

Influence of Previous Heart Failure Hospitalization on Cardiovascular Events in Patients With Reduced and Preserved Ejection Fraction

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Background—Hospitalization for acute heart failure (HF) is associated with high rates of subsequent mortality and readmission. We assessed the influence of the time interval between previous HF hospitalization and randomization in the Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) trials on clinical outcomes in patients with both reduced and preserved ejection fraction.

Methods and Results—CHARM enrolled 7599 patients with New York Heart Association class II to IV HF, of whom 5426 had a history of previous HF hospitalization. Cox proportional hazards regression models were used to assess the association between time from previous HF hospitalization and randomization and the primary outcome of cardiovascular death or unplanned admission to hospital for the management of worsening HF during a median of 36.6 months. For patients with HF and reduced or preserved ejection fraction, rates of cardiovascular mortality and HF hospitalization were higher among patients with previous HF hospitalization than those without. The risk for mortality and hospitalization varied inversely with the time interval between hospitalization and randomization. Rates were higher for patients with HF and reduced ejection fraction within each category. Event rates for those with HF with preserved ejection fraction and a HF hospitalization in the 6 months before randomization were comparable with the rate in patients with HF and reduced ejection fraction with no previous HF hospitalization.

Conclusions—Rates of cardiovascular death or HF hospitalization are greatest in those who have been previously hospitalized for HF. Independent of EF, rates of death and readmission decline as time from HF hospitalization to trial enrollment increased. Recent HF hospitalization identifies a high-risk population for future clinical trials in HF and reduced ejection fraction and HF with preserved ejection fraction.

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Key Words: clinical trials ■ heart failure ■ hospitalization ■ outcomes assessment

Hospitalization for management of acute decompensated heart failure (HF) is associated with high rates of morbidity, mortality, and rehospitalization independent of ejection fraction (EF).^{1,2} Epidemiological studies and data from clinical trials have shown that the early time period after a hospitalization for HF is a particularly vulnerable interval.³⁻⁵ Although survival rates for all patients with HF have improved during the past several decades, the greatest gains have been made in the treatment of patients with HF with reduced EF (HFrEF).⁶

Clinical Perspective on p 595

A better understanding of the effect of hospitalization on the risk of future events is important for several reasons. First, it can help providers target care delivery to those patients at

the highest risk of adverse outcomes. Second, it can be leveraged as part of a strategy to inform the design of future clinical trials in HF. Future trials, particularly in HF with preserved EF (HFpEF), are needed to further the advances that have been made in reducing HF morbidity and mortality. In addition to the development of new therapies, innovations in the design and implementation of randomized clinical trials, including targeted patient recruitment, will become progressively more important to increase the efficiency of these trials.

We hypothesized that the presence of a recent hospitalization for HF can identify a high-risk patient population for enrollment in HF trials. We assessed the influence of time between previous HF hospitalization and randomization in the Candesartan in Heart failure: Reduction in Mortality and

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morbidity (CHARM) program on subsequent mortality and HF hospitalization in patients with HFrEF and HFpEF.

Methods

Patients

The CHARM program (ClinicalTrials.gov registration number NCT00634400) consisted of 3 trials, which enrolled 7599 patients with New York Heart Association class II to IV chronic HF and randomized them to candesartan or placebo in addition to standard HF therapies. Patients were enrolled in the 3 trials based on left ventricular (LV) EF and treatment with an angiotensin-converting enzyme inhibitor. The CHARM trials were approved by an institutional review committee at all sites, and all patients gave informed consent for participation in 1 of the 3 trials. CHARM-Added enrolled 2548 patients with LVEF \leq 40%, who were taking an angiotensin-converting enzyme inhibitor at baseline and had a cardiac hospitalization within 6 months. CHARM-Alternative consisted of 2028 patients with LVEF \leq 40%, who were intolerant to angiotensin-converting enzyme inhibitor. CHARM-Preserved enrolled 3023 patients with LVEF $>$ 40% (regardless of baseline angiotensin-converting enzyme inhibitor use or intolerance) and a previous cardiac hospitalization. Patients were followed up for a median of 38 months overall, ranging from 34 months in CHARM-Alternative to 41 months in CHARM-Added.

