrolled hypertension	9	12	<0.0001	11	12	0.075
Dyspnea at rest	44	44	0.194	46	44	0.022
Dyspnea on exertion	63	62	0.206	62	62	0.719
Rales	63	65	0.001	67	63	<0.0001
Lower extremity edema	62	68	<0.0001	68	68	0.211
Jugular venous pulsation	33	26	<0.0001	32	29	0.0005
Left ventricular EF (mean %)	24.3 ± 7.7	54.7 ± 10.2	<0.0001	45.0 ± 4.0	61.8 ± 7.0	<0.0001
Laboratory values						
Mean serum sodium (mEq/l)	137.7 ± 4.6	137.9 ± 4.8	<0.0001	137.9 ± 4.7	137.8 ± 4.8	0.090
Median serum creatinine (mg/dl [25th, 75th percentile])	1.4 [1.1, 1.9]	1.3 [1.0, 1.8]	<0.0001	1.3 [1.0, 1.9]	1.2 [1.0, 1.8]	<0.0001
Mean serum hemoglobin (g/dl)	12.5 ± 2.0	11.9 ± 2.0	<0.0001	11.9 ± 2.0	11.8 ± 2.0	0.0001
Median BNP (pg/ml [25th, 75th percentile])	1,170.0 [603.0, 2,280.0]	601.5 [320.0, 1,190.0]	<0.0001	757.0 [400.0, 1,460.0]	537.0 [287.0, 996.5]	<0.0001
Median troponin I (ng/ml [25th, 75th percentile])	0.1 [0.1, 0.3]	0.1 [0.0, 0.3]	<0.0001	0.1 [0.1, 0.3]	0.1 [0.0, 0.3]	<0.0001
Medications on admission (%)						
ACE inhibitor	45	36	<0.0001	38	34	<0.0001
ARB	11	13	<0.0001	12	14	0.0001
Amlodipine	5	10	<0.0001	9	11	<0.0001
Aldosterone antagonist	10	5	<0.0001	6	4	<0.0001
Beta-blocker	56	52	<0.0001	54	50	<0.0001
Loop diuretic	63	58	<0.0001	59	57	0.039
Digoxin	30	17	<0.0001	19	15	<0.0001
Aspirin	42	38	<0.0001	41	36	<0.0001
Antiarrhythmic	13	8	<0.0001	10	8	<0.0001
Hydralazine	3	3	0.021	3	3	0.346
Nitrate	22	21	0.013	23	20	<0.0001
Statin*	40	39	0.021	41	37	<0.0001

*Statin use among patients with coronary artery disease, cerebrovascular disease/transient ischemic attack, diabetes, hyperlipidemia, or peripheral vascular disease.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; DBP = diastolic blood pressure; EF = ejection fraction; LVSD = left ventricular systolic dysfunction; PSF = preserved systolic function; SBP = systolic blood pressure; SD = standard deviation.

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Table 2 Patient Examination Findings and Clinical Status at Hospital Discharge by Ventricular Function

