JACC: HEART FAILURE
VOL. 3, NO. 6, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2014.12.017

MINI-FOCUS ISSUE: HEART FAILURE WITH PRESERVED EJECTION FRACTION

The Hospitalization Burden and Post-Hospitalization Mortality Risk in Heart Failure With Preserved Ejection Fraction

Results From the I-PRESERVE Trial (Irbesartan in Heart Failure and Preserved Ejection Fraction)

Peter E. Carson, MD,* Inder S. Anand, MD, DPHIL (OXON),† Sithu Win, MD,† Thomas Rector, PHD,† Markus Haass, MD,‡ Jose Lopez-Sendon, MD,§ Alan Miller, MD,|| John R. Teerlink, MD,¶ Michel White, MD,# Robert S. McKelvie, MD, PHD,** Michel Komajda, MD,†† Michael R. Zile, MD,‡‡ John J. McMurray, MD,§§ Barry Massie, MD¶

ABSTRACT

OBJECTIVES The aim of this study was to investigate prognosis in patients with heart failure (HF) with preserved ejection fraction and the causes of hospitalization and post-hospitalization mortality.

BACKGROUND Although hospitalizations in patients with HF with preserved ejection fraction are common, there are limited data from clinical trials on the causes of admission and the influence of hospitalizations on subsequent mortality risk.

METHODS Patients (n = 4,128) with New York Heart Association functional class II to IV HF and left ventricular ejection fractions >45% were enrolled in I-PRESERVE (Irbesartan in Heart Failure and Preserved Ejection Fraction). A blinded events committee adjudicated cardiovascular hospitalizations and all deaths using predefined and standardized definitions. The risk for death after HF, any-cause, or non-HF hospitalization was assessed using time-dependent Cox proportional hazard models.

RESULTS A total of 2,278 patients had 5,863 hospitalizations during the 49 months of follow-up, of which 3,585 (61%) were recurrent hospitalizations. For any-cause hospitalizations, 26.5% of patients died during follow-up, with an incident mortality rate of 11.1 deaths per 100 patient-years (PYs) and an adjusted hazard ratio of 5.32 (95% confidence interval: 4.21 to 6.23). Overall, 53.6% of hospitalizations were classified as cardiovascular and 43.7% as noncardiovascular, with 2.7% not classifiable. HF was the largest single cause of initial (17.6%) and overall (21.1%) hospitalizations, although, after HF hospitalization, a substantially higher proportion of readmissions were due to primary HF causes (40%). HF hospitalization occurred in 685 patients, with 41% deaths during follow-up, an incident mortality rate of 19.3 deaths per 100 PYs. The adjusted hazard ratio was 2.93 (95% confidence interval: 2.40 to 3.57) relative to patients who were not hospitalized for HF and was greater in those with longer durations of hospitalization. There were 1,593 patients with only non-HF hospitalizations, 21% of whom died during follow-up, with an incident mortality rate of 8.7 deaths per 100 PYs and an adjusted hazard ratio of 4.25 (95% confidence interval: 3.27 to 5.32). The risk for death was highest in the first 30 days and declined over time for all hospitalization categories. Patients not hospitalized for HF or for any cause had observed incident mortality rates of 3.8 and 1.3 deaths per 100 PYs, respectively.

CONCLUSIONS In I-PRESERVE, HFpEF patients hospitalized for any reason, and especially for HF, were at high risk for subsequent death, particularly early. The findings support the need for careful attention in the post-discharge time period including attention to comorbid conditions. Among those hospitalized for HF, the high mortality rate and increased proportion of readmissions due to HF (highest during the first 30 days), suggest that this group would be an appropriate target for investigation of new interventions. (J Am Coll Cardiol HF 2015;3:429–41) © 2015 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CV = cardiovascular

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

PY = patient-year

Although heart failure (HF) with preserved ejection fraction (HFpEF) represents a substantial proportion of patients with HF, there remain gaps in knowledge and also controversy regarding this syndrome and its prognosis (1-3). There is agreement that hospitalizations in patients with HFpEF are common. However, although cardiovascular (CV) hospitalizations have been reported to account for the majority of events, and HF is the most frequent primary cause, other CV causes have not been well characterized (4,5). Furthermore, although recurrent hospitalizations in patients with HF are an important clinical concern, as well as a performance metric, there are no comprehensive reports of these events in patients with HFpEF.

SEE PAGE 442

The controversy over prognosis involves mortality in patients with HFpEF. Large registries and databases, including a recent meta-analysis, have reported that patients with HFpEF are at high mortality risk (6-8). However, randomized clinical trials in patients with HFpEF have noted markedly lower mortality rates (4,5,9,10), though still higher than those noted in older subjects without HF enrolled in clinical trials of hypertension or diabetes (11). How can these varying event rates be explained? One explanation may be that many HF registries enroll patients during acute HF hospitalizations (6,7,12,13), whereas randomized clinical trials of HFpEF have enrolled stable outpatients. The influence of HF hospitalization on mortality in clinical trials of HFpEF has not previously been reported. Furthermore, although many patients with HFpEF have important comorbidities and are commonly hospitalized for reasons other than for HF, there are no data on the influence of non-HF hospitalizations on prognosis.

Currently, because there is no proven therapy to decrease the hospitalization burden or mortality in patients with HFpEF, better understanding of the composition of events may aid in designing therapeutic strategies and clinical trials.

The I-PRESERVE (Irbesartan in Heart Failure and Preserved Ejection Fraction) clinical trial is the largest study of HFpEF to date (9,14). To evaluate the prognosis in HFpEF, we examined the composition of first and recurrent CV hospitalizations. We also report on the influence of hospitalizations on subsequent mortality.

METHODS

The I-PRESERVE study design and results have been previously described (9,14). Briefly, 4,128 patients with HF symptoms and left ventricular ejection fractions of at least 45% were randomized to receive either irbesartan or placebo. Patients eligible for enrollment were required to have hospitalizations for HF within the previous 6 months and at least New York Heart Association functional class II symptoms or corroborative evidence suggesting diastolic dysfunction and New York Heart Association functional class III or IV symptoms. A clinical end point committee adjudicated all deaths and CV hospitalizations; details of the mortality adjudications have been published previously (15), and both these definitions as well as those for hospitalizations are available in the Online Appendix. The end point committee chair reviewed all hospitalizations that were classified as non-CV in serious adverse event reports, and possible CV events were sent to the full committee. Hospitalizations were defined as admissions of at least 24 h in duration or with calendar date changes if times of admission or discharge were unavailable, and those assessed as HF hospitalizations required specific intravenous therapy or augmented oral medications for that disease. Deaths were adjudicated as CV, non-CV, or of unknown cause. The major CV death subcategories were sudden cardiac death and pump failure. For the purposes of this analysis, other CV

From the *Washington Veterans Affairs Medical Center and Georgetown University, Washington, District of Columbia; †Veterans Affairs Health Care System and University of Minnesota, Minneapolis, Minnesota; ‡Theresienkrankenhaus, Mannheim, Germany; §Hospital Gregorio Maranon, Madrid, Spain; ||University of Florida-Jacksonville, Jacksonville, Florida; ¶San Francisco Veterans Affairs Medical Center and University of California, San Francisco, San Francisco, California; #Montreal Heart Institute Research Center, Montreal, Quebec, Canada; **Population Health Research Institute and McMaster University, Hamilton, Ontario, Canada; ††Université Paris, Pitie Salpetriere Hospital, Paris, France; ‡‡Ralph H. Johnson Veterans Affairs Medical Center and Medical University of South Carolina, Charleston, South Carolina; and the §§British Heart Foundation Glasgow Cardiovascular Research Center, Glasgow, United Kingdom. Bristol-Myers Squibb sponsored the I-PRESERVE trial. The views expressed herein do not necessarily represent the views of the U.S. Department of Veterans Affairs or the U.S. government. Dr. Rector was supported by resources and facilities of the Minneapolis Veterans Affairs Health Care System. Drs. Carson, Anand, Haass, Lopez-Sendon, Miller, Teerlink, White, McKelvie, Komajda, Zile, McMurray, and Massie were consultants to Bristol-Myers Squibb. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 5, 2014; revised manuscript received December 9, 2014, accepted December 23, 2014.

deaths included those due to myocardial infarction, stroke, CV procedures, vascular causes, and other cardiac causes.

