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CME

Association of Heart Rate and Outcomes in a Broad Spectrum of Patients With Chronic Heart Failure

Results From the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) Program

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CME Objective for This Article: At the end of this activity, the learner should be able to describe the relationship between baseline resting heart rate and outcomes in patients with chronic heart failure according to baseline left ventricular ejection fraction and cardiac rhythm.

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Association of Heart Rate and Outcomes in a Broad Spectrum of Patients With Chronic Heart Failure

Results From the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) Program

Objectives The aim of this study was to explore the relationship between baseline resting heart rate and outcomes in patients with chronic heart failure (HF) according to baseline left ventricular ejection fraction (LVEF) and cardiac rhythm.

Background Elevated resting heart rate is associated with worse outcomes in patients with HF and reduced LVEF. Whether this association is also found in patients with HF and preserved LVEF is uncertain, as is the predictive value of heart rate in patients in atrial fibrillation (AF).

Methods Patients enrolled in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) Program were divided into groups by tertiles of baseline heart rate. Cox proportional hazard models were used to investigate the association between heart rate and pre-specified outcomes in the overall population as well as in subgroups defined according to LVEF (≤40% vs. >40%) and presence (or absence) of AF at baseline.

Results After adjusting for predictors of poor prognosis, patients in the highest heart rate tertile had worse outcomes when compared with those in the lowest heart rate group (e.g., for the composite of cardiovascular death or HF hospital stay hazard ratio: 1.23, 95% confidence interval: 1.11 to 1.36, $p < 0.001$). The relationship between heart rate and outcomes was similar across LVEF categories and was not influenced by beta-blocker use (p value for interaction >0.10 for both endpoints). However, amongst patients in AF at baseline, heart rate had no predictive value (p value for interaction <0.001).

Conclusions Resting heart rate is an important predictor of outcome in patients with stable chronic HF without AF, regardless of LVEF or beta-blocker use. (J Am Coll Cardiol 2012;59:1785–95) © 2012 by the American College of Cardiology Foundation

Elevated resting heart rate is an established risk factor for cardiovascular mortality and morbidity in a variety of cardiovascular diseases (1). In patients with reduced left ventricular ejection fraction (LVEF), with or without signs or symptoms of heart failure (HF), high heart rate has been associated with worse outcomes, independently of other known risk factors (2–6). Several pathophysiologic mechanisms, including blunting of the force-frequency relationship, the induction of myocardial ischemia, precipitation of rhythm disturbances, and acceleration of atherosclerosis, have been proposed to explain the association between higher heart rate and worse outcomes in patients with HF (1,7). Higher heart rate might also be a marker of greater neurohumoral activation. The recent findings of the SHIFT (Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial) have confirmed the importance of heart rate in the pathophysiology of HF with reduced LVEF and have suggested heart rate reduction per se as a mechanism responsible for improvement of clinical outcomes (8).

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Whether higher resting heart rate also has prognostic importance in patients with HF and preserved LVEF, representing one-third to one-half of the patients with HF (9,10), is less well-documented. Furthermore, little is known about the relationship between heart rate and outcomes in patients with atrial fibrillation (AF), the prevalence of which increases in parallel with the severity of HF (11). The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) Program enrolled 7,599 patients with a clinical diagnosis of HF,

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irrespective of LVEF, and assessed the effect of the angiotensin receptor blocker candesartan on cardiovascular mortality and morbidity (12). The main aims of this analysis were to examine the relationship between resting heart rate at baseline and fatal and nonfatal cardiovascular outcomes and all-cause mortality in a broad spectrum of patients with HF and to determine whether the relationship between heart rate and outcomes was influenced by LVEF or underlying cardiac rhythm.

Abbreviations and Acronyms

ACE-I = angiotensin-converting enzyme inhibitor
AF = atrial fibrillation
ECG = electrocardiogram
HF = heart failure
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

Methods

The CHARM Program. The design, baseline findings, and overall results of the CHARM Program have been previously reported in detail (12–14). In brief, 7,599 patients with at least 4-week duration of symptomatic HF (New York Heart Association [NYHA] functional class II to IV) receiving standard therapy were enrolled into 1 of 3 component clinical trials according to LVEF and angiotensin-converting enzyme inhibitor (ACE-I) treatment: CHARM-Alternative (n = 2,028, LVEF ≤40% and not receiving an ACE-I due to previous intolerance), CHARM-Added (n = 2,548, LVEF ≤40% receiving ACE-I treatment), and the CHARM-Preserved study (n = 3,023, LVEF >40%) (15–17). Important exclusion criteria were serum creatinine 3 mg/dl (265 μmol/l) or more; serum potassium 5.5 mmol/l or more; known bilateral renal artery stenosis; symptomatic hypotension; critical aortic or mitral stenosis; or recent (in the previous 4 weeks) myocardial infarction, stroke, or heart surgery. Within each of the component trials, patients were randomly allocated to candesartan or matching placebo, initiated at 4 mg or 8 mg (at the discretion of the investigator) once daily at the enrollment visit. The dose was increased toward the target dose (32 mg once daily) in a stepwise fashion as tolerated but not faster than every 2 weeks. Because the rate of recruitment varied between the CHARM trials, follow-up ranged from a median of 34 months in CHARM-Alternative and 37 months in the