Ascertainment of Time Since Hospitalization and Outcomes

The time between hospitalization and enrollment was investigator reported. Investigators were asked whether the patient had a documented previous HF hospitalization and the month and year of the most recent previous hospitalization was recorded by the enrolling investigator on the case report form at the baseline visit. The total number of months between previous HF hospitalization and randomization were calculated and used for this analysis. If data were missing on the month of previous hospitalization ($n=53$), then it was imputed as January. If data were missing on the year of previous hospitalization, then the individual was excluded from this analysis ($n=4$). Two patients were excluded because of inconsistent dates. The primary outcome was the composite of cardiovascular death or HF hospitalization in each of the individual trials, and all-cause mortality in the overall CHARM program. All first major cardiovascular end points, including HF hospitalization, myocardial infarction, stroke, and resuscitated sudden death, as well as all deaths, were reviewed and adjudicated by an independent clinical events committee. HF hospitalization was defined as the presence of typical symptoms and signs, treatment with an intravenous diuretic, and at least an overnight hospitalization. All deaths were classified as cardiovascular, which was further categorized as secondary to progressive HF, myocardial infarction, sudden death, or other, versus noncardiovascular. The detailed study design, entry criteria, and main results have all been previously described.⁷⁻¹¹

Statistical Analysis

Baseline characteristics were stratified by substudy (Alternative and Added were compared with Preserved) and history of HF hospitalization before enrollment. Categorical variables were compared using χ^2 tests, and continuous variables were compared using t tests. All tests were 2 sided, and a P value of <0.05 was considered statistically significant. Event rates and 95% confidence intervals (CIs) comparing previous HF hospitalization were estimated. Rates were compared using the log-rank test stratified by substudy. Patients were grouped by EF (\leq or $>$ 40%), and the univariate association between EF and the primary outcome of all-cause mortality, as well as cardiovascular death or unplanned admission to hospital for the management of worsening HF, was analyzed in proportional hazards regression models and displayed on a Kaplan–Meier plot according to EF and previous HF hospitalization status. Covariate-adjusted hazard ratios (HRs) were calculated using the baseline predictors identified in previous analyses.¹² The 5421 patients who had complete data on the timing

of previous HF hospitalization were further stratified by elapsed time from previous HF hospitalization to randomization, and event rates were calculated for the primary outcomes. The trend in event rates across categories of months between HF hospitalization and randomization was compared using Poisson regression. We explored the relationship between a HF hospitalization within the trial and subsequent rehospitalization or death by fitting a Cox model in which participants were considered to be at risk for the event starting at the time of discharge for the first hospitalization. Stata/SE version 12.1 (StataCorp, College Station, TX) was used for all analyses.

Results

Baseline Analyses

Of the 7599 patients enrolled in the CHARM program, Table 1 lists the baseline characteristics of the 7593 CHARM patients with complete data (99.9%) included in this analysis broken down by EF above or below 40% and by history of previous hospitalization for HF. A total of 5421 (71%) patients had a HF hospitalization before enrollment in the CHARM program. Overall, those patients with a previous hospitalization were more likely to be women, with more advanced HF symptomatology, a longer duration of HF, and higher rates of hypertension, diabetes mellitus, and atrial fibrillation. Conversely, they were less likely to have had a previous myocardial infarction. There were no statistically significant differences between groups in rates of smoking, previous stroke, or assignment to candesartan.

Of those patients with a HF hospitalization before enrollment, 3346 had HFrEF (LVEF \leq 40%) and 2075 had HFpEF (LVEF $>$ 40%). When compared with patients with HFrEF, patients with HFpEF and a previous hospitalization were slightly older, more likely to be women, and be in a lower New York Heart Association class. Patients with HFpEF were also more likely to be hypertensive with higher blood pressures and have hypertensive, rather than ischemic heart disease, as the cause of their HF.