Characteristics at Discharge	Patients With LVSD (n = 20,118)	Patients With PSF (n = 21,149)	p Value (LVSD vs. PSF)	Patients With 40% ≤ EF ≤ 50% (n = 7,321)	Patients With EF >50% (n = 10,072)	p Value (40% ≤ EF ≤ 50% vs. EF >50%)
Median weight change from admission (kg [25th, 75th percentile])	−2.0 [−5.0, 0.0]	−2.0 [−4.5, 0.0]	<0.0001	−2.0 [−4.5, 0.0]	−1.9 [−4.1, 0.0]	0.006
Median BNP (pg/ml [25th, 75th percentile])	782.0 [408.0, 1,650.0]	432.0 [223.0, 820.5]	<0.0001	527.5 [282.0, 1,027.0]	390.0 [206.0, 736.0]	<0.0001
Median serum creatinine (mg/dl [25th, 75th percentile])	1.4 [1.1, 1.9]	1.3 [1.0, 1.9]	<0.0001	1.4 [1.0, 1.9]	1.3 [1.0, 1.8]	<0.0001
Mean heart rate (beats/min)	77.0 ± 14.1	74.9 ± 14.0	<0.0001	74.9 ± 13.8	74.5 ± 13.9	0.103
Mean SBP (mm Hg)	119.0 ± 21.0	129.4 ± 22.3	<0.0001	128.3 ± 22.0	130.3 ± 22.5	<0.0001
Jugular venous pulsation (%)	4	2	<0.0001	2	2	0.004
Rales (%)	15	15	0.866	15	15	0.958
Lower extremity edema (%)	25	28	<0.0001	28	28	0.692
HF symptoms at discharge (%)			<0.0001			0.993
Worse	2.4	1.8		1.8	1.7	
Unchanged	1.8	1.1		1.2	1.2	
Better, symptomatic	41.0	41.5		42.2	42.3	
Better, asymptomatic	50.0	51.1		50.1	50.2	
Unable to determine	4.9	4.5		4.7	4.6	
Medications at discharge (%)						
ACE inhibitor	62	48	<0.0001	52	44	<0.0001
ARB	11	13	<0.0001	12	14	0.0007
Amlodipine	5	10	<0.0001	10	11	0.002
Aldosterone antagonist	18	8	<0.0001	10	7	<0.0001
Beta-blocker	73	60	<0.0001	66	57	<0.0001
Loop diuretic	77	73	<0.0001	74	72	0.001
Digoxin	38	19	<0.0001	22	17	<0.0001
Aspirin	51	45	<0.0001	48	43	<0.0001
Antiarrhythmic	15	9	<0.0001	11	9	<0.0001
Hydralazine	5	4	0.006	5	4	0.0158
Nitrate	24	25	0.256	28	23	<0.0001
Statin*	42	39	<0.0001	42	37	<0.0001

*Statin use among patients with coronary artery disease, cerebrovascular disease/transient ischemic attack, diabetes, hyperlipidemia, or peripheral vascular disease.
Abbreviations as in Table 1.

18%; $p < 0.0001$). At the time of discharge, statistically significant differences in weight loss, HF symptoms, and certain other clinical variables were observed between patients with LVSD and PSF (Table 2). These statistical differences were likely detected owing to the large population size, but the values for these variables were clinically similar. Overall, patients with LVSD and PSF were equally likely to be discharged with symptoms of congestion. Patterns of medication use at hospital discharge were somewhat similar to those at admission, with a lower percentage of patients with PSF than with LVSD receiving ACE inhibitors and beta-blockers (Table 2). Whereas the percentage of patients with LVSD taking an ACE inhibitor increased from 45% on admission to 62% at hospital discharge ($p < 0.0001$), the increase in ACE inhibitor usage in the PSF group was smaller, rising from 36% to 48% ($p < 0.0001$). Similarly, beta-blocker usage increased from 56% to 73% in patients with LVSD ($p < 0.0001$) but increased from 52% to 60% in those with PSF ($p < 0.0001$). There were some modest differences in treatment patterns within the PSF group in patients with EF between 40% and 50% and those with EF >50% (Table 2).

Length of hospital stay was similar in both groups, averaging 6.0 ± 6.4 days (median 4 [interquartile range 3 to 7] days) in patients with LVSD and 5.7 ± 5.5 days (median 4 [3 to 7] days) in those with PSF. Unadjusted in-hospital mortality rates were significantly higher in patients with LVSD: 3.9% versus 2.9% for those with PSF (unadjusted odds ratio [OR] 1.34; 95% confidence interval [CI] 1.19 to 1.50; $p < 0.0001$). There were no differences in in-hospital outcomes seen within the PSF group in patients with EF between 40% and 50% and those with EF >50% (3.0% vs. 2.9%, respectively; $p = 0.65$) (Table 3).