STATISTICAL ANALYSIS. Baseline characteristics of patients were compared using 2-sample Student *t* tests for continuous variables, and cross tabulations with chi-square tests for categorical variables between patients admitted for any cause or with no hospitalization, or for an admission for HF or no hospitalization. Similar comparisons were made between the same groups of patients by vital status. Data are presented as mean ± SD or percent. Echocardiographic variables are from a 745-patient substudy. The effect of the first hospitalization for any reason and for HF on the risk for mortality was determined by Cox regression analyses with the first hospitalization as a time-dependent variable. A similar analysis was done for the non-HF hospitalizations, and this group was composed of patients who did not experience HF admissions during the study. A 30-day readmission was defined as rehospitalization for any reason within 30 days of discharge from any HF hospitalization. An overall (time) unadjusted hazard ratio (HR) and an HR adjusted for established predictors of deaths in the I-PRESERVE cohort were estimated for each hospitalization end point (16). Similarly, because a previous study (17) had indicated that the risk for dying decreases with time post-discharge, a Cox model was used to estimate HRs for several discrete periods of time after discharge. Furthermore, separate analyses were done for different causes of death and the length of stay for the first hospitalization. Other types of deaths were censored in these analyses. The person-time mortality rates within each discrete time period were calculated to complement the HRs. In separate analyses, the first hospitalization for either HF or any cause was considered the index hospitalization. Subsequent hospitalizations of any type after discharge from the index hospitalization were considered recurrent events. Patients were censored at the time of death, study termination, or last known follow-up date.

A 2-sided p value ≤0.05 was considered to indicate statistical significance in this secondary analysis of the I-PRESERVE database. Stata version 13 (StataCorp LP, College Station, Texas) was used for all analyses.

RESULTS

HOSPITALIZATIONS. During a mean follow-up period of 49.5 months, 2,278 of 4,128 patients (55%) were hospitalized at least once, and 1,850 patients were never hospitalized. The patients who were hospitalized differed from those not hospitalized in many baseline parameters, including that they were older; were more likely to have ischemic causes of HF, histories of diabetes mellitus, or myocardial infarctions; had recent HF hospitalizations; had higher N-terminal pro-brain natriuretic peptide levels, heart rates, and quality-of-life scores; and lower left ventricular ejection fractions and estimated glomerular filtration rates (**Table 1**). A total of 126 patients died during the initial hospitalization, and among the 2,152 survivors, 1,346 (63%) were readmitted. There were 685 patients (16.6%) hospitalized at least once for a primary diagnosis of HF, while 3,443 patients were not. Patients hospitalized for HF differed from those not hospitalized in being older and more likely to have histories of previous HF hospitalization, diabetes mellitus, and chronic obstructive pulmonary disease; they also had higher N-terminal pro-brain natriuretic peptide levels but lower left ventricular ejection fractions and estimated glomerular filtration rates (**Table 2**). A total of 31 patients died during the first admission for HF. Among the 654 surviving patients, 450 (69%) experienced at least 1 recurrent admission for any cause.

ANY-CAUSE HOSPITALIZATIONS. There were a total of 5,863 any-cause hospitalizations in I-PRESERVE. Of these, 2,278 (39%) were first hospitalizations and 61% (3,585 of 5,863) were recurrent hospitalizations. As seen in **Figure 1A**, 1,226 (53.8%) of the initial hospitalizations were due to CV causes, 997 (43.8%) were non-CV hospitalizations, and 55 (2.4%) were for unknown causes. A primary admission for worsening HF was the largest subcategory of first hospitalizations (400 admissions, 17.6% of all first admissions). CV procedures were the next largest CV subcategory (6.1%). Total hospitalizations by category are seen in **Figure 1B**. As noted above, there were 5,863 admissions for any cause: 3,141 (53.6%) CV, 2,564 (43.7%) non-CV, and 158 (2.7%) unknown. Worsening HF was the largest single subcategory, with 1,236 (21.1%) of all hospitalizations. These results are also seen in Online Table 2.

The distribution of all sequential recurrent hospitalizations without regard to the cause of the initial hospitalization is seen in Online Table 2. For the 1,346 first recurrent hospitalizations, 725 (53.9%) were for a CV cause, and 574 (42.6%) were for a non-CV cause, and 47 (3.5%) were for unknown causes. Worsening HF was the most common subcategory, 268 (19.9%). Subsequent recurrent hospitalizations had a similar distribution of cause of readmission except for worsening HF which tended to be increased.

HF HOSPITALIZATIONS. There were 685 patients with hospitalizations for HF. Among these

TABLE 1 Baseline Characteristics of Patients With and Without Any-Cause Hospitalization

	No Hospitalization (n = 1,850)	Hospitalization (n = 2,278)	p Value
Demographics			
Age, yrs	70.1 ± 6.5	72.9 ± 7.1	<0.001
Women	1,177 (63.6%)	1,314 (57.7%)	<0.001
White	1,712 (92.5%)	2,147 (94.2%)	0.027
Clinical			
NYHA functional class			0.002
II	344 (18.6%)	526 (23.1%)	
III	1,459 (78.9%)	1,685 (74.0%)	
IV	46 (2.5%)	66 (2.9%)	
Heart rate, beats/min	70.8 ± 9.8	72 ± 10.9	<0.001
Systolic BP, mm Hg	136.6 ± 13.6	136.2 ± 16.1	0.353
Diastolic BP, mm Hg	79.9 ± 8.2	77.8 ± 9.6	<0.001
Body mass index, kg/m^2	29.3 ± 4.7	29.9 ± 5.7	0.001
Ischemic cause of HF	400 (21.6%)	636 (27.9%)	<0.001
Minnesota Living With Heart Failure Questionnaire score	43 (29-57)	41 (26-59)	
Ejection fraction, %	60.1 ± 8.8	58.9 ± 9.4	<0.001
LV mass/BSA, g/m^2	83.5 ± 23.1	87.9 ± 23.6	0.019
E/E′ ratio, lateral	9.6 ± 5	9.9 ± 4.1	0.369
LV hypertrophy on ECG	686 (37.1%)	574 (25.2%)	<0.001
Left bundle branch block on ECG	138 (7.5%)	198 (8.7%)	0.150
Medical history			
Hypertension	1,676 (90.6%)	1,974 (86.7%)	<0.001
Myocardial infarction	393 (21.2%)	576 (25.3%)	0.002
PCI or CABG	158 (8.5%)	390 (17.1%)	<0.001
Atrial fibrillation	423 (22.9%)	786 (34.5%)	<0.001
Diabetes mellitus	412 (22.3%)	722 (31.7%)	<0.001
Stroke or TIA	145 (7.8%)	254 (11.2%)	<0.001
COPD	104 (5.6%)	287 (12.6%)	<0.001
HF hospitalization within 6 months	690 (37.3%)	1,126 (49.4%)	<0.001
Laboratory			
Hemoglobin, g/dl	14.1 ± 1.4	13.9 ± 1.6	<0.001
Anemia, <13 if male, <12 if female	151 (8.4%)	321 (14.5%)	<0.001
Creatinine, mg/dl	0.9 ± 0.3	1.1 ± 0.3	<0.001
GFR, ml/min/1.73 m^2	77 ± 21.3	69 ± 22.6	<0.001
CKD, GFR <60 ml/min/1.73 m^2	402 (22.1%)	847 (37.6%)	<0.001
Sodium, mEq/l	139.7 ± 2.8	139.4 ± 3.2	<0.001
Potassium, mEq/l	4.4 ± 0.5	4.4 ± 0.5	0.544
NT-proBNP, pg/ml	237 (104–637)	465 (180–1,204)	<0.001

