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CLINICAL RESEARCH

The Prognostic Significance of Heart Rate in Patients Hospitalized for Heart Failure With Reduced Ejection Fraction in Sinus Rhythm

Insights From the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) Trial

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Objectives The purpose of this study was to characterize the relationship between heart rate and post-discharge outcomes in patients with hospitalization for heart failure (HHF) with reduced ejection fraction (EF) in sinus rhythm.

Background A reduction in heart rate improves clinical outcomes in patients with chronic heart failure and in sinus rhythm, but the association between heart rate and post-discharge outcomes in patients with HHF is presently unclear.

Methods This post-hoc analysis of the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial examined 1,947 patients with HHF and EF $\leq$40% not in atrial fibrillation/flutter or pacemaker dependent.

Results The median follow-up period was 9.9 months. At baseline, patients with a higher heart rate tended to be younger with lower EF and were more likely to have worse New York Heart Association functional class and higher natriuretic peptide levels. After adjustment for clinical risk factors, baseline heart rate was not predictive of all-cause mortality ($p \geq 0.066$). However, at $\geq$70 beats/min, every 5-beat increase in 1-week post-discharge heart rate was independently associated with increased all-cause mortality (hazard ratio: 1.13 [95% confidence interval: 1.05 to 1.22]; $p = 0.002$). Similarly, every 5-beat increase $\geq$70 beats/min in 4-week post-discharge heart rate was predictive of all-cause mortality (hazard ratio: 1.12 [95% confidence interval: 1.05 to 1.19]; $p = 0.001$).

Conclusions In this large cohort of patients with HHF with reduced EF and in sinus rhythm, baseline heart rate did not correlate with all-cause mortality. In contrast, at $\geq$70 beats/min, higher heart rate in the early post-discharge period was independently predictive of death during subsequent follow-up. Further study of post-discharge heart rate as a potential therapeutic target in this high-risk population is encouraged. (J Am Coll Cardiol HF 2013;1:488–96)

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Elevated resting heart rate is an easily recognized clinical finding in patients with stable chronic heart failure (HF) and sinus rhythm that has demonstrated prognostic significance (1–3). In patients with mild to severe chronic HF, elevated resting heart rate is associated with an increased risk of all-cause mortality (ACM) and cardiovascular mortality (4). Similarly, investigators of the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) study observed that patients with chronic HF and in sinus rhythm who had the highest heart rate were at a 2-fold greater risk of cardiovascular death or hospitalization for HF (HHF) than patients with the lowest heart rate (1). These results are consistent with prior studies that suggest beta-blockers offer greater benefit to patients with elevated heart rate (5), with improved outcomes associated with the magnitude of heart rate reduction (6). Accordingly, more recent investigations have studied the effects of reducing heart rate in patients with HF by other mechanisms and its role as a target for pharmacotherapy (7,8).

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Although an association between heart rate and prognosis in stable chronic HF may be well established, there are limited data specifically investigating the role of heart rate in predicting post-discharge outcomes in patients with HHF. The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) global trial allows the opportunity to perform an in-depth characterization of patients hospitalized for worsening chronic HF and reduced left ventricular (LV) ejection fraction (EF) and evaluate the relationship between resting heart rate, both during and after hospitalization, and mortality.

Methods

Study design. The rationale and study design of the EVEREST trial has been previously reported (9). Briefly, EVEREST was a multicenter, randomized, double-blind, placebo-controlled trial that examined the effects of tolvaptan, a vasopressin-2 receptor antagonist, in patients 18 years of age or older who were hospitalized with worsening HF and EF ≤40% and had signs of fluid overload (10,11).

Patients were randomized within 48 hours of hospitalization to receive either oral tolvaptan (30 mg/day) or placebo in addition to standard therapy. Specific recommendations for guideline-based optimal medical therapy were included in the study protocol, but background medical therapy was left to the discretion of the treating physician. The trial was conducted in full accordance with the Declaration of Helsinki and with institutional review board and ethics committee approval at all sites. Informed consent was obtained from all patients.