Outcomes after hospital discharge. There was no significant difference in unadjusted all-cause mortality during 60- to 90-day post-discharge follow-up (Table 3, Fig. 2). Both groups experienced similarly high event rates: 9.8% in patients with LVSD and 9.5% in those with PSF ($p = 0.459$). There were no significant differences between groups in emergency room visits not leading to hospitaliza-

Table 3 Post-Discharge 60- to 90-Day Clinical Outcomes by Ventricular Function

Outcomes	Patients With LVSD (n = 20,118)	Patients With PSF (EF ≥40%) (n = 21,149)	p Value (LVSD vs. PSF)	Patients With 40% ≤ EF ≤ 50% (n = 7,321)	Patients With EF >50% (n = 10,072)	p Value (40% ≤ EF ≤ 50% vs. EF >50%)
In-hospital mortality: all patients (% [95% CI])	3.9 [3.6–4.2]	2.9 [2.7–3.1]	<0.0001	3.0 [2.6–3.4]	2.9 [2.5–3.2]	0.647
Follow-up cohort	(n = 2,604]	(n = 2,294]		(n = 962]	(n = 1,014]	
Post-discharge mortality at 60–90 days (% [95% CI])	9.8 [8.2–11.4]	9.5 [7.9–11.0]	0.459	9.2 [6.8–11.6]	9.3 [7.0–11.5]	0.887
Rehospitalization at 60–90 days (% [95% CI])	29.9 [28.1–31.6]	29.2 [28.1–31.6]	0.591	29.0 [26.1–31.9]	30.9 [28.0–33.7]	0.366
Post-discharge mortality/rehospitalization at 60–90 days (% [95% CI])	36.1 [34.3–37.9]	35.3 [33.4–37.3]	0.577	35.1 [32.1–38.2]	36.8 [33.8–39.8]	0.436

CI = confidence interval; other abbreviations as in Table 1.

tion (12% in both groups) or in rehospitalizations (29.9% in those with LVSD vs. 29.2% in those with PSF; p = 0.591) in the early follow-up period. The occurrence of death from any cause and/or rehospitalization was similarly high in both groups: 36.1% in those with LVSD and 35.3% in those with PSF (p = 0.577). Importantly, within the PSF group, there was no difference in post-discharge outcomes in patients with EF between 40% and 50% compared with those with EF >50% (Table 3).

Application of performance measures. The ACC and AHA have defined 5 performance measures for inpatients hospitalized with HF (16), 3 of which are irrespective of EF: receipt of complete discharge instructions, smoking-cessation counseling, and warfarin for atrial fibrillation. In the OPTIMIZE-HF registry, adherence to these measures was more frequent in patients with LVSD than in those with PSF (Fig. 3).

Multivariable analyses. After multivariable adjustment, the OR for in-hospital mortality for LVSD versus PSF was 1.28 (95% CI 1.13 to 1.46; p = 0.0002). The adjusted in-hospital mortality risk for patients with EF between 40% and 50% compared with those with EF >50% was similar: OR 1.02 (95% CI 0.86 to 1.20; p = 0.831). As a continuous variable, EF was an independent predictor of in-hospital mortality on multivariable analysis. In-hospital mortality decreased 17% for every 10% increase in EF up to 38% (OR 0.83, 95% CI 0.76 to 0.91; p < 0.0001). Left ventricular function was not further predictive of in-hospital mortality for EF values above 38%. The EF did not predict follow-up all-cause mortality or the combination of all-cause mortality and rehospitalization in the multivariable model.

Influence of pharmacologic therapy. In a risk- and propensity-adjusted model, there were no significant relationships between discharge use of a beta-blocker or an ACE inhibitor/ARB and 60- to 90-day mortality and rehospitalization rates in patients with PSF (Table 4). In contrast, patients with LVSD taking a beta-blocker at discharge experienced significantly lower risk- and propensity-adjusted all-cause mortality during 60 to 90 days of follow-up than those not taking a beta-blocker. In patients with LVSD, there was also lower risk- and propensity-adjusted mortality or rehospitalization rates associated with beta-blocker use, as well as a significant relationship between discharge use of ACE inhibitor/ARB and 60- to 90-day mortality or rehospitalization.