Table 1 Baseline Characteristics of the Overall CHARM Population According to Group Defined by Ts of Baseline Heart Rate

	Heart Rate Group at Baseline (beats/min)			
	T1 n = 2,553 (33.6%) 60 (57–64)*	T2 n = 2,689 (35.4%) 72 (70–75)*	T3 n = 2,355 (31.0%) 85 (80–91)*	p Value for Trend
Patient characteristics				
Age	67 (59–74)	67 (58–74)	65 (57–73)	<0.001
≥75 yrs	609 (23.9)	625 (23.2)	503 (21.4)	0.04
Female	692 (27.1)	905 (33.7)	802 (34.1)	<0.001
LVEF (%)	38 (30–50)	37 (28–50)	35 (25–47)	<0.001
NYHA functional class				
II	1,260 (49.4)	1,202 (44.7)	953 (40.5)	
III/IV	1,293 (50.7)	1,487 (55.3)	1,402 (59.5)	<0.001
AF on ECG	283 (11.1)	398 (14.8)	467 (19.8)	<0.001
Blood pressure (mm Hg)				
Systolic	130 (118–142)	130 (120–142)	130 (118–144)	0.22
Diastolic	75 (70–80)	80 (70–84)	80 (70–85)	<0.001
Medical history				
Current smoking	305 (11.9)	378 (14.1)	431 (18.3)	0.008
Diabetes mellitus	601 (23.5)	789 (29.3)	772 (32.8)	<0.001
Hypertension	1,365 (53.5)	1,529 (56.9)	1,290 (54.8)	0.33
Hospital admission for HF	1,691 (66.2)	1,945 (72.3)	1,789 (76.0)	<0.001
Myocardial infarction	1,510 (59.2)	1,433 (53.3)	1,059 (45.0)	<0.001
Stroke	238 (9.3)	238 (8.9)	187 (7.9)	0.09
History of AF	673 (26.4)	746 (27.7)	664 (28.2)	0.15
Medical treatment				
ACE inhibitors	1,054 (41.3)	1,098 (40.8)	973 (41.3)	0.99
Beta-blockers	1,769 (69.3)	1,445 (53.7)	988 (42.0)	<0.001
Diuretic agents	2,031 (79.6)	2,202 (81.9)	2,051 (87.1)	<0.001
Spironolactone	369 (14.5)	432 (16.1)	470 (20.0)	<0.001
Digoxin/digitalis glycosides	962 (37.7)	1,156 (43.0)	1,136 (48.2)	<0.001

Values are median (interquartile range) or n (%). *Median heart rate (interquartile range).
ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ECG = electrocardiogram; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; T = tertile.

CHARM-Preserved study to 41 months in CHARM-Added (38 months in the overall CHARM Program).

Baseline heart rate measurement and outcomes evaluated. All patients enrolled in the CHARM Program had baseline heart rate measured by the site investigator at the randomization visit, in accordance with the protocol and standard operating procedures. After a resting period of 5 min, heart rate was either assessed by palpation for at least 30 s or from auscultation of the heart or from electrocardiogram (ECG). In addition, a 12-lead ECG was recorded in all patients and interpreted by investigators at each participating center with a structured report taking into account, among others, the presence or absence of AF. In patients for whom both pieces of information were available, we examined the association between baseline resting heart rate, heart rhythm (determined by the baseline ECG) and all-cause death (the primary outcome of the entire CHARM Program), and the composite outcome of cardiovascular death or hospital stay for the management of worsening HF (the primary outcome of each component trial). All endpoints were adjudicated in a blinded fashion. Deaths were considered to be cardiovascular unless another clear cause was apparent. Treatment in hospital for worsening HF was defined as an unplanned admission that was necessitated by HF and required intravenous diuretic agents.