Abbreviations and Acronyms

ACM = all-cause mortality
CI = confidence interval
ECG = electrocardiogram
EF = ejection fraction
HF = heart failure
HHF = hospitalization for heart failure
LV = left ventricular

Because oral tolvaptan has no known chronotropic effect in the setting of HF (10,11), the present post hoc analysis included patients in the treatment and placebo arms. In the EVEREST trial, heart rate was specified to be measured with the patient in the supine position. Given the known mechanistic differences between sinus rhythm and other cardiac rhythms and evidence suggesting the differential significance of heart rate according to underlying rhythm in ambulatory and inpatient HF (12,13), exclusion criteria for this analysis included the following: atrial fibrillation, atrial flutter, or other supraventricular arrhythmia on any electrocardiogram (ECG) acquired from baseline to 4 weeks post-discharge; ECG evidence of a permanent pacemaker at any point from baseline to 4 weeks post-discharge or history of a permanent pacemaker; and absence of a baseline ECG or heart rate measurement. Figure 1 details the overall study design and selection of the study cohort.

Study endpoint. The primary outcome of interest for this non-prespecified analysis was ACM, which was one of the primary co-endpoints used in the main EVEREST trial. The median follow-up period in EVEREST was 9.9 months.

Statistical analysis. For descriptive purposes, patients were assigned to quartiles of heart rate at the time of randomization and baseline characteristics were compared across quartiles using chi-square, analysis of variance, and Kruskal-Wallis tests where appropriate. All continuous variables were reported as mean ± SD if normally distributed or median (interquartile range) if non-normally distributed.

All time-to-event regression analyses were on the basis of Cox proportional hazards models and Kaplan-Meier survival curves. The association between ACM and 5 heart rate measures (baseline heart rate, discharge or day 7 heart rate [whichever came first], 1-week post-discharge heart rate, 4-week post-discharge heart rate, and in-hospital heart rate change [baseline to discharge]) were tested using the landmark principle. Heart rate was evaluated as a continuous variable, and hazard ratios and 95% confidence intervals (CI) were calculated for a 5 beats/min increase or in-hospital change in heart rate. The impact of continuous heart rate was evaluated separately in the heart rate ranges of <70 beats/min and ≥70 beats/min by adding to the model the variable of categorical heart rate ≥70 beats/min and its interaction with continuous heart rate (see the following

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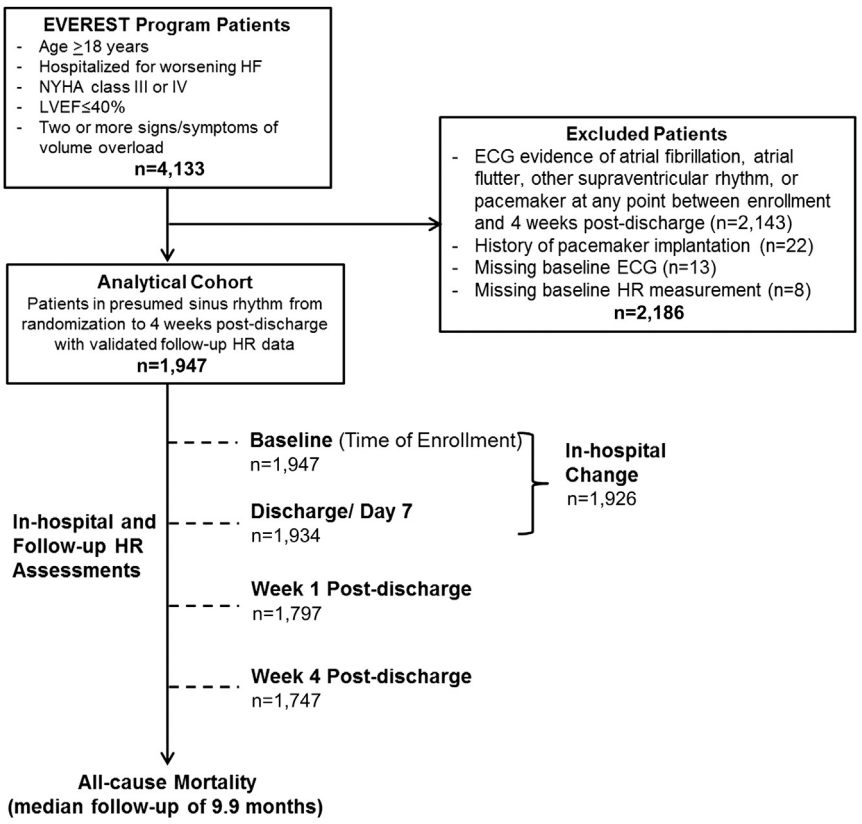