Continued on the next page

patients, there were 551 readmissions, for a total of 1,236 HF hospitalizations. As seen in **Figure 1C**, 306 (68%) of the first recurrent hospitalizations were for primary CV diagnoses, while 138 (30%) were for primary non-CV causes, with 6 (1.3%) of unknown cause. Worsening HF was the primary diagnosis in 189 (42%) of these first recurrent events, and they accounted for approximately the same proportion of second and subsequent recurrent events (Online Table 3). There were 1,371 recurrent hospitalizations for any cause after an initial HF event, 866 (63.2%) were CV, 482 (35.2%) were non-CV, and 1.7% were unknown. There were 551 (40.2%) HF rehospitalizations (**Figure 1D**). The distribution of subsequent recurrent hospitalizations subcategories is seen in Online Table 3 with a similar pattern of events.

30-DAY READMISSIONS. Of the 1,236 HF hospitalizations, 30-day follow-up was available for 1,111 events, because of either death or loss to follow-up. There were 205 (18%) readmissions within 30 days of HF hospitalizations. Of these, 150 readmissions (73%) were due to CV causes, with 99 (48%) being due to worsening HF (Online Table 4, Online Figure 1).

MORTALITY RISK POST-HOSPITALIZATION. Mortality risk post-any-cause hospitalization. There were 2,278 patients with hospitalizations for any reason: 126 (5.5%) died during the initial hospitalization, and another 603 (26.5%) died by the end of the trial, resulting in 32% deaths (729 of 2,278) in this group and 28% (603 of 2,152) among those who were discharged. Among the 1,850 patients who did not have hospitalizations during the study, 152 (8.2%) died. The complete list of baseline characteristics of patients hospitalized versus never hospitalized and vital status is shown in Online Table 1A. Patients who died after hospitalization differed from those who did not in a number of characteristics associated with worse outcomes.

After discharge, the unadjusted HR was 8.53 (95% confidence interval [CI]: 7.06 to 10.31) and the adjusted HR was 5.32 (95% CI: 4.21 to 6.73) for all-cause mortality compared with those never hospitalized for any reason (**Table 3**). The overall death rate in the patients after any hospitalization was 11.1 deaths/100 patient-years [PYs], while in those never hospitalized, it was 1.3 deaths/100 PYs. The risk for mortality and the incident mortality rate were highest in the first month and decreased thereafter, although they remained significantly elevated throughout the entire follow-up period in both the adjusted and unadjusted analyses (**Table 4**).

Mortality risk post-HF hospitalization. During I-PRESERVE, among the 685 patients with at least 1 hospitalization for HF, 31 (4.5%) died during the initial hospitalization and another 270 (39.4%) died by the end of the trial, resulting in 43.9% (301 of 685) deaths in this group and 41% (270 of 654) among those who were discharged. In contrast, there were 3,443 patients without HF hospitalizations, and 580 of these patients (16.8%) died during the study. Those hospitalized for HF differed in many baseline characteristics from those not hospitalized, as indicated above, and those who died differed from those alive in both subgroups (Online Table 1B). Among patients hospitalized for HF, those who died differed in a number of characteristics, including that they were

older, had higher N-terminal pro-brain natriuretic peptide levels, had higher heart rates, had lower left ventricular ejection fractions, and had worse renal function compared with those who survived.

The overall (time) unadjusted HR for subsequent all-cause mortality in patients discharged after HF hospitalization, compared with a concurrent group that was never hospitalized for HF, was 4.86 (95% CI: 4.19 to 5.76) and was 2.93 (95% CI: 2.40 to 3.57) when adjusted for baseline predictors of mortality (16) (Table 3). The overall mortality rate post-HF hospitalization was 19.3 deaths/100 PYs. The adjusted mortality risk and incident mortality rate were highest in the first month (9.39 and 46 per 100 PYs, respectively) with a subsequent decrease, although the risk for dying remained 2 to 3 times higher until the end of follow-up (Table 4). For those not hospitalized for HF, the mortality rate was 3.8 deaths/100 PYs.

Longer duration of the initial HF hospitalization was associated with increased risk for mortality post-discharge compared with shorter hospitalizations (Figure 2). Patients with HF hospitalizations were at particularly high risk for subsequent HF death. The HRs for different modes of death are graphically displayed in Figure 3. The full analysis on mode of death is available in the Online Appendix.

Mortality risk post-non-HF hospitalizations. Because the entire any-cause hospitalization cohort included patients with HF admissions but the majority of patients were hospitalized for non-HF reasons, we analyzed for mortality after non-HF events and excluded patients who had HF hospitalizations at any point. There were 1,593 patients with only non-HF hospitalizations: 109 (6.8%) died during the initial hospitalization, and another 319 died by the end of the trial, resulting in 27% deaths (428 of 1,593) in this group and 21% (319 of 1,484) among those who were discharged.

After discharge from the first hospitalization for a non-HF reason, the unadjusted HR was 6.55 (95% CI: 45.32 to 8.07), and the adjusted HR was 4.25 (95% CI: 3.27 to 5.32) for all-cause mortality compared with the group that was never hospitalized for a non-HF cause (Table 3). The overall death rate in the patients after non-HF hospitalization was 8.73 deaths/100 PYs. The risk for mortality and the incident mortality rate were again highest in the first month and decreased by 6 months, although they remained significantly elevated throughout the entire follow-up period in both the adjusted and unadjusted analyses (Table 4).

CUMULATIVE MORTALITY POST HF, NON-HF, AND NO HOSPITALIZATION. Figure 4 displays a Kaplan-Meier curve for cumulative mortality incidence for subjects after HF or non-HF hospitalization and also for those never hospitalized since randomization.