HF Hospitalization, Ejection Fraction, and Event Rates

For patients with both HFrEF and HFpEF, event rates for the primary end point of time to cardiovascular death or hospitalization for HF were higher among those with a hospitalization for HF before randomization than those without a previous HF hospitalization (Figure 1). The magnitude of increased risk associated with a previous hospitalization was similar regardless of EF (EF \leq 40%: unadjusted HR, 1.74; $P<0.001$; adjusted HR, 1.56; 95% CI, 1.38–1.76; $P<0.001$ and EF $>$ 40%: unadjusted HR, 1.81; $P<0.001$; adjusted HR, 1.59; 95% CI, 1.32–1.91; $P<0.001$), and there was no significant interaction between EF and previous hospitalization ($P=0.76$).

Among patients with HFpEF, annualized event rates of cardiovascular death or HF hospitalization for those with a HF hospitalization before randomization were comparable with the rate in patients with HFrEF and no previous HF hospitalization (10.1; 95% CI, 9.3–11.0 versus 10.1; 95% CI, 9.1–11.2 per 100 patient years; Table 2). Overall, patients with HFpEF had lower rates of all-cause mortality (unadjusted HR, 0.52; $P<0.001$ and adjusted HR, 0.86; 95% CI, 0.72–1.03; $P=0.10$) and the composite end point of cardiovascular death/HF hospitalization (unadjusted HR, 0.55; $P<0.001$ and adjusted HR, 0.94; 95% CI, 0.80–1.09; $P=0.39$) compared with patients with HFrEF

Table 1. Baseline Characteristics

	Overall (n=7593)			HFrEF (n=4572)			HFpEF (n=3021)		
	No Previous HF Hospitalization	Previous HF Hospitalization	P Value	No Previous HF Hospitalization	Previous HF Hospitalization	P Value	No Previous HF Hospitalization	Previous HF Hospitalization	P Value
n	2172	5421	...	1226	3346	...	946	2075	...
Age, y	66 (11)	65 (11)	0.88	65 (10)	65 (11)	0.53	66 (11)	67 (11)	0.29
Women	634 (29)	1764 (33)	0.004	289 (24)	898 (27)	0.03	345 (37)	866 (42)	0.001
Current smoker	322 (15)	792 (15)	0.81	179 (15)	526 (16)	0.35	143 (15)	266 (13)	0.09
BMI, kg/m ²	28.4 (5.1)	28.2 (5.6)	0.07	27.9 (4.7)	27.6 (5.3)	0.09	29.2 (5.6)	29.2 (5.9)	0.98
Candesartan	1078(50)	2721 (50)	0.66	602 (49)	1684 (50)	0.46	476 (50)	1037 (50)	0.86
NYHA class			<0.001			0.01			<0.001
II	1077 (50)	2338 (43)		460 (38)	1120 (33)		617 (65)	1218 (59)	
III–IV	1095 (50)	3083 (57)		766 (62)	2226 (67)		329 (35)	857 (41)	
Time since HF dx, y	3.1 (3.8)	3.9 (4.6)	<0.001	3.4 (3.9)	4.1 (4.5)	<0.001	2.7 (3.6)	3.5 (4.6)	<0.001
Hypertension	1125 (52)	3056 (56)	<0.001	550 (45)	1689 (51)	0.001	575 (61)	1367 (66)	0.01
Previous MI	1315 (61)	2684 (50)	<0.001	785 (64)	1878 (56)	<0.001	530 (56)	808 (39)	<0.001
Diabetes mellitus	483 (22)	1677 (31)	<0.001	267 (22)	1037 (31)	<0.001	216 (23)	640 (31)	<0.001
Previous stroke	185(9)	478 (9)	0.68	100 (8)	295 (9)	0.48	85 (9)	183 (9)	0.88
Atrial fibrillation	434 (20)	1649 (30)	<0.001	238 (19)	964 (29)	<0.001	196 (21)	685 (33)	<0.001
Cause of HF									
Ischemic	1519 (70)	3157 (58)	<0.001	853 (70)	2119 (63)	<0.001	666 (70)	1038 (50)	<0.001
Idiopathic	290 (13)	1036 (19)	<0.001	246 (20)	817 (24)	0.002	44 (5)	219 (11)	<0.001
Hypertensive	235 (11)	746 (14)	0.001	69 (6)	228 (7)	0.15	166 (18)	518 (25)	<0.001
HR, bpm	71 (13)	74 (13)	<0.001	72 (13)	74 (13)	<0.001	69 (12)	72 (12)	<0.001
SBP, mm Hg	131 (19)	131 (19)	0.22	128 (18)	127 (19)	0.048	135 (18)	137 (19)	0.05
DBP, mm Hg	77 (10)	77 (11)	0.12	76 (10)	76 (11)	0.14	78 (10)	78 (11)	0.97

