

# Discharge Heart Rate After Hospitalization for Myocardial Infarction and Long-Term Mortality in 2 US Registries

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**Background**—Although admission heart rate predicts higher mortality after acute myocardial infarction (AMI), less is known about discharge heart rate. We tested the hypothesis that higher discharge heart rate after AMI is related to increased long-term mortality independent of admission heart rate, and assessed whether  $\beta$  blockers modify this relationship.

**Methods and Results**—In 2 prospective US multicenter registries of AMI, we evaluated the associations of discharge and admission heart rate with 3-year mortality using Cox models. Among 6576 patients with AMI, discharge heart rate was modestly associated with initial heart rate ( $r=0.28$ ), comorbidities, and infarct severity. In this cohort, 10.7% did not receive  $\beta$  blockers at discharge. After full adjustment for demographic, psychosocial, and clinical covariates, discharge heart rate (hazard ratio [HR]=1.14 per 10 beats per minute [bpm]; 95% CI=1.07–1.21 per 10 bpm) was more strongly associated with risk of death than admission heart rate (HR=1.05 per 10 bpm; 95% CI=1.02–1.09 per 10 bpm) when both were entered in the same model ( $P=0.043$  for comparison). There was a significant interaction between discharge heart rate and  $\beta$ -blocker use ( $P=0.004$ ) on mortality, wherein risk of death was markedly higher among those with high discharge heart rate and not on  $\beta$  blockers (HR=1.35 per 10 bpm; 95% CI=1.19–1.53 per 10 bpm) versus those with a high discharge heart rate and on  $\beta$  blockers at discharge (HR=1.10 per 10 bpm; 95% CI=1.03–1.17 per 10 bpm).

**Conclusions**—Higher discharge heart rate after AMI was more strongly associated with 3-year mortality than admission heart rate, and the risk associated with higher discharge heart rate was modified by  $\beta$  blockers at discharge. These findings highlight opportunities for risk stratification and intervention that will require further investigation. (*J Am Heart Assoc.* 2019;8:e010855. DOI: 10.1161/JAHA.118.010855.)

**Key Words:**  $\beta$  blocker • discharge • mortality • myocardial infarction

Numerous studies have documented that an elevated heart rate at the time of hospital admission for acute myocardial infarction (AMI) is an independent predictor of mortality both near and longer-term after hospital discharge.<sup>1–9</sup> As a result, admission heart rate is included in risk-stratification algorithms for AMI, such as the GRACE (Global Registry of Acute Coronary

Events) and Thrombolysis in Myocardial Infarction (TIMI) risk scores.<sup>10–12</sup> More recent studies of patients with AMI have reported that heart rate at discharge is also associated with higher long-term mortality.<sup>13,14</sup> Such studies have been limited to European populations and have not formally assessed whether the relationship is independent of admission heart rate.

It is well established that  $\beta$  blockers are effective agents for lowering resting heart rate and, in the setting of AMI, for reducing infarct size, recurrent infarction, and long-term mortality.<sup>15,16</sup> Therefore,  $\beta$ -blocker use during and after AMI is a widely applied performance metric for comparing AMI treatment among hospitals. However, the current measure is a binary assessment as to whether  $\beta$  blockers were used and not whether the use of  $\beta$  blockers achieved a particular target heart rate, a presumed mechanism of the drugs' benefit.<sup>17</sup> As a result, it is important to determine whether the use of  $\beta$ -blocker therapy alone confers benefit or if an association between discharge heart rate and long-term mortality after AMI is modified by treatment with  $\beta$  blockers.

To address current information gaps surrounding this question, we sought to determine whether discharge heart

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## Clinical Perspective

### What Is New?

- After acute myocardial infarction (AMI), this is the first study in a racially diverse US population (1) to demonstrate that discharge heart rate is independently associated with long-term mortality after adjustment for psychosocial, socioeconomic, and healthcare quality variables, as well as standard demographic and clinical variables; (2) to show that this association is both independent and stronger than admission heart rate; and (3) to document that this relationship is modified by  $\beta$ -blocker treatment, such that patients leaving the hospital without receiving  $\beta$  blockers have a much higher risk of mortality than those who receive  $\beta$  blockers.

### What Are the Clinical Implications?

- Although additional investigations are required, these findings suggest that discharge heart rate could improve risk stratification over admission heart rate, a measure included in available risk-prediction indexes for shorter-term mortality after AMI.
- The documented effect modification by  $\beta$ -blocker treatment suggests that post-AMI patients leaving the hospital with higher heart rates ( $\geq 80$  beats per minute and, especially,  $\geq 90$  beats per minute) may require closer follow-up, and underscores the importance of maximizing use of these medications after AMI.
- Whether the use of other heart rate-lowering medications or intensifying  $\beta$ -blocker therapy to achieve lower heart rate targets could modify the observed association between discharge heart rate and mortality after AMI merits further study.

rate predicts mortality after AMI in a more racially heterogeneous US population after accounting for clinical covariates, including admission heart rate, as well as socioeconomic and psychosocial factors. We also examined the associations with mortality for discharge and admission heart rate separately for comparative purposes. In addition, we explicitly evaluated whether the long-term prognosis of patients with elevated discharge heart rate is modified by  $\beta$ -blocker therapy.

## Methods

The data that support the findings of this study are available from the principal investigator of the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) and TRIUMPH (Transitional Research Investigating Underlying Disparities in Myocardial Infarction Patients' Health Status) registries, John A. Spertus (spertusj@umkc.edu), on reasonable request.

## Study Population

We performed our analyses in combined data from the PREMIER and the TRIUMPH prospective registries. PREMIER included 2498 consecutive patients hospitalized with AMI in 19 US hospitals between January 1, 2003, and June 28, 2004.<sup>18</sup> TRIUMPH included 4340 patients hospitalized with AMI in 24 US hospitals between April 11, 2005, and December 21, 2008.<sup>19</sup> To be eligible for inclusion, patients needed to be  $\geq 18$  years, to have elevated biomarkers (troponin or creatine kinase-MB), supporting evidence of AMI (prolonged ischemic signs/symptoms, electrocardiographic ST changes), and to present at the enrolling institution or transfer thereto within the first 24 hours of symptom onset. Incarcerated patients and patients without a preexisting MI whose elevated cardiac biomarkers were related to a revascularization procedure were excluded. All participants provided written informed consent, and the study protocols were approved by the institutional review board at each participating site.