TABLE 1 Continued

	No Hospitalization (n = 1,850)	Hospitalization (n = 2,278)	p Value
Medications			
Diuretic agents	1,507 (81.5%)	1,911 (84.0%)	0.037
Loop	799 (43.2%)	1,351 (59.4%)	<0.001
Thiazide	877 (47.4%)	678 (29.8%)	<0.001
Spironolactone	231 (12.5%)	402 (17.7%)	<0.001
ACE inhibitors	445 (24.1%)	588 (25.8%)	0.193
Digoxin	205 (11.1%)	356 (15.6%)	<0.001
Beta-blockers	1,118 (60.5%)	1,309 (57.5%)	0.055
Antiarrhythmic agents	120 (6.5%)	239 (10.5%)	<0.001
Calcium-channel blockers	784 (42.4%)	853 (37.5%)	0.001
Nitrates	439 (23.7%)	669 (29.4%)	<0.001
Lipid-lowering agents	524 (28.3%)	755 (33.2%)	0.001

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; BP = blood pressure; BSA = body surface area; CABG = coronary artery bypass graft; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ECG = electrocardiography; GFR = glomerular filtration rate; HF = heart failure; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

DISCUSSION

In I-PRESERVE, we also found that 55% of patients experienced at least 1 hospital admission, and the majority of hospitalized patients who survived the admission (63%) were readmitted. CV hospitalizations were more common than those for non-CV causes. Whereas HF hospitalizations were the most common type of CV event, they were a minority of all hospitalizations (~20%), whether they were the first or subsequent hospitalizations. However, after HF hospitalization, more recurrent events were for HF (~40%). During the 30 days after discharge, nearly one-half of readmissions were for HF.

In examining post-hospitalization mortality, we found that patients with HFpEF were at high risk for mortality after any hospitalization. The risk was highest early after discharge and was independent of measured prognostic variables available in this database. We observed the highest post-hospitalization mortality event rates in those admitted primarily for HF, but those hospitalized for non-HF reasons also experienced substantial mortality risk. Patients who were not hospitalized for any reason had a low mortality rate.

HOSPITALIZATIONS IN HFpEF. While it is known that HF patients are frequently hospitalized, the primary reasons for these events have not been well defined, particularly in HFpEF. HF registries and

TABLE 2 Baseline Characteristics of Patients With and Without HF Hospitalizations

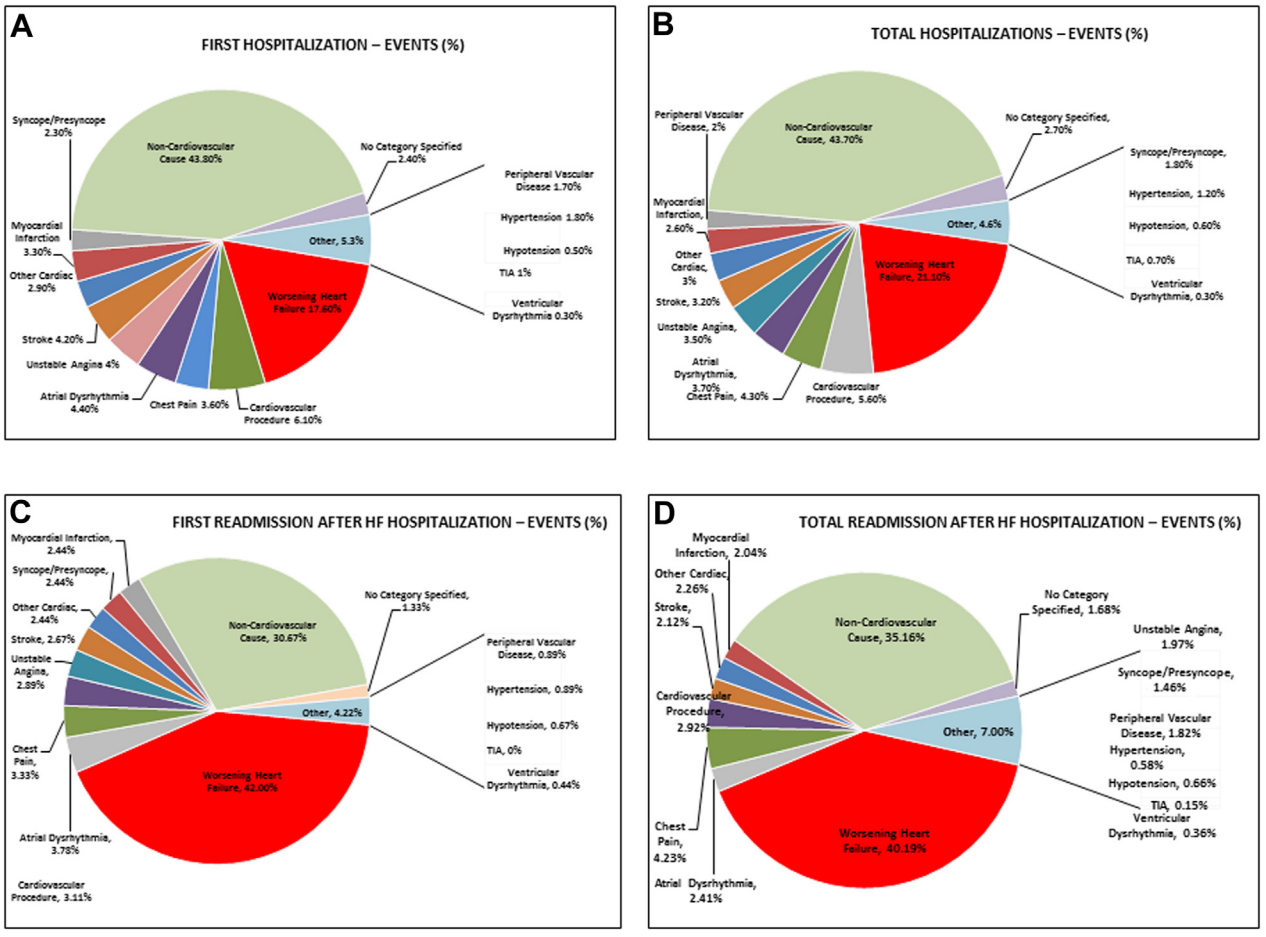
	No HF Hospitalization (n = 3,443)	HF Hospitalization (n = 685)	p Value
Demographics			
Age, yrs	71.1 ± 6.9	74.1 ± 6.9	<0.001
Women	2,083 (60.5%)	408 (59.6%)	0.647
White	3,208 (93.2%)	651 (95%)	0.071
Clinical			
NYHA functional class			0.003
II	682 (19.8%)	188 (27.5%)	
III	2,681 (77.9%)	463 (67.6%)	
IV	78 (2.3%)	34 (5.0%)	
Heart rate, beats/min	71 ± 10.3	73.5 ± 11.1	<0.001
Systolic BP, mm Hg	136.5 ± 14.8	135.5 ± 15.8	0.113
Diastolic BP, mm Hg	79.1 ± 8.9	76.8 ± 9.6	<0.001
Body mass index, kg/m^2	29.5 ± 5.1	30.2 ± 6	0.002
Ischemic cause of HF	842 (24.5%)	194 (28.3%)	0.033
Minnesota Living With Heart Failure Questionnaire score	41 (27-57)	46 (30-63)	<0.001
Ejection fraction, %	59.8 ± 9.1	57.7 ± 9.1	<0.001
LV mass/BSA, g/m^2	84.2 ± 22.8	95.4 ± 25.3	<0.001
E/E′ ratio, lateral	9.8 ± 4.6	9.8 ± 4.1	0.917
LV hypertrophy on ECG	1,079 (31.3%)	181 (26.4%)	0.011
Left bundle branch block on ECG	268 (7.8%)	68 (9.9%)	0.061
Medical history			
Hypertension	3,051 (88.6%)	599 (87.4%)	0.382
Myocardial infarction	791 (23%)	178 (26%)	0.089
PCI or CABG	433 (12.6%)	115 (16.8%)	0.003
Atrial fibrillation	880 (25.6%)	329 (48.0%)	<0.001
Diabetes mellitus	872 (25.3%)	262 (38.2%)	<0.001
Stroke or TIA	317 (9.2%)	82 (12.0%)	0.025
COPD	283 (8.2%)	108 (15.8%)	<0.001
HF hospitalization within 6 months	1,355 (39.4%)	461 (67.3%)	<0.001
Laboratory			
Hemoglobin, g/dl	14.1 ± 1.5	13.7 ± 1.6	<0.001
Anemia, <13 if male, <12 if female	343 (10.2%)	129 (19.3%)	<0.001
Creatinine, mg/dl	1 ± 0.3	1.1 ± 0.4	<0.001
GFR, ml/min/1.73 m^2	74.2 ± 22.2	64.4 ± 21.7	<0.001
CKD, GFR <60 ml/min/1.73 m^2	941 (27.7%)	308 (45.5%)	<0.001
Sodium, mEq/l	139.6 ± 2.9	139.3 ± 3.2	0.02
Potassium, mEq/l	4.4 ± 0.5	4.5 ± 0.5	0.25
NT-proBNP, pg/ml	287 (119-797)	852.5 (323-1,778)	<0.001
Medications			
Diuretic agents	2,783 (80.9%)	635 (92.7%)	<0.001
Loop	1,631 (47.4%)	519 (75.8%)	<0.001
Thiazide	1,383 (40.2%)	172 (25.1%)	<0.001
Spironolactone	452 (13.1%)	181 (26.4%)	<0.001
ACE inhibitors	846 (24.6%)	187 (27.3%)	0.135
Digoxin	414 (12.0%)	147 (21.5%)	<0.001
Beta-blockers	2,030 (59%)	397 (58%)	0.608
Antiarrhythmic agents	255 (7.4%)	104 (15.2%)	<0.001
Calcium-channel blockers	1,383 (40.2%)	254 (37.1%)	0.127
Nitrates	895 (26%)	213 (31.1%)	0.006
Lipid-lowering agents	1,072 (31.2%)	207 (30.2%)	0.626