Figure 1 Patient Disposition and Selection of Analytical Cohort

ECG = electrocardiogram; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

text for further explanation). All multivariable Cox regression models were adjusted for pre-selected covariates including: age, sex, geographic region, EF, ischemic HF etiology, sodium level, B-type natriuretic peptide (BNP) level, N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, blood urea nitrogen level, QRS duration on baseline ECG, New York Heart Association functional class IV, systolic blood pressure, randomization to tolvaptan, medical history (HHF, hypertension, coronary artery disease, chronic obstructive pulmonary disease, diabetes, renal insufficiency), and medications (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, digoxin, and intravenous inotropic agents). For serum sodium level, blood urea nitrogen level, systolic blood pressure, BNP level, NT-proBNP level, and medications, baseline data were used in the multivariable model for baseline heart rate and discharge data were used in the multivariable model for the 4 other heart rate parameters. Baseline heart rate was added to the multivariable model for in-hospital change in heart rate. No suspicion of collinearity was present for the estimates related to the primary predictors in our final models (tolerance $\geq$0.83). Testing for interaction between both beta-blocker use (baseline beta-blocker use for baseline heart rate; discharge beta-blocker use for all other heart rate parameters) and treatment with tolvaptan with all heart rate measures was performed.

The linearity of effect for each heart rate predictor across the range of available values was evaluated, and violations of linearity were found for baseline, discharge, 1-week post-discharge, and 4-week post-discharge heart rate. A spline model was constructed that showed a differential heart rate effect using the cutoff of 69 beats/min. Given that other large recent investigations of heart rate in chronic HF and left ventricular dysfunction have used a heart rate cutoff of 70 beats/min for analysis (1,7,8), the present study separately evaluated the effect of continuous heart rate at values $\geq$70 and $<$70 beats/min for ease of comparison with existing studies. Using this cutoff, linearity was rechecked and there were no further violations of linearity. The proportional hazards assumption was evaluated, and no violations were seen with the exception of discharge or day 7 heart rate for values $\geq$70 beats/min ($p = 0.011$). For this predictor, the follow-up period was divided into 2 phases

Table 1 Patient Characteristics by Baseline Resting Heart Rate Quartile

	Heart Rate				
	Q1: 42–68 beats/min (n = 484)	Q2: 69–78 beats/min (n = 510)	Q3: 79–87 beats/min (n = 433)	Q4: 88–138 beats/min (n = 520)	p Value
Baseline heart rate (beats/min)	62.0 ± 5.1	73.9 ± 2.9	82.3 ± 2.4	96.9 ± 8.2	—
In-hospital heart rate change (beats/min)	3.3 ± 9.1	−2.1 ± 9.2	−6.7 ± 10.1	−13.7 ± 12.9	<0.001
Discharge heart rate (beats/min)	65.3 ± 8.8	71.8 ± 9.2	75.6 ± 10.1	83.2 ± 12.7	<0.001
Treatment with tolvaptan	243 (50.2)	271 (53.1)	220 (50.8)	262 (50.4)	0.772
Demographic characteristics					
Age (yrs)	65.8 ± 11.5	63.8 ± 11.4	62.3 ± 11.7	59.9 ± 12.8	<0.001
Male	350 (72.3)	351 (68.8)	322 (74.4)	381 (73.3)	0.242
Race					0.210
White	407 (84.1)	416 (81.6)	351 (81.1)	411 (79.0)	
Black	39 (8.1)	56 (11.0)	38 (8.8)	61 (11.7)	
Hispanic	30 (6.2)	27 (5.3)	26 (6.0)	31 (6.0)	
Other	8 (1.7)	11 (2.2)	18 (4.2)	17 (3.3)	
Region					0.304
Eastern Europe	221 (45.7)	225 (44.1)	192 (44.3)	200 (38.5)	
North America	122 (25.2)	118 (23.1)	105 (24.2)	129 (24.8)	
South America	86 (17.8)	112 (22.0)	84 (19.4)	126 (24.2)	
Western Europe	55 (11.4)	55 (10.8)	52 (12.0)	65 (12.5)	
Weight (kg)	82.7 ± 18.4	82.0 ± 17.8	83.2 ± 18.4	82.1 ± 19.6	0.728
NYHA class IV	129 (26.7)	172 (33.9)	161 (37.2)	245 (47.1)	<0.001
Physical examination and laboratory findings					
Systolic BP (mm Hg)	124.9 ± 20.1	121.9 ± 20.0	123.4 ± 19.3	120.5 ± 20.1	0.004
Diastolic BP (mm Hg)	72.8 ± 12.0	73.3 ± 12.4	75.4 ± 12.0	75.5 ± 12.8	<0.001
Dyspnea	429 (89.6)	447 (89.2)	391 (92.4)	470 (90.9)	0.338
Jugular venous distention ≥10 cm	101 (21.2)	140 (28.1)	102 (24.2)	131 (25.7)	0.089
Rales	379 (79.1)	400 (79.5)	344 (81.1)	429 (83.0)	0.394
Peripheral edema*	385 (80.4)	381 (75.7)	324 (76.4)	408 (78.9)	0.271
Ejection fraction (%)	29.1 ± 7.5	28.5 ± 8.5	27.4 ± 8.1	25.8 ± 7.8	<0.001
BUN (mg/dl)	24 (18–33)	25 (19–32)	23 (18–31)	22 (17–29)	0.006
Creatinine (mg/dl)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.4)	1.1 (1.0–1.4)	0.008
Sodium (mEq/l)	140 (138–142)	140 (138–142)	140 (138–143)	140 (137–142)	0.115
BNP (pg/ml)†	526 (176–1409)	533 (226–1301)	757 (294–1567)	899 (337–1652)	<0.001
NT-proBNP (pg/ml)‡	2,999 (1,099–7,615)	3,385 (1,484–7,138)	3,952 (1,514–8,791)	4,711 (2,352–10,149)	0.019
QRS (ms)	120 (96–141)	121 (95–143)	116 (95–137)	109 (94–134)	0.017