All values presented as n (%) or mean (SD). BMI indicates body mass index; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, HF with preserved EF; HR, heart rate; MI, myocardial infarction; NYHA, New York Heart Association; and SBP, systolic blood pressure.

although the difference did not persist after adjustment for significant covariates. Event rates for patients with HFpEF were similar if HFpEF was defined as an EF \geq 50% (Table 3). When the time period between previous hospitalization and enrollment in CHARM was further broken down, patients with the shortest interval between hospitalization and randomization were at the greatest risk of death or hospitalization for HF during the trial (Figure 2). Event rates were higher for patients with HFrEF within each time period, and the trend in event rates was statistically significant for patients with both HFpEF and HFrEF.

Within all 4 subgroups, annualized event rates for a second HF hospitalization or death after a hospitalization for HF

within CHARM were markedly elevated when compared with the rates of a first HF hospitalization or death (Table 2). After a HF hospitalization within CHARM, those patients who were hospitalized for HF before enrollment continued to display an elevated risk for a second event (HF hospitalization or death) during the trial when compared with those who were not hospitalized before enrollment (Figure 3). Although patients with HFpEF continued to have lower rates of a second hospitalization for HF or death than those with HFrEF overall (HR, 0.79; 95% CI, 0.68–0.90), patients with HFpEF and a previous hospitalization for HF had higher second event rates after an in-trial hospitalization for HF than those with a HFrEF who only

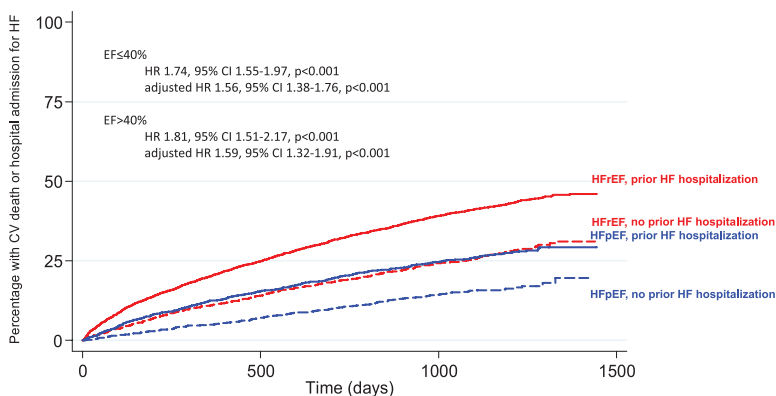


Figure 1. Previous hospitalization for heart failure (HF) is associated with increased risk of cardiovascular (CV) death and HF hospitalization independent of ejection fraction (EF). CI indicates confidence interval; and HR, hazard ratio.