Values are mean ± SD, n (%), or median (interquartile range).
Abbreviations as in Table 1.

other observational databases have reported on mortality and cause of hospitalizations during follow-up but do not provide detailed data on adjudicated causes of hospitalizations (12,13,18). Clinical trials are often designed to look at hospitalizations, particularly for HF as part of a composite endpoint, as a time to first event analysis. Thus, other causes of hospitalization are often not reported and subsequent hospitalizations not adjudicated. Further most previous reports on the hospitalization burden in HF have been largely from patients with a reduced ejection fraction (HFrEF) which also found that the most hospitalizations were for CV causes, with the majority of these for HF (19–22). However, only 2 HFrEF studies, EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) have presented detailed description of CV hospitalizations (21,22). Not surprisingly in these advanced HFrEF patients, HF hospitalizations were the predominant component of CV hospitalizations: In EVEREST, HF hospitalizations were 46% of any cause and 76% of CV; while in COPERNICUS (placebo arm) HF hospitalizations were 53% of any cause and 64% of CV. Other CV causes were infrequent. Treatments that have reduced hospitalizations in studies of HFrEF have showed significant reduction in cardiovascular hospitalizations, which in turn has been due largely to a reduction in the common HF hospitalizations.

As noted in this paper in a HFpEF cohort, CV hospitalizations were also the majority of events and there was a wide range of CV causes with HF hospitalizations a lower proportion than in HFrEF. The only previously published data describing causes of hospitalization in an HFpEF cohort are the unadjudicated results from the ancillary DIG (Digitalis Investigation Group) study that only described the first hospitalization of each type, and reported a wide range of CV hospitalizations consistent with the current data (4). The population enrolled in I-PRESERVE was, as in HFpEF epidemiologic databases, an older cohort with multiple CV risk factors, particularly hypertension, as well as multiple non-CV comorbidities. Not surprisingly, hospitalized patients had more comorbidities and more unfavorable physiologic variables than those not hospitalized, including those previously reported to be associated with worse outcomes in I-PRESERVE (9). In considering the composition of the hospitalizations, it is notable that many CV causes were infrequent despite the age and comorbidities present. For example, while it might be expected that events related to cardiac ischemia would be infrequent given the modest numbers with

FIGURE 1 First and Total Hospitalizations and First and Total Readmissions After HF Hospitalization: Primary Causes



(A) For the 2,278 first hospitalizations, the subcategories of the 1,226 (53.8%) cardiovascular hospitalizations are shown. The 997 (43.8%) noncardiovascular first hospitalizations are shown as a single category. **(B)** For the 5,863 total hospitalizations, the subcategories of the 3,141 (53.6%) cardiovascular hospitalizations are shown. The 2,564 (43.7%) noncardiovascular total hospitalizations are shown as a single category. **(C)** For the 551 rehospitalizations after heart failure (HF) events, the subcategories of the 306 (68%) cardiovascular hospitalizations are shown. The 138 (30%) noncardiovascular first readmissions are shown as a single category. **(D)** For the 1,371 total rehospitalizations after HF events, the subcategories of the 866 (63.2%) cardiovascular hospitalizations are shown. The 138 (30%) noncardiovascular first readmissions are shown as a single category.

a previous myocardial infarction or ischemic etiology, it is perhaps surprising that hospitalizations due to atrial arrhythmias or cerebrovascular accidents were also relatively uncommon. CV procedures were the most frequent non HF admission subcategory and these were <6% of recurrent events. The wide range of CV hospitalizations and common non-CV hospitalizations, together with a lower proportion of HF events, make total or CV hospitalization reduction difficult to achieve in a cohort with HFpEF.

Nonetheless, HF was the most common single cause of hospitalization in the overall I-PRESERVE cohort, with a proportion similar to reports from CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) Preserved (5) as well as the ancillary DIG study (4). These events would be a target for therapy. However, in this overall cohort of patients, who were clinically stable outpatients when enrolled, over a mean follow-up of more than 49 months, only 16% experienced HF hospitalizations, which represented only 21% of total events. Therefore, an intervention to reduce HF admissions would require a large clinical trial with a long follow-up time. A recent approach to the challenge of such clinical trials has been statistical analyses, which have included recurrent hospitalizations

TABLE 3 Unadjusted and Adjusted Risk for All-Cause Mortality After Discharge From HF, Any-Cause, or Non-HF Hospitalization

	Any-Cause Hospitalization		HF Hospitalization		Non-HF Hospitalization	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Model 1: unadjusted (n = 4,128)						
Discharge for first hospitalization for HF	8.53 (7.06–10.31)	<0.001	4.86 (4.19–5.63)	<0.001	6.55 (5.32–8.07)	<0.001
Model 2: adjusted (n = 2,722)						
Discharge for first hospitalization for HF	5.32 (4.21–6.73)	<0.001	2.93 (2.40–3.57)	<0.001	4.25 (3.27–5.52)	<0.001
Hospitalized for HF in past 6 months	1.06 (0.88–1.29)	0.521	1.02 (0.85–1.23)	0.829	1.24 (0.97–1.59)	0.079
Age, per 10-yr increase	1.39 (1.20–1.60)	<0.001	1.47 (1.28–1.68)	<0.001	1.53 (1.28–1.84)	<0.001
LVEF, per 5% decrease	1.07 (1.02–1.13)	0.010	1.07 (1.02–1.13)	0.009	1.07 (1.00–1.14)	0.06
Heart rate, per 5 beats/min increase	1.08 (1.04–1.12)	<0.001	1.07 (1.03–1.11)	0.001	1.05 (0.99–1.10)	0.096
Minnesota Living With Heart Failure Questionnaire score, per 5-U increase	1.03 (1.01–1.05)	0.004	1.02 (1.00–1.04)	0.021	1.04 (1.01–1.07)	0.005
GFR, per 5 ml/min/1.73 m^2 decrease	0.99 (0.97–1.01)	0.468	1.00 (0.98–1.02)	0.826	0.97 (0.94–1.00)	0.023
NT-pro-BNP (log)	1.46 (1.35–1.58)	<0.001	1.39 (1.29–1.50)	<0.001	1.52 (1.37–1.69)	<0.001
Neutrophils (log)	1.36 (1.04–1.76)	0.023	1.50 (1.17–1.92)	0.001	1.59 (1.11–2.27)	0.012
Ischemic cause of HF	1.12 (0.89–1.40)	0.343	1.21 (0.98–1.51)	0.081	1.08 (0.82–1.44)	0.573
History of myocardial infarction	1.23 (0.98–1.55)	0.078	1.19 (0.96–1.49)	0.120	1.57 (1.18–2.07)	0.002
History of diabetes mellitus	1.38 (1.14–1.68)	0.001	1.47 (1.22–1.76)	<0.001	1.59 (1.24–2.04)	<0.001
History of COPD	1.15 (0.88–1.50)	0.300	1.18 (0.91–1.53)	0.0224	1.47 (1.03–2.08)	0.032