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at 100 days post-randomization (the cutoff point was established by a combination of visual inspection of standardized score process plots and review of other published reports [14]). All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina) at a 5% two-tailed level of significance.

Results

Baseline characteristics. The final analytical cohort included 1,947 patients in presumed sinus rhythm from the time of study randomization to 4 weeks post-discharge. Table 1 shows the baseline characteristics for all patients included in this analysis by quartile of heart rate at the time of randomization. Patients with a lower heart rate at baseline tended to be older with higher EF and lower natriuretic peptide levels. They were more likely to have a history of myocardial infarction or coronary artery bypass grafting and to have hypercholesterolemia or coronary artery disease. Additionally, they were more likely to be treated with beta-blockers and less likely to be treated with digoxin.

Post-discharge outcomes. Outcome analyses by continuous heart rates ≥70 and <70 beats/min are shown in Tables 2 and 3, respectively. The effects of all heart rate measures did not differ by randomization to tolvaptan (all $p > 0.5$) or by beta-blocker use (all $p > 0.7$) (interaction analyses not shown).

After accounting for known risk factors, at a heart rate ≥70 beats/min, baseline heart rate was not associated with mortality (hazard ratio: 1.05; 95% CI: 1.00 to 1.11). A higher discharge/day 7 heart rate was significantly associated with increased mortality at ≤100 days (hazard ratio: 1.20;