Table 2. Event Rates Stratified by Substudy and Previous HF Hospitalization

Complete Study Data*	HFrEF (n=4572)		HFpEF (n=3021)	
	No Previous HF Hospitalization	Previous HF Hospitalization	No Previous HF Hospitalization	Previous HF Hospitalization
CV death/HF hospitalization	10.1 (9.1–11.2)	17.9 (17.0–18.8)	5.5 (4.7–6.5)	10.1 (9.3–11.0)
CV death	6.4 (5.6–7.2)	9.7 (9.1–10.3)	2.9 (2.3–3.6)	4.3 (3.8–4.8)
All-cause mortality	7.6 (6.7–8.6)	11.7 (11.0–12.4)	4.0 (3.4–4.9)	6.1 (5.5–6.8)
All death or HF hospitalization	11.3 (10.2–12.5)	19.5 (18.5–20.5)	6.5 (5.6–7.5)	11.5 (10.6–12.4)
HF hospitalization	5.4 (4.7–6.2)	12.3 (11.5–13.0)	3.2 (2.6–4.0)	7.9 (7.2–8.7)
HF death	1.2 (0.9–1.7)	3.5 (3.1–3.9)	0.6 (0.4–1.0)	1.4 (1.1–1.7)
Second HF hospitalization or death after a HF hospitalization (n=1525)	45.0 (36.5–55.5)	78.7 (72.7–85.1)	29.1 (19.7–43.1)	60.9 (53.8–69.0)

Rates are per 100 patient years. CV indicates cardiovascular; HFpEF, heart failure with preserved ejection fraction; and HFrEF, HF with preserved EF.

*P value <0.05 for all event rate comparisons between no previous and previous HF hospitalization within HFrEF and HFpEF categories.

experienced a HF hospitalization during the trial (HR, 0.76; 95% CI, 0.59–0.97; P=0.027).

Discussion

The CHARM program enrolled patients with symptomatic HF across a broad spectrum of EF s. The majority of patients in CHARM (71%) experienced a hospitalization for HF before enrollment, and the current analysis demonstrates that this history of an acute HF event is a powerful predictor of adverse cardiovascular outcomes for patients with both HFrEF and HFpEF during the trial. Moreover, the time between the last HF hospitalization and enrollment was itself a powerful predictor of subsequent event rates. These findings have implications for the design of future clinical trials.

Previously published findings from acute and chronic HF populations have reported varied estimates of subsequent mortality and rehospitalization rates for patients with HFpEF and HFrEF.^{13–25} Some studies have shown that patients with HF face a similar magnitude of risk regardless of EF,^{13–15,19,25} whereas others have demonstrated lower event rates in patients with HFpEF when compared with HFrEF.^{16–18,22–24} This disparate finding about the effect of EF on event rates is also seen when the studies are grouped into acute HF,^{13–17} versus chronic, prevalent HF.^{18–25} The admixture of different combinations of patients into single studies is likely responsible for some of the published disparities in risk.

Table 3. Event Rates in Patients With HFpEF and EF≥50%

	HFpEF (EF≥50%; n=1949)	
	No Previous HF Hospitalization (n=642)	Previous HF Hospitalization (n=1307)
CV death/HF hospitalization	5.4 (4.4–6.6)	10.8 (9.7–11.9)
CV death	2.7 (2.0–3.5)	4.3 (3.7–5.0)
All-cause mortality	4.2 (3.4–5.2)	6.5 (5.7–7.3)
All death or HF hospitalization	6.7 (5.6–8.0)	12.3 (11.2–13.6)
HF hospitalization	3.1 (2.4–4.0)	8.5 (7.6–9.5)
HF death	0.6 (0.3–1.0)	1.4 (1.1–1.8)
Second HF hospitalization or death after a HF hospitalization (n=311)	21.1 (12.3–36.4)	61.4 (52.7–71.6)

Rates are per 100 patient years. CV indicates cardiovascular; and HFpEF, heart failure with preserved ejection fraction.

The current analysis that stratified CHARM patients by EF and the presence or absence of a recent hospitalization for HF before enrollment provides clarification of the previous discrepant findings. Overall, and for patients with both HFpEF and HFrEF, we observed an inverse relationship between time from HF hospitalization and randomization into the trial and event rates within the trials. In addition, although the magnitude of increased hazard seen with a previous HF hospitalization was similar regardless of EF, patients with low EF had consistently higher event rates than those with HFpEF.