Multivariate models are adjusted per models in Komajda et al. (16).
CI = confidence interval; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

(22,23). Alternatively, patients hospitalized for HF might provide an attractive target for an intervention, given that a greater proportion of HF events as suggested by the present data in which 40% of rehospitalizations were for this cause.

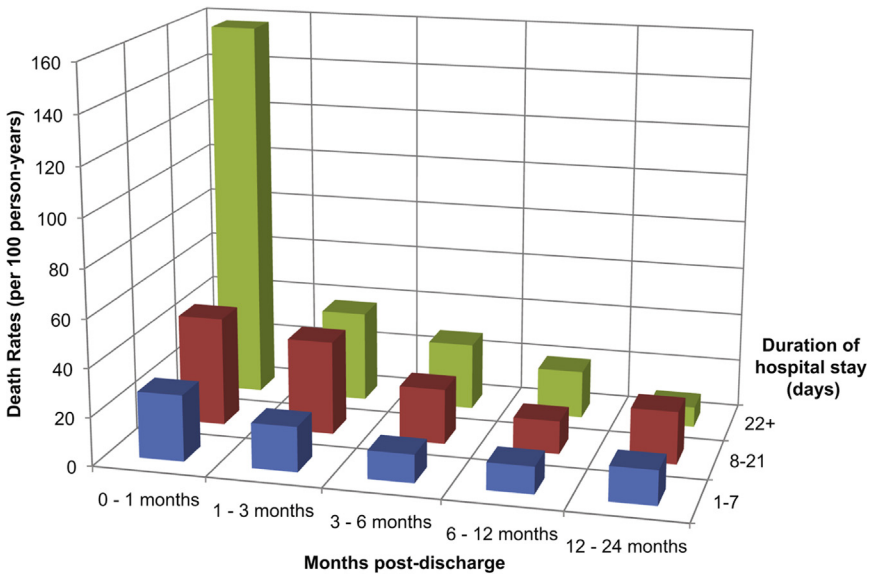
This study also examined recurrent hospitalizations in the 30-day period after HF admission. This has become an important hospital performance measure. There have been no previous reports from a clinical trial or registry to provide insight on 30-day readmission rates in a HFpEF population and only 1 from a HFrEF clinical trial: the A-HeFT (African-American Heart Failure Trial); 23.6% 30-day readmission rate after the first HF hospitalization in the

TABLE 4 Unadjusted and Adjusted Risk for All-Cause Mortality by Time Since Discharge After HF, Any-Cause, or Non-HF Hospitalization

	Any-Cause Hospitalization		HF Hospitalization		Non-HF Hospitalization	
Time Since Discharge	HR (95% CI)	Deaths (Rate/100 PYs)	HR (95% CI)	Deaths (Rate/100 PYs)	HR (95% CI)	Deaths (Rate/100 PYs)
Model 1: unadjusted (n = 4,128)						
0–1 months	17.09 (11.99–24.37)	39 (22.4)	12.59 (8.35–18.97)	24 (46)	15.73 (10.42–23.74)	27 (22.5)
1–3 months	11.56 (8.36–15.98)	50 (14.9)	7.89 (5.39–11.56)	28 (28.7)	10.53 (7.23–15.33)	34 (14.6)
3–6 months	11.13 (8.34–14.83)	71 (14.8)	4.78 (3.17–7.20)	24 (17.6)	11.10 (8.04–15.33)	51 (15.5)
6–12 months	6.59 (4.97–8.75)	76 (8.5)	3.49 (2.44–5.00)	32 (12.9)	4.91 (3.44–7.00)	40 (6.6)
12–24 months	7.43 (5.86–9.42)	154 (10.2)	4.19 (3.24–5.42)	67 (16.7)	5.44 (4.09–7.25)	78 (7.7)
>24 months	7.03 (5.54–8.92)	213 (10.4)	4.63 (3.67–5.83)	95 (20.4)	4.04 (3.01–5.41)	89 (6.6)
No hospitalization	1.0 (reference group)	152 (1.3)	1.0 (reference group)	580 (3.8)	1.0 (reference group)	152 (1.4)
Model 2: adjusted (n = 2,722)						
0–1 months	11.45 (7.18–18.25)		9.39 (5.72–15.42)		10.52 (5.97–18.51)	
1–3 months	8.36 (5.52–12.64)		6.37 (4.10–9.90)		6.61 (3.87–11.26)	
3–6 months	7.48 (5.18–10.81)		3.08 (1.85–5.13)		7.88 (5.15–12.07)	
6–12 months	4.08 (2.84–5.86)		2.01 (1.27–3.18)*		3.52 (2.24–5.55)	
12–24 months	4.96 (3.70–6.65)		2.65 (1.92–3.64)		3.75 (2.61–5.41)	
>24 months	4.00 (2.98–5.36)		2.40 (1.79–3.22)		2.69 (1.87–3.87)	
No hospitalization	1.0 (reference group)		1.0 (reference group)		1.0 (reference group)	

Multivariate models are adjusted per models in Komajda et al. (16). All p values <0.001 except as indicated. *p = 0.003.
PY = patient-year; other abbreviations as in Tables 1 and 2.

FIGURE 2 Duration of HF Hospitalization and Relation to Subsequent Mortality

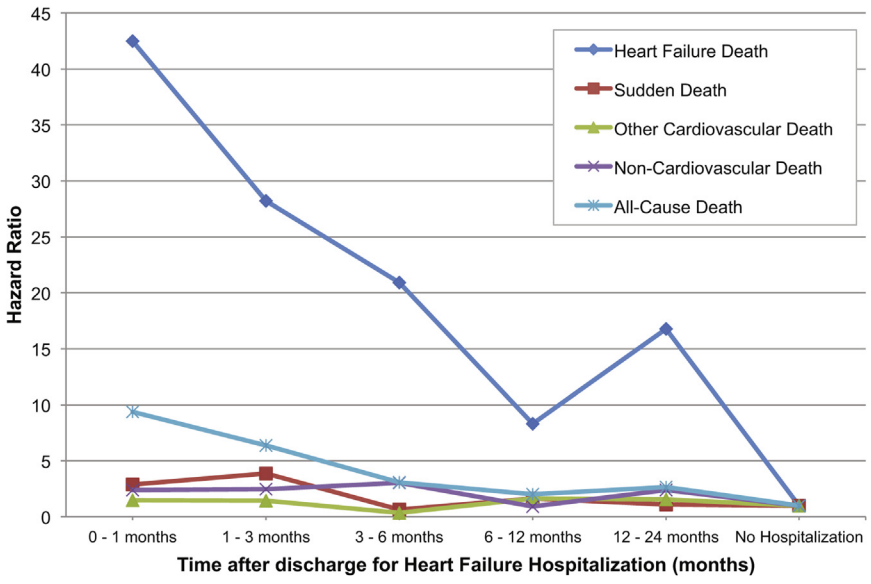


Influence of time from discharge and length of heart failure (HF) hospital stay on death rates after discharge from a hospitalization for HF.

placebo group (24). The I-PRESERVE data also indicates a slightly lower readmission rate (18%) but there still was a high proportion of 30-day readmissions due to CV and HF cause.