Table 1 Continued

	Heart Rate				
	Q1: 42–68 beats/min (n = 484)	Q2: 69–78 beats/min (n = 510)	Q3: 79–87 beats/min (n = 433)	Q4: 88–138 beats/min (n = 520)	p Value
Medical history					
Previous hospitalization for HF	369 (76.4)	396 (78.3)	311 (72.0)	386 (74.2)	0.135
Coronary artery disease	383 (79.5)	352 (69.2)	309 (71.4)	308 (59.2)	<0.001
Hypertension	369 (76.2)	370 (72.5)	320 (73.9)	335 (64.4)	<0.001
Hypercholesterolemia	273 (56.5)	256 (50.3)	221 (51.3)	221 (42.7)	<0.001
Previous MI	310 (64.0)	265 (52.0)	245 (56.6)	209 (40.3)	<0.001
Diabetes	195 (40.3)	210 (41.2)	178 (41.1)	194 (37.3)	0.552
Previous CABG	102 (21.1)	104 (20.4)	74 (17.1)	56 (10.8)	<0.001
Chronic kidney disease	110 (22.7)	98 (19.2)	71 (16.4)	75 (14.4)	0.005
Peripheral vascular disease	97 (20.1)	106 (20.8)	85 (19.6)	87 (16.8)	0.373
PCI	96 (19.8)	88 (17.3)	83 (19.2)	66 (12.7)	0.012
AICD	41 (8.5)	30 (5.9)	23 (5.3)	26 (5.0)	0.098
COPD	36 (7.4)	42 (8.2)	39 (9.0)	53 (10.2)	0.456
Baseline medication use					
Diuretic	471 (97.3)	498 (97.6)	420 (97.2)	500 (96.5)	0.742
ACE-I/ARB	425 (87.8)	457 (89.6)	377 (87.3)	452 (87.3)	0.625
Beta-blocker	392 (81.0)	390 (76.5)	315 (72.9)	300 (57.9)	<0.001
MRA	276 (57.0)	276 (54.1)	237 (54.9)	304 (58.7)	0.449
Digoxin	160 (33.1)	171 (33.5)	161 (37.3)	219 (42.3)	0.007
Intravenous inotropes	12 (2.5)	8 (1.6)	14 (3.2)	22 (4.2)	0.070
Discharge medication use					
Diuretic	428 (89.7)	464 (92.6)	402 (93.7)	485 (94.7)	0.019
ACE-I/ARB	416 (87.2)	449 (89.6)	377 (87.9)	457 (89.3)	0.604
Beta-blocker	396 (83.0)	404 (80.6)	339 (79.0)	358 (69.9)	<0.001
MRA	282 (59.1)	298 (59.5)	255 (59.4)	346 (67.6)	0.013
Digoxin	144 (30.2)	171 (34.1)	147 (34.3)	221 (43.2)	<0.001
Intravenous inotropes	3 (0.6)	4 (0.8)	2 (0.5)	7 (1.4)	0.438
Outcomes					
All-cause mortality	107 (22.1)	93 (18.2)	81 (18.7)	110 (21.2)	0.361
CV mortality or hospitalization for HF	172 (35.5)	151 (29.6)	159 (36.7)	176 (33.8)	0.097
CV mortality	80 (16.5)	75 (14.7)	64 (14.8)	83 (16.0)	0.827
CV mortality or CV hospitalization	211 (43.6)	176 (34.5)	184 (42.5)	207 (39.8)	0.017
Worsening HF§	144 (29.8)	131 (25.7)	135 (31.2)	150 (28.8)	0.281
Hospitalization for HF	112 (23.1)	100 (19.6)	116 (26.8)	120 (23.1)	0.078
Hospitalization for MI	9 (1.9)	4 (0.8)	6 (1.4)	6 (1.2)	0.498

Values are mean ± SD, n (%), or median (interquartile range). *Defined as slight/moderate/marked pedal or sacral edema. †Data were available for 363, 369, 323, and 378 patients for Q1 to Q4, respectively. ‡Data were available for 159, 181, 137, and 157 patients for Q1 to Q4, respectively. §Defined as death from HF, hospitalization for HF, or an unscheduled medical office visit for HF.

ACE-I = angiotensin converting enzyme inhibitors; AICD = automated implantable cardioverter-defibrillator; ARB = angiotensin II receptor blockers; BNP = B-type natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CV = cardiovascular; HF = heart failure; IQR = interquartile range; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; Q = quartile; QRS = QRS duration on electrocardiogram.

95% CI: 1.10 to 1.30) but not >100 days (hazard ratio: 1.01; 95% CI: 0.92 to 1.10). At levels ≥70 beats/min, an increased heart rate measured 1 week post-discharge was independently predictive of increased ACM (hazard ratio: 1.13; 95% CI: 1.05 to 1.22). Likewise, a higher 4-week post-discharge heart rate predicted higher ACM during subsequent follow-up (hazard ratio: 1.12; 95% CI: 1.05 to 1.19). In adjusted models, at rates <70 beats/min, there was no significant association between risk of death and heart rate at baseline, discharge, and 1 and 4 weeks post-discharge (all $p > 0.07$).

On Kaplan-Meier analysis, curves stratified by baseline heart rate quartile did not differ significantly for ACM (Fig. 2). Kaplan-Meier survival curves revealed significant separation for survival across heart rate quartiles at post-discharge week 1 (Fig. 3) ($p < 0.001$) and week 4 (Fig. 4) ($p < 0.001$). After controlling for other risk factors, an increase in in-hospital heart rate change was associated with risk of death with borderline significance (hazard ratio: 1.06; 95% CI: 1.00 to 1.11; $p = 0.046$).