Statistical analysis. To illustrate the relationship between resting heart rate and baseline characteristics, we divided patients into groups by tertiles of heart rate. Tertiles were chosen according to the resting heart rate distribution at baseline. Each of these heart rate bands was centered round a multiple of 10, because we observed a substantial "digit preference" for investigator-reported heart rate. Differences in baseline characteristics across tertiles of baseline heart rate were assessed with a test for trend by means of variance weighted least square regression for continuous variables and with a nonparametric test for trend (18) for categorical variables in the overall CHARM population as well as in subgroups defined according to LVEF (i.e., reduced vs. preserved) and heart rhythm (presence or absence of AF). Kaplan-Meier survival analysis stratified according to tertiles of baseline heart rate for death from any cause and for the composite of cardiovascular death or hospital stay for worsening HF were determined and presented as event curves, compared by means of log-rank test. Incidence rates were calculated/100 person-years. The association be-

Table 2 Baseline Characteristics According to Group Defined by Ts of Baseline Heart Rate in Patients With Reduced and Preserved LVEF

	Reduced LVEF				Preserved LVEF			
	T1 n = 1,414 (30.9%) 60 (58–64)*	T2 n = 1,617 (35.3%) 72 (70–76)*	T3 n = 1,545 (33.8%) 86 (80–92)*	p Value for Trend	T1 n = 1,060 (35.1%) 60 (56–63)*	T2 n = 1,037 (34.3%) 71 (68–74)*	T3 n = 924 (30.6%) 84 (80–90)*	p Value for Trend
Patient characteristics								
Age	66 (58–74)	67 (58–73)	65 (56–72)	<0.001	68 (61–75)	68 (59–75)	68 (58–75)	0.03
≥75 yrs	311 (22.0)	329 (20.4)	290 (18.8)	0.03	281 (26.5)	275 (26.5)	251 (27.2)	0.75
Female	303 (21.4)	447 (27.6)	438 (28.4)	<0.001	360 (34.0)	429 (41.4)	422 (45.7)	<0.001
LVEF (%)	30 (25–35)	30 (24–35)	29 (22–35)	<0.001	53 (46–60)	52 (46–60)	53 (46–60)	0.73
NYHA functional class								
II	536 (37.9)	561 (34.7)	483 (31.3)		672 (63.4)	630 (60.8)	533 (57.7)	
III/IV	878 (62.1)	1056 (65.3)	1,062 (68.7)	<0.001	388 (36.6)	407 (39.3)	391 (42.3)	0.01
Blood pressure (mm Hg)								
Systolic	125 (110–140)	126 (114–140)	128 (113–140)	0.09	135 (120–150)	135 (120–150)	140 (124–150)	0.007
Diastolic	75 (68–80)	77 (70–80)	80 (70–85)	<0.001	78 (70–82)	80 (70–86)	80 (70–88)	<0.001
Medical history								
Current smoking	171 (12.1)	230 (14.2)	304 (19.7)	0.01	127 (12.0)	139 (13.4)	143 (15.5)	0.72
Diabetes mellitus	311 (22.0)	486 (30.1)	509 (32.9)	<0.001	269 (25.4)	297 (28.6)	290 (31.4)	0.003
Hypertension	650 (46.0)	812 (50.2)	781 (50.6)	0.01	660 (62.3)	690 (66.5)	591 (64.0)	0.39
Hospital admission for HF	981 (69.4)	1,186 (73.4)	1,183 (76.6)	<0.001	651 (61.4)	736 (71.0)	688 (74.5)	<0.001
Myocardial infarction	917 (64.9)	968 (59.9)	779 (50.4)	<0.001	555 (52.4)	459 (44.3)	324 (35.1)	<0.001
Stroke	130 (9.2)	141 (8.7)	124 (8.0)	0.26	98 (9.3)	93 (9.0)	77 (8.3)	0.48
History of AF	366 (25.9)	444 (27.5)	393 (25.4)	0.76	286 (27.0)	292 (28.2)	302 (32.7)	0.006
Medical treatment								
ACE inhibitors	808 (57.1)	903 (55.8)	838 (54.2)	0.11	226 (21.3)	192 (18.5)	158 (17.1)	0.02
Beta-blockers	984 (69.6)	868 (53.7)	667 (43.2)	<0.001	736 (69.4)	578 (55.7)	369 (39.9)	<0.001
Diuretic agents	1,206 (85.3)	1,411 (87.3)	1,410 (91.3)	<0.001	764 (72.1)	760 (73.3)	733 (79.3)	<0.001
Spironolactone	247 (17.5)	303 (18.7)	370 (24.0)	<0.001	112 (10.6)	126 (12.2)	113 (12.2)	0.24
Digoxin/digitalis glycosides	699 (49.4)	845 (52.3)	868 (56.2)	<0.001	241 (22.7)	293 (28.3)	308 (33.3)	<0.001