Among 6833 patients enrolled across both registries, 6797 (99%) survived until discharge, and discharge heart rate was available in 6580 (96%) of patients. This high survival rate reflects the studies' focus on patient-centered outcomes, which required patient participation in detailed interviews after AMI admission.<sup>18,19</sup> After excluding outlier values for discharge heart rate (namely,  $< 35$  and  $> 150$  beats per minute [bpm]), 6576 patients were available for inclusion in the present analysis.

## Variables

Baseline data were collected through chart abstraction and standardized interviews by trained hospital research staff between 24 and 72 hours after AMI admission. Admission heart rate was defined as the first available heart rate from the initial patient encounter, whereas discharge heart rate was defined as the last heart rate measure available in the 24 hours before discharge. In addition, extensive clinical and nonclinical information was collected on each patient, including demographics (age, sex, and race), socioeconomic factors (marital status, education, access to health insurance, and employment status), psychosocial factors (social support and Patient Health Questionnaire 9 for Depression), and clinical variables (body mass index, hypertension, diabetes mellitus, hypercholesterolemia, smoking, family history of coronary artery disease, prior AMI, prior angina, prior coronary artery bypass grafting or percutaneous coronary intervention [PCI], chronic heart failure, peripheral arterial disease, prior stroke, chronic renal failure, chronic lung disease, nonskin cancer, and history of depression or current treatment for depression). Data were also obtained on AMI subtype (ST-segment-

elevation versus non-ST-segment-elevation AMI [STEMI versus non-STEMI]), left ventricular (LV) ejection fraction (categorized as normal, mild, moderate, and severe LV dysfunction), Killip class, number of coronary arteries with  $\geq 75\%$  stenosis, systolic blood pressure at both AMI presentation and discharge, and presence of atrial fibrillation or flutter during hospitalization. Laboratory values, including admission glucose and serum creatinine, as well as admission and discharge hematocrit were also recorded. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation. Finally, evaluation and treatment information (coronary angiography, PCI, and coronary artery bypass grafting), patient instructions at discharge (cardiac rehabilitation, diet counselling, exercise counselling, follow-up lipid assessment, and smoking cessation), and data on the percentage and number of the Joint Commission on Accreditation of Healthcare Organizations' quality-of-care indicators received at hospital discharge (eg, appropriate use of aspirin,  $\beta$  blockers, thienopyridines, and other medications) were collected.

## Outcome

The primary outcome of mortality was defined as death from any cause over the 3-year follow-up period and was determined by matching patients' social security numbers, names, and dates of birth with the National Death Index.

## Statistical Analysis

Patients' discharge heart rate was evaluated as a continuous variable and also divided into 5 groups: group 1,  $<60$  bpm ( $n=749$ ); group 2, 60 to  $<70$  bpm ( $n=1985$ ); group 3, 70 to  $<80$  bpm ( $n=1998$ ); group 4, 80 to  $<90$  bpm ( $n=1239$ ); and group 5,  $\geq 90$  bpm ( $n=605$ ). (There were too few participants [ $n=164$ ] with discharge heart rate  $\geq 100$  bpm for separate categorization.) The same approach was used for admission heart rate, which was assessed for comparative purposes and as a covariate. The correlation between discharge and admission heart rates was determined by their Pearson correlation coefficient. Baseline characteristics were compared using  $\chi^2$  tests for categorical variables and 1-way analysis of variance for continuous variables. The functional form of the association between continuous heart rate on admission or discharge and all-cause mortality was assessed with unadjusted cubic splines; because these were consistent with linear relationships for both discharge and admission heart rate, continuous heart rate values were the primary exposure measure, whereas heart rate categories were presented secondarily for descriptive purposes. A site-stratified multivariable Cox proportional hazards model was then developed to determine if discharge heart rate was

independently associated with 3-year mortality after adjusting for possible confounders. Model covariates were selected on the basis of biological mechanisms and known associations. These included age, sex, and race; body mass index, hypertension, diabetes mellitus, hypercholesterolemia, and smoking status; documented cancer, congestive heart failure, peripheral arterial disease, and prior stroke; patient-reported socioeconomic and psychosocial factors (depressive symptoms, self-report of monthly financial situation, avoidance of health care attributable to costs, absence of health insurance, graduation from high school, and marital status); admission heart rate; log-transformed glucose, hematocrit, and estimated glomerular filtration rate; index STEMI, LV systolic function, Killip class, PCI during hospitalization, coronary artery bypass grafting during hospitalization, and in-hospital atrial fibrillation; provision of discharge instructions on smoking cessation; and discharge medications, including aspirin,  $\beta$  blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and thienopyridines. The magnitude of the regression coefficients for discharge and admission heart rate was compared using a Wald test.

To assess whether the relationship of discharge heart rate with mortality varied in the presence and absence of  $\beta$ -blocker therapy, we added a first-order interaction term for discharge heart rate and  $\beta$ -blocker use. We also tested for effect modification by age, sex, race, type of AMI (STEMI versus non-STEMI), LV dysfunction, and chronic lung disease through inclusion of corresponding interaction terms. In an additional exploratory analysis, we tested for 3-way interaction between discharge heart rate,  $\beta$ -blocker therapy, and LV dysfunction.

Approximately 22% of patients had any missing covariate data (the highest missing proportion for any single variable was for depression at 5.2%). Missing covariate data were modest, but were imputed using IVEWARE.<sup>20</sup> All other analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC), and R, version 3.4.1. All analyses were prespecified, and a 2-sided  $P<0.05$  was considered statistically significant.