Discussion

In this large cohort of patients with HHF, at rates ≥70 beats/min, a higher resting heart rate at both 1 week and 4 weeks post-discharge was independently predictive of increased mortality during subsequent follow-up. In

Table 2 All-Cause Mortality by Continuous Heart Rate Change (≥70 beats/min)

Heart Rate Measure	n	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
Baseline	1,444	1.08 (1.03–1.14), p = 0.003	1.05 (1.00–1.11), p = 0.066
Discharge/day 7†	1,220		
≤100 days		1.23 (1.14–1.33), p < 0.001	1.20 (1.10–1.30), p < 0.001
>100 days		1.02 (0.94–1.11), p = 0.642	1.01 (0.92–1.10), p = 0.901
1 week post-discharge	1,170	1.17 (1.12–1.23), p < 0.001	1.13 (1.05–1.22), p = 0.002
4 weeks post-discharge	1,110	1.18 (1.13–1.24), p < 0.001	1.12 (1.05–1.19), p = 0.001

HRs and 95% CIs were calculated for an increase in heart rate of 5 beats/min. HRs were calculated using Cox proportional hazards models. *Adjusted for age, sex, geographic region, ejection fraction, ischemic HF etiology, sodium level, BNP level, NT-proBNP level, BUN level, QRS duration on baseline electrocardiogram, NYHA functional class IV, systolic blood pressure, randomization to tolvaptan, medical history (hospitalization for HF, hypertension, coronary artery disease, COPD, diabetes, renal insufficiency), and medications (ACE-I/ARB, beta-blockers, MRA, digoxin, and intravenous inotropic agents). For serum sodium level, BUN, systolic blood pressure, BNP level, NT-proBNP level, and medications, baseline data were used in the multivariable model for baseline heart rate and discharge data were used in the multivariable model for discharge and post-discharge heart rate. †For discharge/day 7 heart rate, the proportional hazards assumption did not hold and the follow-up was divided into 2 phases at 100 days post-randomization.

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

contrast, a higher baseline heart rate was not significantly associated with mortality in final multivariable models. At levels ≥70 beats/min, higher heart rate at discharge/day 7 was predictive of increased ACM in the early post-discharge period. At values <70 beats/min, there was no association between death and heart rate at any time point tested. Lastly, greater in-hospital increases in heart rate demonstrated borderline significance for increased risk of death. To our knowledge, this is the first study specifically investigating the relationship between heart rate and post-discharge outcomes in patients with HHF.

Heart rate in "acute" versus "chronic" heart failure: mechanistic differences. In our study, the lack of a significant predictive value for baseline heart rate and the failure of discharge heart rate to predict long-term outcomes conflict with the strong body of evidence demonstrating the prognostic importance of heart rate in chronic stable HF (1,15). In ambulatory patients, the relationship between resting heart rate and prognosis may be related to the effects of chronically elevated heart rate on myocardial energy balance (16,17). Moreover, elevated heart rate is associated with increased effective arterial elastance and may lead to persistent myocardial strain and LV remodeling over time (18). This is consistent with results from a study in patients with a pacemaker and LV systolic dysfunction that compared 2 different pacing rates (60 vs. 80 beats/min) in the setting of chronic beta-blocker use, with the higher heart rate group demonstrating worsening of LV volumes and EF while the lower heart rate group had improvements in both (19). In contrast, among patients with HHF, changes in heart rate during the unstable period surrounding admission are partly related to the compensatory efforts of the cardiovascular system to maintain a stable cardiac output in the setting of increased stress. The transient rise in heart rate that could be expected in many patients hospitalized with worsening HF may produce a rate markedly different from the resting heart rate as an outpatient. It is likely that at the time of admission for worsening HF, heart rate is more a reflection of the patient's hemodynamic status at that point in time rather than long-term up-regulation of the neurohormonal axis (20).

In-hospital heart rate. Our results for baseline heart rate contrast with prior observational data demonstrating a significant association between admission heart rate and risk of in-hospital mortality (21). Recent registry data found a J-shaped relationship between admission heart rate and risk of in-hospital mortality, with lowest risk seen at rates of 70 to 75 beats/min (13). In the present study, there was only a nonsignificant trend toward increased ACM with a higher baseline heart rate ≥70 beats/min. However, our study used data from a clinical trial and evaluated outcomes beyond the inpatient period with a median follow-up period of 9.9 months, perhaps partially explaining differences with prior published reports.