Discussion

Heart failure with PSF. The OPTIMIZE-HF registry provides a large dataset from which the characteristics, treatments, quality of care, and early outcomes for patients with HF and PSF can be evaluated. These results confirm previous observations that PSF is very common and accounts for a large proportion of patients hospitalized with HF outside the clinical trial setting (2–7). The ADHERE (Acute Decompensated Heart Failure National Registry) study included observations from more than 26,000 patients hospitalized with HF and PSF, and the ADHERE findings were remarkably similar to those of the OPTIMIZE-HF registry (2). Both datasets confirm that, demographically,

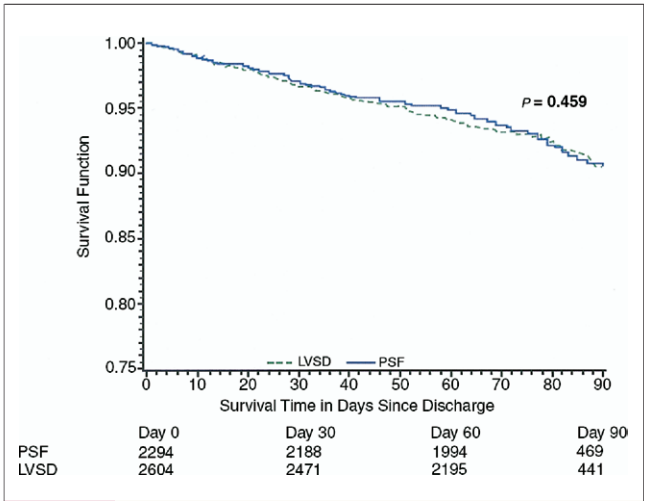

Figure 2 Survival After Hospital Discharge in Patients With LVSD Compared With PSF

Kaplan-Meier survival curves after hospital discharge in patients with left ventricular systolic dysfunction (LVSD) compared with patients with preserved systolic function (PSF) in the follow-up cohort.

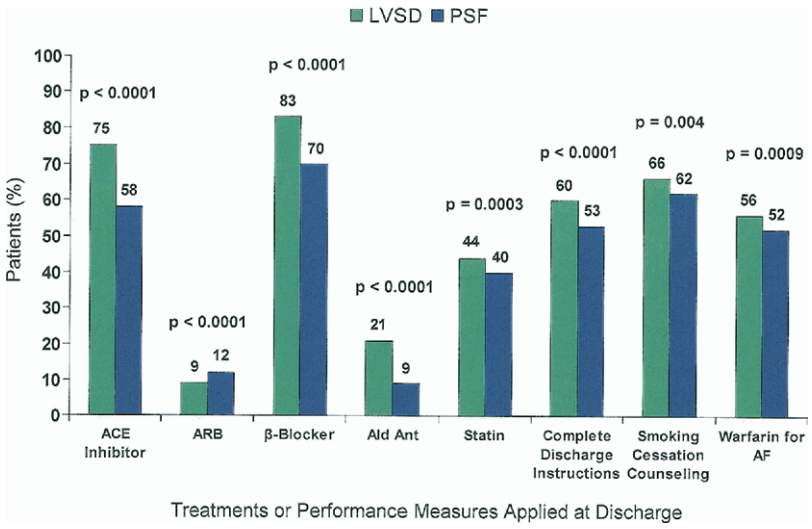

Figure 3 Discharge Medications and Application of Performance Measures in Patients With LVSD Compared With PSF

Note that only discharge instructions, smoking cessation counseling, and anticoagulation for AF are current American College of Cardiology/American Heart Association performance measures for which heart failure patients with PSF are included. ACE = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; Ald Ant = aldosterone antagonist; ARB = angiotensin receptor blocker; other abbreviations as in Figure 2.

patients with HF and PSF are usually older, more likely to be women, less likely to be African American, and more likely to have hypertension. Heart failure with PSF is also more likely to have a hypertensive rather than ischemic etiology (2,17). Despite more frequent hypertension and diabetes, African-American HF patients were more likely to have LVSD, which may reflect a substantially younger age at presentation. Data from both studies show that patients with PSF were not clinically distinguishable from those with LVSD in terms of HF symptoms or physical examination findings at admission, despite the differences in underlying patient characteristics and etiology. This clinical similarity between acutely decompensated HF patients with and without PSF has been noted previously (2,18). However, definitions for PSF have varied, and the choice of an appropriate EF cutoff has been subjected to debate. In the present analysis, findings were mostly similar whether PSF was defined as EF ≥40% or EF >50%, although patients with EF >50% were even more likely to be female and less likely to have an ischemic etiology.