Event rates in cardiovascular clinical trials continue to decline over time because new interventions that have been tested and proven efficacious in previous trials are applied to clinical care.²⁶ As a result, increasing numbers of patients are needed to show a difference between treatment groups because the net number of clinical events, rather than the number of patients enrolled in a trial, ultimately determines a trial’s overall power to detect a significant difference.^{26,27} Historically, the development of the composite end point was one of the first ways trial design was adapted to leverage this knowledge.²⁸ Further innovations in the design and implementation of clinical trials, including targeted patient recruitment, can increase the efficiency of HF trials. The present data demonstrate that event rates for patients with HFpEF and a recent HF hospitalization approximate those of patients with HFrEF and no hospitalization before enrollment. This relationship persisted when HFpEF is defined more rigorously as clinical HF with an EF≥50%. A history of recent hospitalization for HF, therefore, provides a means to identify a high-risk patient population. Although mitigating risk in a high-risk population may not be the goal of every trial, we think that this strategy can inform enrollment strategies for some future clinical trials. It is important to design trials with a recruitment strategy that most effectively identifies the target population (eg, if a therapy is designed to work in lower risk patients, a recent hospitalization for HF is unlikely to identify those individuals).

The current analysis also reinforces the concept that a HF hospitalization is a sentinel event that can be used to identify patients who are at an increased risk for additional events. Patients who were hospitalized for HF before the trial were more likely to have recurrent hospitalizations or die during the trial, regardless of EF. During the course of a HF trial, such as CHARM, many patients experience multiple events that are positively adjudicated by the clinical events committee. A previous analysis of CHARM

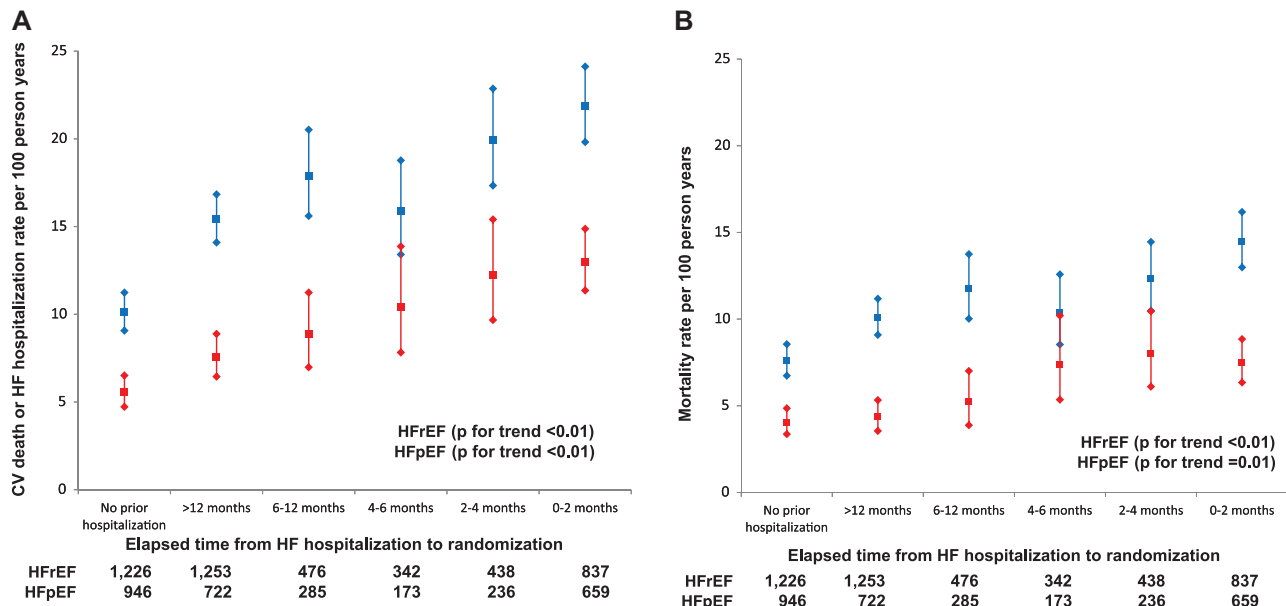


Figure 2. **A**, Increasing rates of cardiovascular (CV) death and heart failure (HF) hospitalization with more recent hospitalization before enrollment. **B**, Mortality rates increase as time between previous hospitalization and enrollment decreases. EF indicates ejection fraction.