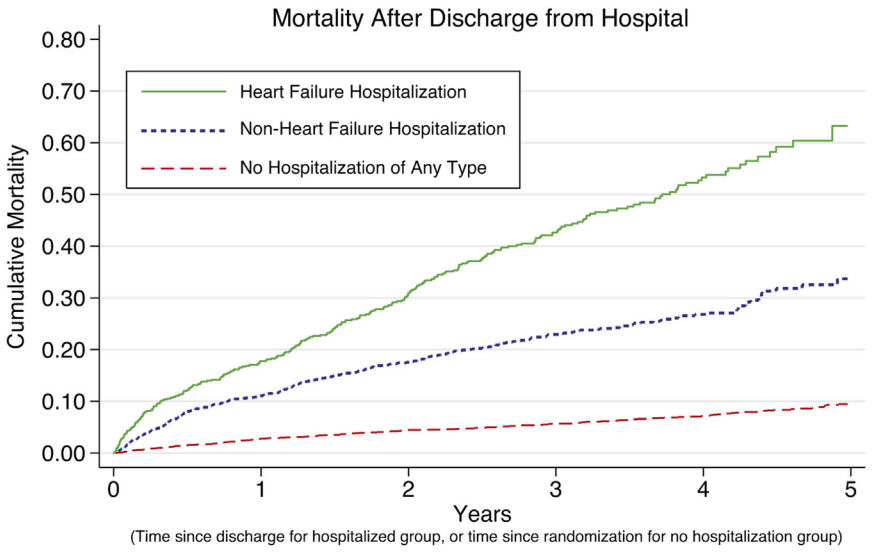
POST-HOSPITALIZATION MORTALITY IN HFpEF. Our findings demonstrate that patients with HFpEF enrolled as stable outpatients in a randomized clinical trial have substantial mortality risk after

FIGURE 3 Mode of Death After a Heart Failure Hospitalization



Hazard ratios of various causes of death after discharge from the hospital for heart failure hospitalization at various time intervals after discharge adjusted for other baseline predictors of all-cause mortality. CV = cardiovascular.

FIGURE 4 Cumulative Mortality Post-Hospitalization (HF and Non-HF) and No Hospitalization



Mortality by Kaplan-Meier analysis after a hospitalization for heart failure (HF), not for heart failure (from time of admission), or from randomization for patients with no hospitalization for any cause.

hospitalization for any cause, particularly after HF admission. There are no comparable data from a randomized clinical trials involving patients with HFpEF, but there have been 2 previous reports from predominantly or entirely HFrEF studies that have used a similar time-dependent statistical methodology. Both SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) (25) and CHARM (26) found that mortality risk was highest early after HF hospitalization and decreased over time, though it remained substantially elevated compared with patients never hospitalized or yet to be hospitalized. The methodology in the present analysis differs slightly in that the patient time before a hospitalization, so-called immortal time, was not included in the calculation of risk ratios, but the pattern of risk over time is consistent with these previous studies. In considering post-HF hospitalization mortality rates, those in I-PRESERVE are substantially lower than the unadjusted event rates reported from the HFrEF cohort in SHIFT, a finding that would be consistent with the data from the recent MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) meta-analysis of cohort studies and clinical trial databases (8). The CHARM Program publication did not provide separate mortality rates for its HFpEF cohort (37% of total patients) or provide event rates for the overall cohort (18). The only previous reports of post-HF hospitalization mortality results in a HFpEF cohort have come from registries. For example, in the DIAMOND (Danish Investigations of Arrhythmia and Mortality) registry, the post-HF hospitalization mortality rate was 19% at 1 year (27).

Why were patients hospitalized for HF in I-PRESERVE at such high risk? The baseline characteristics of those hospitalized for HF, including both comorbidities and indicators of more severe disease, differed from those not hospitalized, and those who died differed further from those who did not. However, even after adjustment for the baseline predictors associated with mortality risk in the overall I-PRESERVE database, the HF hospitalization event remained independently associated with a worse outcome. This may seem surprising, because HF hospitalization could be due to progression of the disease but also could be due to other causes, such as nonadherence, poor follow-up, or inadequate therapy. Although the present analysis does not provide a good explanation for the high post-HF hospitalization mortality risk, the mode-of-death analysis showed a particularly high risk for HF death early after discharge, suggesting worsening of the disease process in these subjects. The hospital experience itself may contribute, as noted below. The finding that an HF hospitalization is a salient event in a patient's

course, which requires careful post-discharge attention, has been reported in numerous HFrEF databases (4,23,26), but our data extend these findings to patients with HFpEF, indicating a need for careful attention early after discharge, although specific therapies for this period of high risk have not been established.

We also found a high risk for death after a nonelective hospitalization for any cause, with a similar pattern to that observed after HF admission. However, these findings need to be interpreted with caution, because both initial and subsequent HF hospitalizations were included in all-cause hospitalizations and therefore would affect the risk of the time intervals and event rates of the all-cause events. For this reason, we have included an analysis of patients who were hospitalized for any cause but not for HF. We observed a lower risk for mortality after these hospitalizations than that observed after HF hospitalization, but the event rate for these patients is still substantially higher than that for patients without hospitalizations. The excess risk associated with any hospitalization, HF or not, may be related to factors associated with the in-hospital experience. As noted by Krumholz (28), these include alterations in cognitive and physiologic function, including deconditioning and malnutrition, which then also affect the early post-discharge phase. These factors are suggested in the data of the current study, in which prolonged HF hospitalization was associated with the highest early post-discharge mortality risk. An older population is particularly vulnerable to what has been described as the "post-hospital syndrome." This excess risk also points to a need for careful attention to the treatment of comorbidities in HFpEF, as suggested by Ather et al. (29) as part of a strategy to reduce overall mortality risk.

Our study also identified a group of patients at lower mortality risk who were not hospitalized for HF and an even lower risk group who were never hospitalized for any reason. The patients not hospitalized for HF differed from those hospitalized for HF in many characteristics, as did the group hospitalized for any reason compared with those never hospitalized. The finding that most patients in I-PRESERVE were not hospitalized for HF, and many were not hospitalized at all, indicates that some subjects may have a mild variant of the disease, and others may not have HF at all. Although the I-PRESERVE inclusion criteria required the presence of signs and symptoms as well as structural and functional abnormalities, many of these features, such as shortness of breath and ankle edema, are nonspecific, underscoring the difficulty in diagnosing HFpEF (30).