## Results

### Baseline Characteristics

Among 6576 patients with AMI, the mean age was  $60 \pm 13$  years, 33% were women, and 24% were of black race. Table 1 describes the baseline characteristics of the study cohort across the 5 discharge heart rate groups. Compared with patients with lower discharge heart rates, patients with higher discharge heart rates were younger, were more often women, and were less likely to have a history of smoking; however, they had a higher body mass index, higher

**Table 1.** Characteristics of Study Population by Discharge Heart Rate

Covariates	Discharge Heart Rate					P Value
	Group 1 (<60 bpm) (N=749)	Group 2 (60–69 bpm) (N=1985)	Group 3 (70–79 bpm) (N=1998)	Group 4 (80–89 bpm) (N=1239)	Group 5 (>90 bpm) (N=605)	
<b>Demographic and clinical</b>						
Age, y	60.5±12.2	60.7±12.4	59.3±12.8	58.5±12.3	58.4±13.2	<0.001
Male sex, n (%)	543 (72.5)	1329 (67.0)	1324 (66.3)	801 (64.6)	418 (69.1)	0.004
Race category, n (%)						0.076
White	539 (72.3)	1426 (72.0)	1351 (67.9)	834 (67.8)	427 (70.8)	
Black	161 (21.6)	450 (22.7)	511 (25.7)	314 (25.5)	142 (23.5)	
Other	45 (6.0)	104 (5.3)	129 (6.5)	82 (6.7)	34 (5.6)	
Initial BMI, kg/m <sup>2</sup>	28.7±5.8	29.4±6.1	29.8±6.5	29.5±6.4	29.3±6.4	<0.001
Hypertension, n (%)	471 (62.9)	1303 (65.6)	1313 (65.7)	826 (66.7)	392 (64.8)	0.524
Diabetes mellitus, n (%)	181 (24.2)	548 (27.6)	628 (31.4)	422 (34.1)	201 (33.2)	<0.001
Hypercholesterolemia, n (%)	374 (49.9)	998 (50.3)	962 (48.1)	600 (48.4)	300 (49.6)	0.680
History of smoking, n (%)	505 (67.4)	1166 (58.7)	1193 (59.7)	754 (60.9)	358 (59.2)	<0.001
Congestive heart failure, n (%)	58 (7.7)	182 (9.2)	184 (9.2)	126 (10.2)	80 (13.2)	0.009
Prior stroke, n (%)	46 (6.1)	97 (4.9)	116 (5.8)	60 (4.8)	38 (6.3)	0.390
Peripheral arterial disease, n (%)	42 (5.6)	107 (5.4)	114 (5.7)	81 (6.5)	40 (6.6)	0.623
Chronic lung disease, n (%)	55 (7.3)	158 (8.0)	180 (9.0)	139 (11.2)	84 (13.9)	<0.001
Cancer, n (%)	49 (6.5)	144 (7.3)	165 (8.3)	81 (6.5)	54 (8.9)	0.181
Chronic renal failure, n (%)	53 (7.1)	152 (7.7)	167 (8.4)	113 (9.1)	57 (9.4)	0.324
<b>Socioeconomic and psychosocial factors</b>						
Education of high school or more, n (%)	586 (78.7)	1555 (79.3)	1552 (78.6)	987 (80.6)	461 (77.3)	0.528
Monthly financial situation, n (%)						0.001
Some money left over	358 (49.0)	935 (48.5)	826 (42.5)	520 (43.2)	271 (46.4)	
Just enough to make ends meet	254 (34.7)	645 (33.5)	737 (37.9)	439 (36.5)	190 (32.5)	
Not enough to make ends meet	119 (16.3)	348 (18.0)	382 (19.6)	244 (20.3)	123 (21.1)	
Avoided getting health care because of cost, n (%)	185 (25.0)	439 (22.6)	435 (22.2)	281 (23.3)	138 (23.4)	0.594
Lack of insurance/self-pay, n (%)	1135 (18.5)	343 (17.8)	391 (20.1)	231 (19.3)	125 (21.2)	0.255
Married, n (%)	445 (59.7)	1097 (55.7)	1079 (54.4)	670 (54.4)	312 (52.3)	0.058
Enriched social support score	22.2±4.2	21.9±4.6	21.8±4.5	22.0±4.3	22.1±4.5	0.253
PHQ9 score ≥10, n (%)	137 (18.9)	354 (18.7)	369 (19.6)	297 (25.3)	123 (21.9)	<0.001
<b>Acute care</b>						
STEMI as index event, n (%)	313 (41.8)	821 (41.4)	899 (45.0)	566 (45.7)	258 (42.6)	0.061
Initial systolic BP, mm Hg	143.0±31.2	143.8±31.0	142.3±30.6	140.7±30.0	136.0±30.8	<0.001
Initial diastolic BP, mm Hg	79.6±18.3	81.0±19.5	81.9±19.6	82.3±19.7	81.0±19.6	0.026
Initial heart rate, bpm	71.5±18.3	77.9±18.4	82.5±18.6	86.7±19.6	90.7±20.0	<0.001
Killip class, n (%)						<0.001
I	644 (89.6)	1675 (88.8)	1649 (86.9)	981 (84.2)	456 (81.9)	
II	62 (8.6)	171 (9.1)	195 (10.3)	140 (12.0)	72 (12.9)	
III	10 (1.4)	25 (1.3)	36 (1.9)	28 (2.4)	17 (3.1)	
IV	3 (0.4)	15 (0.8)	17 (0.9)	16 (1.4)	12 (2.2)	
Log glucose, mg/dL	4.9±0.4	4.9±0.4	5.0±0.4	5.0±0.4	5.0±0.4	<0.001