Although both groups lost a similar amount of weight during the hospitalization, only one-half of the patients in each group had complete resolution of symptoms, and both groups were equally likely to be discharged with persistent

Table 4 Discharge Medications and Risk- and Propensity-Adjusted Outcomes After Hospital Discharge in Patients With Reduced and Preserved Systolic Function

Outcome	Hazard Ratio	95% Confidence Limits		Chi-Square	p Value
LVSD					
Mortality at 60–90 days					
ACE inhibitor/ARB vs. no ACE inhibitor/ARB	0.610	0.351	1.062	3.048	0.081
Beta-blocker vs. no beta-blocker	0.484	0.295	0.794	8.242	0.004
Mortality and/or rehospitalization at 60–90 days					
ACE inhibitor/ARB vs. no ACE inhibitor/ARB	0.515	0.339	0.781	9.797	0.002
Beta-blocker vs. no beta-blocker	0.727	0.550	0.960	5.062	0.025
PSF					
Mortality at 60–90 days					
ACE inhibitor/ARB vs. no ACE inhibitor/ARB	1.141	0.812	1.603	0.579	0.447
Beta-blocker vs. no beta-blocker	1.209	0.872	1.675	1.298	0.255
Mortality and/or rehospitalization at 60–90 days					
ACE inhibitor/ARB vs. no ACE inhibitor/ARB	0.909	0.692	1.196	0.462	0.497
Beta-blocker vs. no beta-blocker	0.923	0.723	1.179	0.410	0.523

Abbreviations as in Table 1.

signs of congestion. There was no significant difference in hospital length of stay for the 2 groups, and both groups exhibited similar change in HF symptom status. As in the ADHERE study (2), in-hospital mortality rates in patients with PSF were slightly lower than in patients with LVSD. Notably, at the time of hospital discharge, patients with PSF were less likely to receive ACE inhibitors, beta-blockers, or aldosterone antagonists, a result which mirrors the ADHERE report (2). In the OPTIMIZE-HF registry, it was further noted that patients with PSF were also less likely to receive aspirin and statins.

The use of a prespecified follow-up cohort in the OPTIMIZE-HF registry contributes new observations and insights into the early post-discharge period. The data show that although patients with PSF are more likely to survive an HF hospitalization than patients with LVSD, they remain at equally high risk for mortality and for mortality or rehospitalization in the first 60 to 90 days after index hospitalization. A study among patients hospitalized with new-onset HF also showed that the post-discharge survival of patients with HF with preserved EF was similar to that of patients with reduced EF (19). The 90-day post-discharge mortality rates for patients with reduced and preserved EF HF in that study were similar to those observed in the OPTIMIZE-HF registry. However, that study was limited in that only 42% of potentially eligible patients had a documented assessment of left ventricular function and it drew from only a single province in Canada (19). An analysis of 4,596 patients from a single community showed that, over a 15-year period, the prevalence of HF with preserved EF increased but the rate of death did not change (20).

Despite this alarming risk, clinical trial data to support treatment approaches are sparse for patients with HF and PSF. Current HF guideline recommendations for patients with PSF include control of systolic and diastolic hypertension, ventricular rate control in patients with atrial fibrillation, and use of diuretics to control pulmonary congestion and peripheral edema (17). The OPTIMIZE-HF registry reveals new insights into the quality of care provided to patients with PSF. Patients with PSF were admitted to the hospital with markedly elevated systolic blood pressure. Patients with PSF were slightly less likely than patients with LVSD to be treated with diuretics, at both admission and discharge, despite similar signs and symptoms of congestion. This group was less likely than patients with LVSD to receive anticoagulation therapy for atrial fibrillation, smoking-cessation counseling, or complete discharge instructions, quality measures that should be applied to all patients with HF regardless of EF. Despite the large number of patients that are affected, overall quality of HF care for patients with PSF lags behind that provided to patients with HF with reduced EF. Although specific data are lacking on effective therapeutic strategies in this population, the OPTIMIZE-HF registry demonstrates an opportunity to improve the care of these patients.

The CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)-Preserved study observed a reduction in HF hospitalizations for outpatients with HF and PSF who were treated with the ARB candesartan in addition to standard background therapy (21). In the OPTIMIZE-HF registry, patients with PSF were more likely to be treated with an ARB than were patients with LVSD. An ACE inhibitor or ARB and beta-blockers may be potentially beneficial in patients with HF and PSF who also have other indications for these agents, such as coronary artery disease, diabetes, or hypertension. However, no association was observed between the use of ACE inhibitor/ARB or beta-blockers at the time of hospital discharge and clinical outcomes in the first 60 to 90 days of follow-up in patients admitted with HF and PSF. The benefits observed in the CHARM-Preserved study occurred over a median follow-up of 36.6 months, and the Kaplan-Meier curves did not visually appear to separate until approximately 6 months (21). Thus, a relationship may have been observed in OPTIMIZE-HF if follow-up had been longer. No other medications have proven to be effective in patients with HF and PSF. In the Digitalis Investigation Group ancillary trial, digoxin had no effect on natural history end points such as mortality and all-cause or cardiovascular hospitalizations in ambulatory patients with chronic mild-to-moderate diastolic HF and normal sinus rhythm (22). It must also be emphasized that the OPTIMIZE-HF registry was not a randomized trial, and it was not prospectively designed to test the efficacy of pharmacologic therapy in the PSF population. Given the high post-discharge clinical event rate and the lack of proven effective therapies for this condition, there is a clear need to test treatment strategies for patients with HF and PSF in randomized clinical trials.

Although these OPTIMIZE-HF data are consistent with earlier observations in patients with PSF, it should be noted that the OPTIMIZE-HF registry involved a much larger and more diverse group of patients than the majority of earlier reports (3–6,19,20,23,24). With the added contribution of early post-discharge outcomes, these data may be valuable in designing the prospective randomized trials that are much needed to identify agents to reduce risk and improve outcomes in patients with HF and PSF.

Study limitations. The results of the present study should be interpreted in the context of several limitations. The present observations include only hospitalized patients with HF, a population known to be at increased risk of adverse outcomes, including readmission for HF and mortality after hospital discharge (25,26). In addition, left ventricular function was not assessed in 7,345 patients (15%), and these patients were excluded from the analysis. Some of the observed differences may not be clinically relevant, although they were statistically significant because of the large number of patients studied overall. Follow-up data were collected only from a pre-specified subset of patients and extended only 60 to 90 days after hospital discharge. The

follow-up period may have been too short to observe potential efficacy of pharmacologic interventions. Outcomes may have been different over longer follow-up. Medication contraindications and intolerance were as documented in the medical record. Some patients may have had contraindications or intolerance that were present but not documented. This study was not a prospective randomized clinical trial, and residual measured and unmeasured confounders may have influenced clinical outcome.

Conclusions

Preserved systolic function was present in a large proportion of patients enrolled in this large unselected representative registry of patients hospitalized with HF. Although patients with HF and PSF differ significantly from those with HF and LVSD, both groups experience similarly high rates of mortality and morbidity. Furthermore, no differences in clinical outcomes were seen with different definitions for PSF. Specific therapeutic strategies are lacking for patients with HF and PSF. Given the substantial risk of adverse clinical events and the lack of an appropriate body of evidence to guide management in patients with HF and PSF, large well designed clinical trials are critically needed to identify effective management strategies for this population.

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APPENDIX

For variables used in the models and linear spline transformations for continuous variables, please see the online version of this article.