demonstrated that the risk of death is directly related to the duration and frequency of HF hospitalization.¹ The current analysis demonstrates that this principle holds true in patients with HFrEF and HFpEF and extends the period of elevated risk to include hospitalizations that occurred before the trial start date. Because this analysis includes only patients who survived their previous hospitalization and lived to be randomized in the CHARM program, the increased risk associated with a previous hospitalization is likely underestimated because the sickest patients likely died during or shortly after hospitalization before they could be randomized. In general, current methods of survival analysis are based on a time to first event model and do not take into account these other events, which are important to both patients and providers. Future strategies in trial design, such as time to multiple events, may also be a novel way to use more of the data collected during a trial and provide composite end points that are easy to interpret.^{29,30}

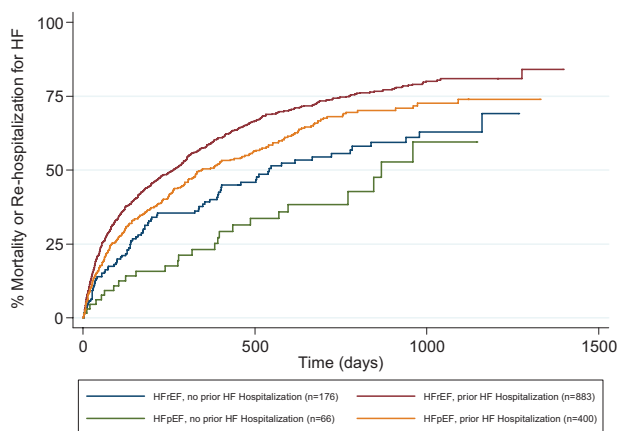


Figure 3. Time to death or second heart failure (HF) hospitalization after an in-trial HF hospitalization in Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) in patients stratified by ejection fraction (EF) and presence or absence of a HF hospitalization before enrollment. HFpEF indicates heart failure with preserved ejection fraction; and HFrEF, HF with preserved EF.

Some limitations of this analysis should be noted. The HF hospitalizations before randomization in CHARM were not formally adjudicated events. It is possible that some of those events would not meet the standards of a clinical end points committee; however, nondifferential misclassification of HF hospitalization would dilute our findings and have biased the results toward the null. However, event rates at 24 months in CHARM patients who fit enrollment criteria for Efficacy of Vasopressin antagonism in heart failure: outcome Study with Tolvaptan (EVEREST),³¹ a trial of acute HF, are similar; all-cause mortality (EVEREST 26% versus CHARM 28%) and cardiovascular death or HF hospitalization (EVEREST 41% versus CHARM 41%). The EFs in CHARM were site reported using several techniques and not verified by a core laboratory. Any noise created by the different techniques or imprecise measurement should be diminished in light of the large number of events. Finally, as with other clinical trials, these findings may not be generalizable to the general population of patients with HF.

In summary, rates of cardiovascular death or HF hospitalization are greatest in those with a previous HF hospitalization and decline with time between hospitalization and randomization across a broad spectrum of EF. The use of a history of recent HF hospitalization as an inclusion criterion for future clinical trials can increase trial efficiency. Acute exacerbations of HF requiring hospitalization signify a vulnerable time period in a patient's life and should trigger intensified management and heightened surveillance for additional events.

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Disclosures

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CLINICAL PERSPECTIVE

Patients who were hospitalized for a heart failure (HF) exacerbation before enrollment in the Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) program experienced higher event rates than those without a baseline history of HF hospitalization. Independent of ejection fraction, patients with a recent HF hospitalization were at the highest risk of death and readmission, with a steady decline in the rates observed as time between HF hospitalization and randomization increased. The identification of baseline patient characteristics associated with risk for future events, such as a history of a recent HF hospitalization, can be used to inform enrollment criteria for future HF trials. Targeted enrollment of individuals with a high risk for events can increase the efficiency of future HF trials.

Influence of Previous Heart Failure Hospitalization on Cardiovascular Events in Patients With Reduced and Preserved Ejection Fraction

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