Continued

Table 1. Continued

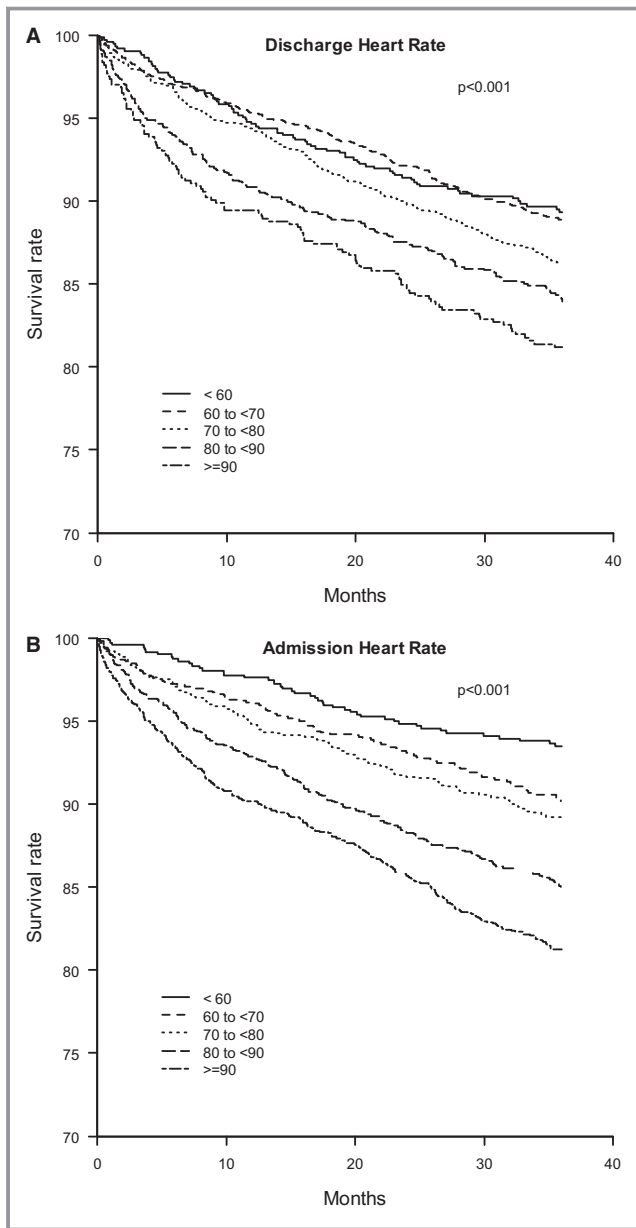
Covariates	Discharge Heart Rate					P Value
	Group 1 (<60 bpm) (N=749)	Group 2 (60–69 bpm) (N=1985)	Group 3 (70–79 bpm) (N=1998)	Group 4 (80–89 bpm) (N=1239)	Group 5 (≥90 bpm) (N=605)	
eGFR, mL/min per 1.73 m <sup>2</sup>	76.3±26.3	74.0±27.7	75.6±28.4	76.1±32.5	76.0±30.6	0.159
Critically diseased vessels, n (%)						<0.001
0	60 (8.8)	166 (9.2)	174 (9.6)	96 (8.5)	39 (7.3)	
1	334 (49.0)	842 (46.5)	817 (45.1)	472 (41.9)	204 (38.3)	
2	151 (22.2)	466 (25.7)	433 (23.9)	288 (25.6)	134 (25.1)	
3	136 (20.0)	336 (18.6)	386 (21.3)	270 (24.0)	156 (29.3)	
LV systolic function, n (%)						<0.001
Normal	486 (65.0)	1257 (63.5)	1184 (59.3)	635 (51.3)	290 (47.9)	
Mild	146 (19.5)	399 (20.2)	402 (20.2)	256 (20.7)	128 (21.2)	
Moderate	86 (11.5)	222 (11.2)	253 (12.7)	184 (14.9)	97 (16.0)	
Severe	30 (4.0)	102 (5.2)	156 (7.8)	163 (13.2)	90 (14.9)	
PCI, n (%)	506 (67.6)	1334 (67.2)	1318 (66.0)	753 (60.8)	299 (49.4)	<0.001
CABG, n (%)	17 (2.3)	117 (5.9)	170 (8.5)	195 (15.7)	154 (25.5)	<0.001
In-hospital atrial fibrillation/flutter, n (%)	49 (6.5)	144 (7.3)	142 (7.1)	95 (7.7)	55 (9.1)	0.0437
Final systolic BP, mm Hg	120.4±19.3	120.9±19.9	120.2±18.7	119.0±19.5	118.1±18.9	0.007
Final systolic BP ≤100 mm Hg, n (%)	111 (14.9)	291 (14.8)	278 (14.0)	209 (17.0)	120 (20.0)	0.003
Final diastolic BP, mm Hg	66.8±11.2	67.8±11.5	69.1±11.6	69.5±11.8	70.0±12.2	<0.001
Final hematocrit, %	37.7±5.4	36.9±5.2	36.6±5.5	35.6±5.7	35.0±5.9	<0.001
Discharge medications and instructions, n (%)						
Aspirin	709 (94.7)	1867 (94.1)	1859 (93.0)	1149 (92.7)	548 (90.6)	0.017
β Blocker	660 (88.1)	1807 (91.0)	1788 (89.5)	1107 (89.3)	513 (84.8)	<0.001
Nondihydropyridine CCB	10 (1.3)	41 (2.1)	58 (2.9)	33 (2.7)	25 (4.1)	0.008
ACEI or ARB	603 (80.5)	1480 (74.6)	1533 (76.7)	882 (71.2)	376 (62.1)	<0.001
Statin	661 (88.3)	1719 (86.6)	1718 (86.0)	1056 (85.2)	480 (79.3)	<0.001
Thienopyridine	576 (76.9)	1519 (76.5)	1467 (73.4)	857 (69.2)	338 (55.9)	<0.001
Warfarin	67 (8.9)	185 (9.3)	197 (9.9)	158 (12.8)	91 (15.0)	<0.001
Diuretic	153 (20.4)	440 (22.2)	437 (21.9)	352 (28.4)	220 (36.4)	<0.001
Nitrate	165 (22.0)	384 (19.3)	385 (19.3)	210 (16.9)	95 (15.7)	0.014
Amiodarone	31 (4.1)	91 (4.6)	83 (4.2)	52 (4.2)	27 (4.5)	0.963
Sotalol	8 (1.1)	11 (0.6)	4 (0.2)	4 (0.3)	0 (0)	0.011
Instructions on smoking cessation	308 (41.1)	707 (35.6)	698 (34.9)	441 (35.6)	208 (34.4)	0.034

Data are given as mean±SD unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; LV, left ventricular; PCI, percutaneous coronary intervention; PHQ9, Patient Health Questionnaire 9 for Depression; STEMI, ST-segment–elevation myocardial infarction.

frequencies of diabetes mellitus, chronic lung disease, congestive heart failure, and elevated depressive-symptom scores, and a worse self-reported monthly financial situation. Patients with higher discharge heart rates more commonly had a higher admission heart rate, but lower admission systolic blood pressure, as well as lower discharge systolic blood pressure but higher discharge diastolic blood pressure. They also exhibited

higher Killip class and initial glucose levels, and were more likely to have multivessel disease and moderate or severe LV systolic dysfunction, but had lower hematocrit at discharge. During their hospitalization, patients with a higher discharge heart rate were less likely to undergo PCI and more likely to receive coronary artery bypass grafting than low-discharge heart rate patients. They also had a higher frequency of atrial fibrillation or flutter. At