Values are median (interquartile range) or n (%). *Median heart rate (interquartile range).
Abbreviations as in Table 1.

tween baseline heart rate and risk was assessed with either univariate and multivariable Cox proportional hazards models, fitting heart rate both as a continuous (hazard ratio for each 10-beats/min change in heart rate) and as a categorical variable (hazard ratio calculated for the lowest tertile as reference). Multivariable analysis adjusted for the 10 strongest predictors of outcome, as expressed by decreasing chi-square statistic, previously identified in the CHARM Program (19): age (years), LVEF, diabetes, previous HF hospital stay, NYHA functional class, body mass index, diastolic blood pressure, sex, radiologic cardiomegaly (defined as a cardiothoracic ratio ≥0.5 at chest x-ray), and candesartan treatment. In addition, beta-blocker use at baseline was added into the model, because of the direct heart rate-lowering effect of beta-blockers and because of their beneficial effect on morbidity and mortality in patients with HF. The proportional hazards assumption was checked both graphically and by means of scaled Schoenfeld residuals. Interaction testing was used to assess whether the relation between baseline heart rate and outcome was modified by LVEF (modeled either as a continuous variable or categorized ≤40% vs. >40%) and beta-blocker use at randomization. Formal interaction testing was also used to ascertain whether the relation between baseline heart rate and outcomes differed in specific subgroups: patients with and without AF, diabetic and non-diabetic patients, current smokers and non-smokers. Continuous variables were expressed as medians and interquartile ranges (IQR), and categorical variables were expressed as counts and percentages. All p values were 2-sided, and $p < 0.05$ was used to determine statistical significance, except for tests for interaction, for which $p < 0.10$ was used. Analyses were all based on intention-to-treat and were performed with STATA (version 11.2, StataCorp LP, College Station, Texas).

Results

Baseline characteristics. Information about baseline resting heart rate and rhythm were available for 7,597 (99.9%) participants in the CHARM Program, and the median heart rate overall was 72 beats/min (IQR 64 to 80). Baseline demographic and clinical characteristics in the overall CHARM population grouped by tertiles of baseline heart rate are shown in Table 1. Patients with a higher heart rate

Table 3 Baseline Characteristics According to Group Defined by Ts of Baseline Heart Rate in Patients Without and With AF

	No AF at Randomization				AF at Randomization			
	T1 n = 2,270 (35.2%) 60 (57–64)*	T2 n = 2,058 (31.9%) 72 (70–74)*	T3 n = 2,121 (32.9%) 84 (80–90)*	p Value for Trend	T1 n = 453 (39.5%) 64 (60–68)*	T2 n = 352 (30.7%) 76 (72–80)*	T3 n = 343 (29.9%) 90 (86–100)*	p Value for Trend
Patient characteristics								
Age	67 (59–74)	67 (57–73)	65 (56–72)	<0.001	70 (64–76)	70 (63–77)	69 (61–75)	0.009
≥75 yrs	519 (22.9)	429 (20.9)	414 (19.5)	0.007	149 (32.9)	125 (35.5)	101 (29.5)	0.36
Female	636 (28.0)	684 (33.2)	731 (34.5)	<0.001	109 (24.1)	127 (36.1)	112 (32.7)	0.005
LVEF (%)	38 (30–50)	37 (28–50)	35 (25–46)	<0.001	37 (28–50)	38 (29–51)	38 (29–50)	0.94
NYHA functional class								
II	1,151 (50.7)	949 (46.1)	853 (40.2)		174 (38.4)	136 (38.6)	152 (44.3)	
III/IV	1,119 (49.3)	1,109 (53.9)	1,268 (59.8)	<0.001	279 (61.6)	216 (61.4)	191 (55.7)	0.11
Blood pressure (mm Hg)								
Systolic	130 (120–142)	130 (120–142)	130 (118–144)	0.57	130 (112–140)	130 (120–145)	130 (120–145)	0.005
Diastolic	75 (70–80)	80 (70–84)	80 (70–85)	<0.001	75 (70–82)	80 (70–85)	80 (70–90)	<0.001
Medical history								
Current smoking	276 (12.2)	310 (15.1)	390 (18.4)	0.001	44 (9.7)	38 (10.8)	56 (16.3)	0.93
Diabetes mellitus	531 (23.4)	613 (29.8)	732 (34.5)	<0.001	112 (24.7)	91 (25.9)	83 (24.2)	0.90
Hypertension	1,217 (53.6)	1,153 (56.0)	1,174 (55.4)	0.24	247 (54.5)	201 (57.1)	192 (56.0)	0.65
Hospital admission for HF	1,466 (64.6)	1,458 (70.9)	1,572 (74.1)	<0.001	358 (79.0)	291 (82.7)	280 (81.6)	0.32
Myocardial infarction	1,393 (61.4)	1,176 (57.1)	1,024 (48.3)	<0.001	183 (40.4)	109 (31.0)	117 (34.1)	0.05
Stroke	211 (9.3)	165 (8.0)	166 (7.8)	0.08	49 (10.8)	37 (10.5)	35 (10.2)	0.78
History of AF	406 (17.9)	328 (15.9)	252 (11.9)	<0.001	432 (95.4)	335 (95.2)	330 (96.2)	0.59
Medical treatment								
ACE inhibitors	911 (40.1)	829 (40.3)	911 (43.0)	0.06	227 (50.1)	128 (36.4)	119 (34.7)	<0.001
Beta-blockers	1,627 (71.7)	1,143 (55.5)	884 (41.7)	<0.001	229 (50.6)	156 (44.3)	163 (47.5)	0.34
Diuretic agents	1,764 (77.7)	1,638 (79.6)	1,820 (85.8)	<0.001	422 (93.2)	324 (92.1)	316 (92.1)	0.57
Spironolactone	311 (13.7)	297 (14.4)	405 (19.1)	<0.001	105 (23.2)	83 (23.6)	70 (20.4)	0.38
Digoxin/digitalis glycosides	754 (33.2)	773 (37.6)	881 (41.5)	<0.001	330 (72.9)	265 (75.3)	251 (73.2)	0.87