Table 3 All-Cause Mortality by Continuous Heart Rate Change (<70 beats/min)

Heart Rate Measure	n	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
Baseline	503	1.10 (0.92–1.32), p = 0.300	1.07 (0.87–1.30), p = 0.530
Discharge/day 7	714	0.91 (0.77–1.06), p = 0.224	0.87 (0.74–1.02), p = 0.079
1 week post-discharge	627	1.08 (0.99–1.18), p = 0.086	0.89 (0.68–1.15), p = 0.368
4 weeks post-discharge	637	1.18 (1.08–1.29), p = 0.001	0.96 (0.76–1.20), p = 0.701

HRs and 95% CIs were calculated for an increase in heart rate of 5 beats/min. HRs were calculated using Cox proportional hazards models. *Adjusted for age, sex, geographic region, ejection fraction, ischemic HF etiology, sodium level, BNP level, NT-proBNP level, BUN level, QRS duration on baseline electrocardiogram, NYHA functional class IV, systolic blood pressure, randomization to tolvaptan, medical history (hospitalization for HF, hypertension, coronary artery disease, COPD, diabetes, renal insufficiency), and medications (ACE-I/ARB, beta-blockers, MRA, digoxin, and intravenous inotropic agents). For serum sodium level, BUN level, systolic blood pressure, BNP level, NT-proBNP level, and medications, baseline data were used in the multivariable model for baseline heart rate and discharge data were used in the multivariable model for discharge and post-discharge heart rate.

Abbreviations as in Tables 1 and 2.

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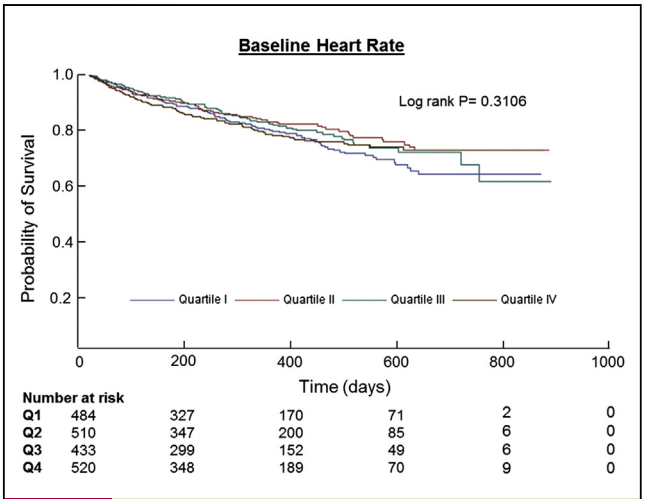

Figure 2 Kaplan-Meier Curves for All-Cause Mortality by Baseline Admission Heart Rate Quartile

Times to events were compared using log-rank tests.

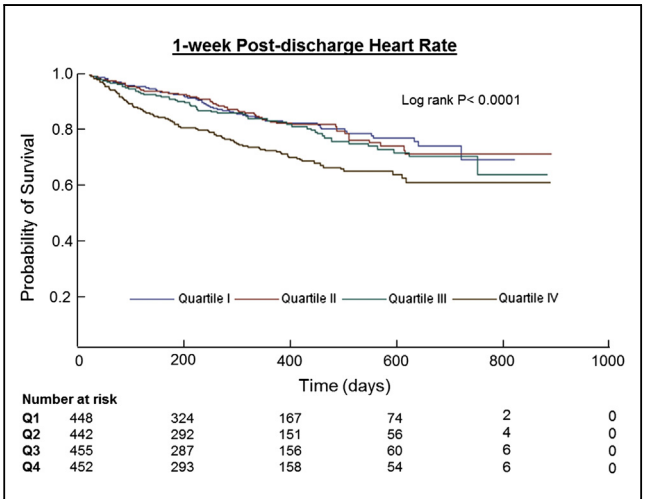

Figure 3 Kaplan-Meier Curves for All-Cause Mortality by 1-Week Post-Discharge Heart Rate Quartile

Times to events were compared using log-rank tests.

The time-dependent relationship between discharge/day 7 heart rate at rates ≥70 beats/min and outcomes further highlights potential differences between heart rate in the inpatient versus outpatient settings. Similar to admission heart rate predicting short-term in-hospital outcome in the aforementioned registry data but not long-term death in our study, heart rate at the time of hospital discharge or late in a prolonged hospital stay may have similar time-sensitive implications.