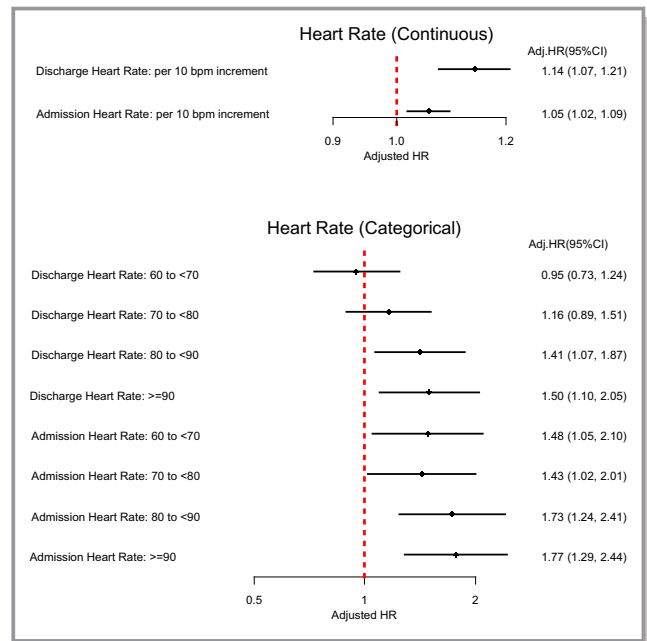


**Figure 1.** Kaplan-Meier analysis of 3-year all-cause mortality by discharge heart rate (A) and admission heart rate (B).

discharge, patients in the higher discharge heart rate groups were less likely to be treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers,  $\beta$  blockers, statins, thienopyridines, statins, and sotalol, but were more likely to be treated with diuretics, nondihydropyridine calcium-channel blockers, and warfarin.

### Unadjusted Association of Discharge Heart Rate With Mortality

Kaplan-Meier plots for survival, according to discharge and admission heart rate groups, are shown in Figure 1A and 1B,



**Figure 2.** Forest plot showing results of multivariable analysis of discharge and admission heart rate and 3-year mortality. Models are adjusted for age, sex, race, body mass index, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, cancer, congestive heart failure, peripheral arterial disease, stroke, depressive symptoms, self-report of monthly financial situation, avoidance of health care because of costs, lack of health insurance, education, marital status, glucose, hematocrit, estimated glomerular filtration rate, index ST-segment–elevation myocardial infarction, left ventricular systolic function, Killip class, percutaneous coronary intervention during hospitalization, coronary artery bypass graft surgery during hospitalization, in-hospital atrial fibrillation, provision of discharge instructions on smoking cessation, and discharge medications, including aspirin,  $\beta$  blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, statins, and thienopyridines. Bpm indicates beats per minute; HR, hazard ratio.

respectively. These show clear separation of the curves for all groups, except group 1 and group 2 for discharge heart rate and group 2 and group 3 for admission heart rate. Unadjusted cubic splines, however, suggested a linear relationship for discharge and admission heart rates, each with all-cause mortality. The correlation between admission and discharge heart rates was modest ( $r=0.28$ ).

### Multivariable Analysis

After adjustment for potential confounders, discharge heart rate remained significantly associated with all-cause mortality (HR=1.15 per 10-bpm increment; 95% CI=1.09–1.22 per 10-bpm increment). As shown in Figure 2, this was not materially influenced by additional adjustment for admission heart rate. Specifically, after such adjustment, discharge heart rate was associated with a 14% (95% CI, 7%–21%) increased risk of

mortality for every 10-bpm increment in discharge heart rate. As also presented in Figure 2, the association for admission heart rate with mortality was also significant in this model, with a 5% (95% CI, 2%–9%) increased risk for every 10-bpm increment. The magnitude of the association for discharge heart rate was significantly greater than for admission heart rate ( $P=0.043$ ). When assessed as 5 categories of heart rates, patients with a discharge heart rate of 80 to 89 bpm (group 4) and  $\geq 90$  bpm (group 5) had 41% (95% CI, 7%–87%) and 50% (95% CI, 10%–105%) increased risks of long-term mortality in comparison to patients with a discharge heart rate  $<60$  bpm (group 1). In the case of admission heart rate in the same model, significant associations were seen for all heart rate categories compared with heart rate  $<60$  bpm (group 1) (Figure 2).

### Discharge Heart Rate and $\beta$ -Blocker Use

Compared with the 33.4% of patients admitted on  $\beta$  blockers, 89.3% were discharged on  $\beta$ -blocker therapy. By contrast, the proportions of participants receiving nondihydropyridine calcium-channel blockers on admission and discharge were 2.3% and 2.5%, respectively. As shown in Table 2, patients discharged without  $\beta$ -blocker therapy differed in several respects from those who received such therapy at discharge. In particular, patients not discharged on  $\beta$  blockers were more often black, with a lower body mass index, but with more frequent histories of smoking, chronic lung disease, and congestive heart failure, compared with those discharged on  $\beta$  blockers. Patients not receiving  $\beta$  blockers were less educated and less frequently married, reported a more adverse monthly financial situation, and had more frequent depression relative to their counterparts who received  $\beta$  blockers. Among those not prescribed  $\beta$  blockers at discharge, the index event was less often a STEMI, there was a lower frequency of critical coronary artery stenosis, and there were lower levels of both initial and final systolic blood pressure, initial glucose, and final hematocrit. In comparison to patients who were discharged on  $\beta$ -blockers, patients who were not discharged on those medications less commonly underwent PCI for the index event, but more frequently had in-hospital atrial fibrillation or flutter. Patients off  $\beta$  blockers at discharge were also less frequently discharged on aspirin, thienopyridines, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins, and less often received discharge instructions on smoking cessation, but were more often discharged on amiodarone.