IMPLICATIONS. The finding that hospitalized patients are at higher risk than those not hospitalized is not surprising, although this has not been previously quantitated for non-HF hospitalization or in the HFpEF population. This underscores the need to focus more on the clinical care of such hospitalized patients. These data further support the importance of enrolling patients during acute decompensated HF hospitalizations in clinical trials of patients with HFpEF, as the enrollment of stable outpatients is more likely to be dominated by low-risk subjects. This problem is magnified in HFpEF because of the lack of specificity of the clinical symptoms and findings that are often present. Our data suggest that enrolling subjects during their HF hospitalizations would result in a cohort with a high subsequent risk for HF hospitalizations and mortality. It is important to note that the HF hospitalizations in the I-PRESERVE database were carefully adjudicated by an event committee. It should also be emphasized that when HF hospitalization is used as an inclusion criterion in clinical trials, the definition of HF hospitalization needs to be carefully considered. This might avoid the difficulties encountered in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study, in which a low-risk cohort was reported in those entry criteria pathway that was a history of hospitalization with a "a major component of the care provided" (10,31).

STRENGTHS AND LIMITATIONS. We studied well-characterized patients in the I-PRESERVE trial, the largest study of patients with HFpEF, which had adjudicated data and excellent follow-up data. In addition, we were able to adjust for prognostic variables previously described in this population. However, this was a secondary analysis of data from a randomized controlled trial, and patients were defined according to events occurring after enrollment. Furthermore, some of the baseline characteristics may have changed by the time of the hospitalization. The inclusion and exclusion criteria, including a history of hospitalization within 6 months and limitations on non-CV comorbidities, may have contributed to the distribution of hospitalizations over the duration of the study, although the proportion of hospitalizations for HF is similar to that in a recent community-based report of hospitalizations after a new diagnosis of HF (17). Judgments about the mode of death can be influenced by a recent HF hospitalization. Non-CV hospitalizations did not undergo full committee review, as these events were initially assessed by the sponsor, on the basis of

serious adverse events reports, and then reviewed by the events committee chair, who sent potential CV hospitalizations to review.

CONCLUSIONS

In the HFpEF population of I-PRESERVE, hospitalizations were common, and the majority of patients were readmitted. CV causes for hospitalization were most common, but non-CV hospitalizations were frequent, as both first and recurrent events. After an initial HF hospitalization, a greater proportion of recurrent admissions were due to HF, particularly during the initial 30-day interval. Additionally, patients hospitalized for any reason but particularly for HF were at high risk for subsequent death. Substantial post-hospitalization mortality risk was present also in patients with non-HF hospitalizations, suggesting a need for careful attention to comorbid conditions. These findings support the need for intensive follow-up in the early post-discharge time period. The outcomes after a HF hospitalization also suggest that this would be an optimal group in which to test interventions in future HFpEF clinical trials.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Peter E. Carson, Washington Veterans Affairs Medical Center, Department of Cardiology, 151D, 50 Irving Street, NW, Washington, DC 20422-0001. E-mail: peter.carson@med.va.gov.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Hospitalizations for HF represent a minority of the overall hospitalization burden in patients with HFpEF. However, there is a high post-hospitalization mortality risk after these events, and subsequent hospitalizations are more likely to be for HF. These patients need careful attention post-hospitalization, particularly early, when risk is highest. Additionally, patients admitted for non-HF causes also are at substantial risk for subsequent mortality and therefore also require careful follow-up with attention to comorbidities. Finally, patients with the diagnosis of HFpEF but not requiring hospitalization are at low mortality risk.

TRANSLATIONAL OUTLOOK: Clinical trials in HFpEF have been hampered by low event rates, due partly to large proportions of enrolled subjects who do not experience outcomes such as hospitalizations and death. This may indicate a mild version of the disease or an inaccurate diagnosis. A clinical trial composed of subjects admitted for HF would have the advantage of greater certainty in the diagnosis of a condition that can be difficult to diagnose correctly and a high event rate, including death and recurrent HF hospitalizations. Better understanding of patients with HFpEF who do not experience clinical events is necessary in considering large clinical trials that enroll stable outpatients.

REFERENCES

1. Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.

2. Hogg K, Swedberg K, McMurray JJ. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317–27.

3. Packer M. Can brain natriuretic peptide be used to guide the management of patients with heart failure and a preserved ejection fraction? The wrong way to identify new treatments for a nonexistent disease. Circ Heart Fail 2011;4:538–40.

4. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006;114:397–403.

5. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.

6. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.

7. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

8. Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33:1750–7.

9. Massie BD, Carson PD, McMurray JD, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–67.

10. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

11. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-Preserved, and I-PRESERVE? J Am Coll Cardiol 2012;60:2349–56.

12. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) database. J Am Coll Cardiol 2006;47:76–84.

13. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768–77.

14. McMurray JJ, Carson PE, Komajda M, et al. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail 2008;10:149–56.

15. Zile MR, Gaasch, Anand IS, et al., for the I-PRESERVE Investigators. Mode of death in patients with heart failure and a preserved ejection fraction: results from Irbesartan in Heart Failure

with Preserved Ejection Fraction Study (I-PRESERVE) trial. Circulation 2010;121:1393–405.

16. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circ Heart Fail 2011; 4:27–35.

17. Dunlay SM, Redfield MM, Weston SA, et al. Hospitalizations after heart failure diagnosis: a community perspective. J Am Coll Cardiol 2009; 54:1696–702.

18. Hjalmarson A, Goldstein S, Fagerberg B, et al., for the MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). JAMA 2000;283:1295–302.

19. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.

20. O'Connor CM, Miller AB, Blair JE, et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) program. Am Heart J 2010;159:841–9.

21. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Cumulative Randomized Survival (COPERNICUS) study. Circulation 2002;106: 2194–9.

22. Rogers JK, McMurray JJ, Pocock SJ, et al. Eplerenone in patients with systolic heart failure and mild symptoms: analysis of repeat hospitalizations. Circulation 2012;126:2317–23.

23. Rogers JK, Pocock SJ, McMurray JJ, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur J Heart Fail 2014;16:33–40.

24. Anand IS, Sithu W, Rector TS, et al. Effect of fixed-dose combination of isosorbide dinitrate and hydralazine on all hospitalizations and on 30-day readmission rates in patients with heart failure results from the African-American Heart Failure Trial. Circ Heart Fail 2014;7:759–65.

25. Abrahamsson P, Swedberg K, Borer JS, et al. Risk following hospitalization in stable chronic systolic heart failure. Eur J Heart Fail 2013;15: 885–91.

26. Solomon SD, Dobson J, Pocock S, et al., for the Candesartan in Heart Failure, Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation 2007; 116:1482–7.

27. Gustafsson F, Torp-Pedersen C, Brendorp B, Seibaek M, Burchardt H, Kober L, for the Diamond Study Group. Long-term survival in patients hospitalized with congestive heart failure: relation to preserved and reduced left ventricular systolic function. Eur Heart J 2003;24:863–70.

28. Krumholz H. Post-hospital syndrome—an acquired, transient condition of generalized risk. N Engl J Med 2013;368:100–2.

29. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59: 998–1005.

30. Campbell RT, McMurray JJ. Comorbidities and differential diagnosis in heart failure with preserved ejection fraction. Heart Fail Clin 2004;10: 481–501.

31. Pfeffer MA, Clagget B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131: 34–42.

KEY WORDS heart failure, hospitalizations, preserved ejection fraction, prognosis

APPENDIX For the event classification committee manual for I-PRESERVE and supplemental tables and a figure, please see the online version of this article.