It is notable that increases in heart rate during hospitalization were associated with poor prognosis, albeit with borderline statistical significance. Possible explanations include worsened hemodynamic status after the insult that prompted hospitalization or in-hospital medication changes.

The early post-discharge period: a point of transition. At rates ≥70 beats/min, heart rate at 1 week into the early post-discharge period was predictive of ACM over the entire duration of follow-up. This may represent patients returning to their chronic stable heart rate after resolution of the short-term unstable phase that necessitated hospitalization. This hypothesis is also supported by the previous post hoc EVEREST analysis that demonstrated rapid increases in post-discharge heart rate in patients with the worst outcomes, despite initial reductions in heart rate during hospitalization (22). The precise point in time post-discharge where heart rate begins to share the prognostic significance seen in patients with chronic HF is unclear, but our results suggest that heart rate as early as 1 week post-discharge may be predictive of short-term and long-term outcomes.

Clinical implications. Our findings suggest that post-discharge heart rate has independent prognostic value and elevated heart rate may be a key finding on routine vital signs that identifies high-risk patients during early post-discharge follow-up. Our results for post-discharge heart rate are consistent with the previously reported benefit of lower heart rate in patients with chronic HF treated with beta-blockers (5,6,19,23) and support similar prognostic significance between heart rate in the chronic and early post-discharge settings. In our study, at rates ≥70 beats/min, improved survival was seen in patients with lower post-discharge heart rate irrespective of beta-blocker use, suggesting that the lower heart rate itself may be more important than the particular pharmacological agent used.

HF continues to be a unique medical condition in which hospitalized patients can be discharged with significantly improved symptoms that respond to standard therapies (24,25) yet face a paradoxically high post-discharge event rate (26). Accordingly, there is an unmet need to develop new therapeutic agents and targets for therapy in this population. Future prospective studies are needed to investigate heart rate in the early post-discharge period as a therapeutic target for higher doses of beta-blockers or the addition of digoxin or ivabradine (8).

Study limitations. Measurements of heart rate were not standardized other than being measured with the patient in the supine position. Although robust multivariate modeling techniques were used to account for potential confounders, models for post-discharge heart rate did not include other post-discharge measures, but rather included data collected at time of discharge/day 7 given the greater extent of missing data in the post-discharge period. Furthermore, our baseline measurement of heart rate occurred up to 48 hours after admission, at the time of study enrollment, and may reflect initial in-hospital therapies. Finally, the population in the analysis of post-discharge heart rate naturally excluded those who died prior to the reference time point and thus prevented inclusion of patients with perhaps more severe disease. The authors decided not to extend the analysis of

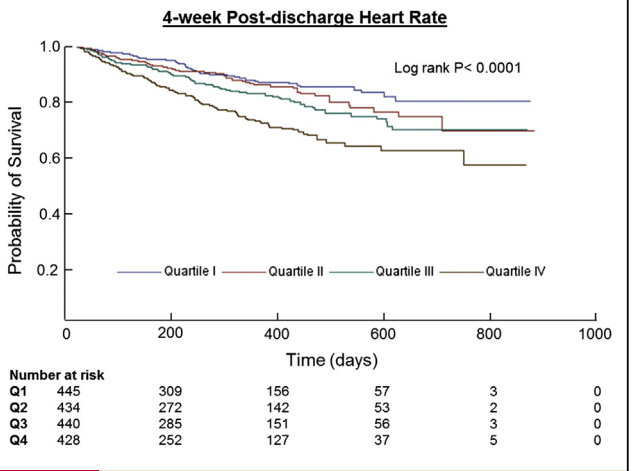

Figure 4 **Kaplan-Meier Curves for All-Cause Mortality by 4-Week Post-Discharge Heart Rate Quartile**

Times to events were compared using log-rank tests.

heart rate beyond 4 weeks post-discharge out of concern for worsening effects of this bias.

Conclusions

In patients with HHF in presumed sinus rhythm, higher resting heart rate in the early post-discharge period was independently associated with increased mortality during subsequent follow-up. Baseline heart rate did not predict risk of death after adjustment for other patient characteristics. Heart rate at the time of discharge was predictive of death within 100 days post-randomization. Future prospective investigations are encouraged to evaluate post-discharge heart rate as a therapeutic target in this high-risk population.

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Key Words: heart failure ■ heart rate ■ hospitalization ■ mortality ■ prognosis.