The relationship between discharge heart rate and mortality differed by whether patients were treated with  $\beta$  blockers at discharge ( $P$  for interaction=0.004). Findings were similar whether admission heart rate was included for adjustment in the model. In the fully adjusted model including admission

heart rate, the adjusted association between discharge heart rate and mortality was markedly stronger among those not discharged on  $\beta$  blockers (35% greater risk per 10-bpm increment [95% CI, 19%–53% greater risk per 10-bpm increment]) compared with those who were discharged on  $\beta$  blockers (10% greater risk per 10-bpm increment [95% CI, 3%–17% greater risk per 10-bpm increment]) (Figure 3). As an illustration, patients with a discharge heart rate  $\geq 90$  bpm and not on a  $\beta$  blocker had a 285% (95% CI, 67%–788%) higher mortality risk compared with untreated patients with a discharge heart rate  $<60$  bpm, whereas patients with a discharge heart rate  $\geq 90$  bpm who were treated with a  $\beta$  blocker had only a 78% (95% CI, 29%–146%) increased mortality risk compared with untreated patients with a discharge heart rate  $<60$  bpm (Figure 3). This was independent of admission heart rate, which was itself also significantly associated with mortality in the same model (6% greater risk per 10-bpm increment [95% CI, 2%–10% greater risk per 10-bpm increment]). In addition, there was no evidence of effect modification of discharge heart rate's association with mortality by other factors, including age, sex, race, type of AMI, LV dysfunction, or chronic lung disease (all  $P\geq 0.079$ ). Nor was there evidence of a differential impact of  $\beta$  blockers in those with and without LV dysfunction in a follow-up exploratory analysis of 3-way interaction ( $P=0.771$ ).

### Discussion

In this large sample of patients with AMI from 2 national registries, we found that discharge heart rate was significantly associated with all-cause mortality after 3 years of follow-up, independent of a broad array of potential confounders. This association was both independent of, and stronger than, admission heart rate, which itself was independently related to mortality. The relationship between discharge heart rate and all-cause death was modified by  $\beta$ -blocker treatment at discharge, such that the risk of mortality with higher discharge heart rate was markedly greater for patients who left the hospital without receiving a  $\beta$ -blocker than those who did receive a  $\beta$ -blocker.

The association between elevated heart rate on admission and outcome in the setting of AMI has been recognized for decades<sup>1,2,6–8</sup> and incorporated into numerous risk-stratification schemes, including the GRACE and TIMI risk scores.<sup>11,12</sup> Fewer investigators have examined the association of discharge heart rate, a potentially modifiable therapeutic target, with post-AMI outcomes. In studies predating the contemporary era of primary or early PCI for AMI, Hjalmarson et al observed that discharge heart rate was an independent predictor of 1-year total mortality after MI,<sup>6</sup> an association confirmed by Zuanetti et al, who documented a progressive increase in 6-month mortality at higher discharge heart rate

**Table 2.** Characteristics of Patients by Prescription of  $\beta$  Blockers at Discharge

Covariates	$\beta$ Blocker at Discharge		P Value
	Yes (N=5875)	No (N=701)	
Age, y	59.6 $\pm$ 12.6	60.2 $\pm$ 12.9	0.238
Male sex, n (%)	3958 (67.4)	457 (65.2)	0.245
Race category, n (%)			<0.001
White	4144 (70.8)	433 (61.9)	
Black	1346 (23.0)	232 (33.2)	
Other	360 (6.2)	34 (4.9)	
Initial BMI, kg/m <sup>2</sup>	29.5 $\pm$ 6.3	29.0 $\pm$ 6.5	0.040
Hypertension, n (%)	3858 (65.7)	447 (63.8)	0.316
Diabetes mellitus, n (%)	1773 (30.2)	207 (29.5)	0.723
Hypercholesterolemia, n (%)	2918 (49.7)	316 (45.1)	0.057
History of smoking, n (%)	970 (59.9)	142 (63.4)	0.021
Congestive heart failure, n (%)	165 (10.2)	41 (18.3)	<0.001
Prior stroke, n (%)	316 (5.4)	41 (5.8)	0.603
Peripheral arterial disease, n (%)	336 (5.7)	48 (6.8)	0.228
Chronic lung disease, n (%)	498 (8.5)	118 (16.8)	<0.001
Cancer, n (%)	440 (7.5)	53 (7.6)	0.946
Chronic renal failure, n (%)	475 (8.1)	67 (9.6)	0.180
Socioeconomic and psychosocial factors			
Education of high school or more, n (%)	4617 (79.5)	524 (75.5)	0.014
Avoided health care because of cost, n (%)	1311 (22.8)	167 (24.3)	0.383
Lack of insurance/self-pay, n (%)	4251 (73.8)	482 (69.6)	0.016
Monthly financial situation, n (%)			0.001
Some money left over	2618 (45.8)	292 (42.9)	
Just enough to make ends meet	2041 (35.7)	224 (32.9)	
Not enough to make ends meet	1052 (18.4)	164 (24.1)	
Married, n (%)	3255 (55.8)	348 (50.2)	0.005
Enriched social support score	22.0 $\pm$ 4.4	21.5 $\pm$ 5.2	0.001
PHQ9 score $\geq$ 10, n (%)	1108 (19.9)	172 (25.7)	<0.001
Acute care			
STEMI as index event, n (%)	2641 (45.0)	216 (30.8)	<0.001
Initial systolic BP, mm Hg	142.5 $\pm$ 30.7	137.6 $\pm$ 31.4	<0.001
Initial diastolic BP, mm Hg	81.6 $\pm$ 19.4	79.0 $\pm$ 19.7	<0.001
Initial heart rate, bpm	81.3 $\pm$ 19.4	82.0 $\pm$ 20.8	0.437
Killip class, n (%)			0.003
I	4860 (87.3)	545 (82.7)	
II	556 (10.0)	84 (12.7)	
III	95 (1.7)	21 (3.2)	
IV	54 (1.0)	9 (1.4)	
Log glucose	5.0 $\pm$ 0.4	4.9 $\pm$ 0.4	0.016
eGFR, mL/min per 1.73 m <sup>2</sup>	75.4 $\pm$ 28.3	74.4 $\pm$ 34.0	0.384
Critically diseased vessels, n (%)			<0.001

Continued



Table 2. Continued

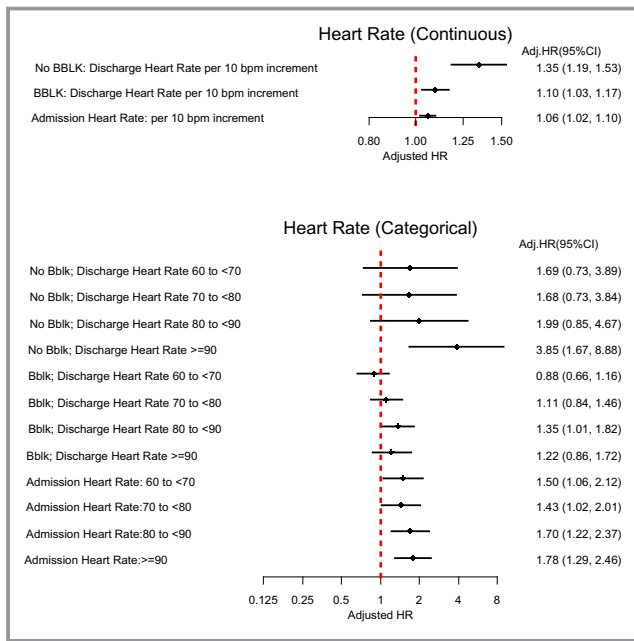
Covariates	β Blocker at Discharge		P Value
	Yes (N=5875)	No (N=701)	
0	419 (7.8)	116 (20.8)	
1	2453 (45.4)	216 (38.8)	
2	1366 (25.3)	106 (19.0)	
3	1165 (21.6)	119 (21.4)	
LV systolic function, n (%)			0.059
Normal	3426 (58.4)	426 (60.8)	
Mild	1210 (20.6)	121 (17.3)	
Moderate	758 (12.9)	84 (12.0)	
Severe	471 (8.0)	70 (10.0)	
PCI, n (%)	3891 (66.2)	319 (45.5)	<0.001
CABG, n (%)	578 (9.8)	75 (10.7)	0.471
In-hospital atrial fibrillation/flutter, n (%)	413 (7.0)	72 (10.3)	<0.001
Final systolic BP, mm Hg	119.8±19.1	121.8±20.4	0.011
Final systolic BP ≤100, mm Hg	904 (15.5)	105 (15.1)	0.803
Final diastolic BP, mm Hg	68.6±11.6	68.7±12.0	0.896
Final hematocrit, %	36.6±5.5	36.0±5.6	0.010
Discharge medications and instructions, n (%)			
Aspirin	5557 (94.6)	575 (82.0)	<0.001
Nondihydropyridine CCB	109 (1.9)	58 (8.3)	<0.001
ACEI or ARB	4472 (76.1)	402 (57.3)	<0.001
Statin	5173 (88.1)	461 (65.8)	<0.001
Thienopyridine	4412 (75.1)	345 (49.2)	<0.001
Warfarin	619 (10.5)	79 (11.3)	0.551
Diuretic	1421 (24.2)	181 (25.8)	0.341
Nitrate	1095 (18.6)	144 (20.5)	0.223
Amiodarone	234 (4.0)	50 (7.1)	<0.001
Sotalol	22 (0.4)	5 (0.7)	0.201
Instructions on smoking cessation	2137 (36.4)	225 (32.1)	0.025

Data are given as mean±SD unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; LV, left ventricular; PCI, percutaneous coronary intervention; PHQ9, Patient Health Questionnaire 9 for Depression; STEMI, ST-segment–elevation myocardial infarction.

values in a separate cohort.<sup>8</sup> Only a third of patients in these studies received β blockers, however, levels well below those seen in modern practice, nor were other current guideline-directed medical therapies, such as statins, angiotensin-converting enzyme inhibitors, or coronary revascularization, as widely used.

Two European studies have since documented associations between elevated discharge heart rate and increased mortality in contemporary practice, characterized by primary revascularization and widespread β-blocker use.<sup>13,14</sup> Among 1453 patients with STEMI treated with primary PCI, Antoni et al found higher discharge heart rate to be associated

with higher all-cause and cardiovascular mortality at follow-up of up to 4 years.<sup>13</sup> The number of deaths was modest, however, precluding extensive adjustment for covariates, including admission heart rate. Similarly, in a separate study of 3079 patients discharged alive after AMI, most of whom had undergone revascularization, Seronde et al documented a significant positive relationship between discharge heart rate and 1- or 5-year mortality.<sup>14</sup> There was evidence of effect modification by LV function, wherein the increased risk was only observed in the subset with depressed LV function, but not by use of β blockade. No concurrent adjustment for admission heart rate was



**Figure 3.** Forest plot showing interaction between discharge heart rate and  $\beta$ -blocker (BBLK) therapy at discharge. Models adjusted for covariates in Figure 2. Bpm indicates beats per minute; HR, hazard ratio

reported. Given prior studies showing an association between admission heart rate and long-term mortality after AMI, it remains unclear to what extent the findings for discharge heart rate in these studies were a surrogate for admission heart rate.

The present study is, to our knowledge, the largest to date to evaluate the association of discharge heart rate with mortality after AMI. It is also the first to do so in a racially diverse US population, and to account for a range of psychosocial, socioeconomic, and healthcare quality measures in addition to the demographic and clinical covariates considered in previous studies. As such, the current study further illuminates the relationship between discharge heart rate after MI and long-term mortality. In fact, we found that the relationship between continuous heart rate at discharge and long-term mortality was independent and significantly stronger than the corresponding association for continuous heart rate on admission, starting with heart rates <60 bpm. Moreover, the current study newly highlights the presence of important effect modification of this association by  $\beta$ -blocker use, although not by LV dysfunction, as previously reported by Seronde et al.<sup>14</sup> Although differences in study populations, practice patterns, and health systems could account for the different findings between the 2 studies, the larger sample size of the present investigation does afford more stable risk estimates in subgroups and greater power to evaluate effect modification, which may explain differences in the results.

That the final in-hospital heart rate emerged as a stronger risk factor for 3-year mortality than admission heart rate among patients with AMI is unsurprising because this measure of autonomic tone and (patho)physiologic stress<sup>21</sup> reflects the clinical evolution and impact of treatment of the index event throughout the hospitalization for those surviving to discharge. As with admission heart rate, higher discharge heart rate in this observational study was associated with adverse sociodemographic, psychosocial, clinical, and care-related characteristics, and residual confounding could explain the associations observed. Hence, although it is not possible herein to determine to what extent discharge heart rate is acting as a risk factor as opposed to a risk marker, the fact that discharge heart rate was robustly associated with mortality despite extensive adjustment supports the value of this readily obtained parameter for risk stratification. Indeed, our findings suggest discharge heart rate as a better measure than admission heart rate for risk stratification after AMI, although incremental performance of discharge heart rate relative to validated risk prediction instruments for short-term outcomes, such as the GRACE score for acute coronary syndromes<sup>22</sup> or the TIMI risk score for STEMI,<sup>12</sup> will require investigation in larger registries with sufficient numbers of events at the 6-month or 30-day time frame.

Stratified analyses by  $\beta$ -blocker use attest to the pronounced increase in risk with higher discharge heart rate for those not receiving this guideline-directed medical therapy, while showing that a significant association of discharge heart rate with higher mortality persists, albeit in attenuated form, for those receiving  $\beta$  blockade. The accentuated risk gradient for discharge heart rate among those not treated with  $\beta$  blockers occurred in the context of a higher proportion of blacks, more common history of smoking, greater psychosocial and economic adversity, and lower associated use of other guideline-directed interventions in this group compared with those treated with  $\beta$  blockers. In comparison to  $\beta$ -blocker users, nonusers also exhibited increased noncardiac comorbidities (namely, chronic lung disease and anemia), as well as more severe cardiac disease, including heart failure and associated atrial dysrhythmias. Although we undertook extensive adjustment for these sociodemographic, psychosocial, and clinical factors, residual confounding by such factors, or confounding by unmeasured factors, may have contributed to the steeper association seen in  $\beta$ -blocker untreated versus treated patients. Still, these findings support the importance of  $\beta$ -blocker treatment and other guideline-directed medical therapies after AMI in those without contraindications.

Of relevance in the context of the current findings is the drug ivabradine, which acts to slow heart rate by blocking the funny current at the sinoatrial node.<sup>23</sup> This medication has been documented to reduce cardiovascular events in stable

patients with reduced LV function, with heart failure symptoms, and in sinus rhythm with a heart rate  $\geq 70$  bpm,<sup>23</sup> and is approved for this indication.<sup>24</sup> Many patients in the current study, whether on or off  $\beta$ -blocker therapy, but with contraindications to nondihydropyridine calcium-channel blockers, would meet eligibility for treatment with this medication. Notably, more patients with a history of heart failure and, marginally, reduced LV function did not receive  $\beta$  blockers at discharge; to the extent that this may have been attributable to concerns about relative hypotension, ivabradine does offer a potential alternative that does not lower blood pressure. Whether use of ivabradine or nondihydropyridine calcium-channel blockers in eligible patients could modify the association between discharge heart rate and mortality or the steeper gradient in those not receiving  $\beta$  blockers observed herein is unknown. But experimental and clinical data showing favorable effects of ivabradine-induced heart rate lowering on LV remodeling and arterial compliance<sup>21</sup> support the role of discharge heart rate not just as a marker but as a modifiable risk factor in such patients.

These considerations apply as well to patients receiving  $\beta$ -blocker therapy, in whom discharge heart rate is likewise both risk marker and, at least partly, modifiable risk factor for adverse post-AMI outcome. The attenuated association observed between discharge heart rate and mortality among those on  $\beta$  blockade is consistent with this concept. The relationship observed in the  $\beta$ -blocker-treated group is also compatible with a prior meta-regression analysis of randomized trials of  $\beta$ -blocker therapy in AMI, which reported that treatment benefit was related to the magnitude of resting heart rate reduction.<sup>17</sup> Our results in patients with AMI, on and off  $\beta$  blockers alike, suggest that heart rate lowering, as tolerated by blood pressure, should be optimized before discharge, and that patients with discharge heart rates  $\geq 80$  bpm and, especially,  $\geq 90$  bpm require particular attention and close postdischarge follow-up. Whether performance assessments should incorporate a specific heart rate target, particularly among those receiving  $\beta$ -blockers, emerges as a more complicated issue given the influence of attendant psychosocial factors and comorbidities on heart rate documented herein, but merits additional investigation in light of these and earlier findings.<sup>13,14</sup>

When interpreting our findings, it is important to consider several potential limitations of this study. The findings reflect practice patterns from 2003 to 2008, and may not be fully generalizable to contemporary practice. We examined the effect of discharge heart rate, a single measure at 1 time point, on outcome over 3 years, and one could argue that this single measure may not be representative of patients' postdischarge heart rates. Although serial outpatient heart rate data might have shed further light on the consistency of the elevated heart rate over time, these data

were not available. Nonetheless, heart rate at discharge is a readily measured parameter and our observed association with long-term mortality can be helpful in identifying higher-risk patients in clinical practice. In addition, we did not examine dose-response of  $\beta$  blockers in relation to discharge heart rate or the specific  $\beta$  blocker used. This was beyond the scope of this observational study, in which type and dose of  $\beta$  blocker used varied by site and according to physician preference, making corresponding interpretation complicated. Furthermore, it is not possible to define whether the greater risk in patients not on a  $\beta$  blocker reflects a selection bias in that those not treated are sicker and the impact of elevated heart rate is more pronounced because of patients' underlying health, as opposed to a modification of this risk with  $\beta$  blockers. Finally, as with all observational data, we cannot exclude residual confounding, despite having performed extensive multivariable adjustment for clinical, as well as socioeconomic and psychological, factors.

The current study in 2 large multicenter US registries of racially heterogeneous patients shows that discharge heart rate was positively associated with 3-year all-cause mortality among AMI survivors, an association that was stronger than for admission heart rate. The association between discharge heart rate and death was modified by use of  $\beta$  blockers, such that a steeper mortality risk was observed for patients who were not treated with these guideline-recommended medications. These findings highlight the importance of discharge heart rate as risk marker and risk factor for mortality after AMI, and support the role of  $\beta$ -blocker treatment after AMI in modifying this risk. Whether treating to lower heart rates, or whether other heart rate-lowering medications could also modify the adverse prognosis associated with discharge heart rate, warrants further investigation.

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