Values are median (interquartile range) or n (%). *Median heart rate (interquartile range).
Abbreviations as in Table 1.

were younger and more often female, diabetic, or a current smoker. A higher resting heart rate was also associated with lower LVEF and with higher diastolic blood pressure and NYHA functional class. More patients in the highest heart rate tertile had been previously admitted to hospital because of HF decompensation, compared with patients in the 2 lower heart rate tertiles. By contrast, patients in the highest heart rate group were less likely to have suffered from myocardial infarction, compared with patients in the other groups. The proportion of patients treated with a beta-blocker decreased as heart rate increased, whereas the use of a diuretic, spironolactone, and digoxin increased with increasing heart rate. In patients with reduced and preserved LVEF as well as in those without AF at baseline, the distribution of baseline characteristics across tertiles of heart rate was similar to that observed in the overall population (Tables 2 and 3). However, some of the differences between heart rate tertiles seen in these other subgroups were not present in patients with AF (Table 3). In particular, there was no gradient in LVEF, NYHA functional class, or history of diabetes. There was also no gradient in history of hospital stay for HF or in use of diuretic agents or digoxin, although the frequency of each of these was higher in patients with AF (irrespective of heart rate) than in patients without AF (Table 3).

Baseline heart rate and all-cause mortality. In the overall CHARM population, during a median follow-up of 37.7 months, 1,831 patients (24.1%) died. Individuals with a higher heart rate at baseline had a greater risk of death from any cause, compared with those with a lower heart rate (overall log-rank test p value <0.001) (Fig. 1A). Beta-blocker use at randomization was associated with a lower risk of death but did not change the association between heart rate and mortality (p for interaction = 0.55) (Fig. 2A). The relationship between heart rate and mortality (and cardiovascular death or HF hospital stay) was also observed when beta-blocker dose was taken into consideration (higher heart rate was associated with worse outcomes whether or not patients were taking ≥50% of recommended dose or ≥median dose). The absolute death rate/100 patient-years of follow-up in patients with reduced LVEF was approximately double that in patients with preserved LVEF, but a concordant increment in death rates was seen with increasing heart rate in each of the 2 LVEF categories (Fig. 3A and Table 4). Similarly, the unadjusted risk of death showed a concordant increase across tertiles of heart rate irrespective of LVEF (p for interaction with continuous LVEF = 0.80; p for interaction with categorical LVEF = 0.68) (Fig. 4A); the findings were similar if LVEF was dichotomized at 50% rather than 40% in the categorical analysis (and this was also true for the outcome of cardiovascular death or HF hospital stay). The association between higher heart rate and the risk of death remained significant in a multivariable model that adjusted for the covariates listed in the Methods in both LVEF subgroups (Table 4); adding baseline treatment, including ACE-inhibitors, beta-blockers, diuretic agents, spironolactone, and digitalis glycosides, to the multivariable model did not change this finding. For each additional 10-beat increase there was—treating baseline heart rate as a linear continuous variable—a 6% and 5% adjusted risk accrual in patients with reduced and preserved LVEF, respectively (Table 4).

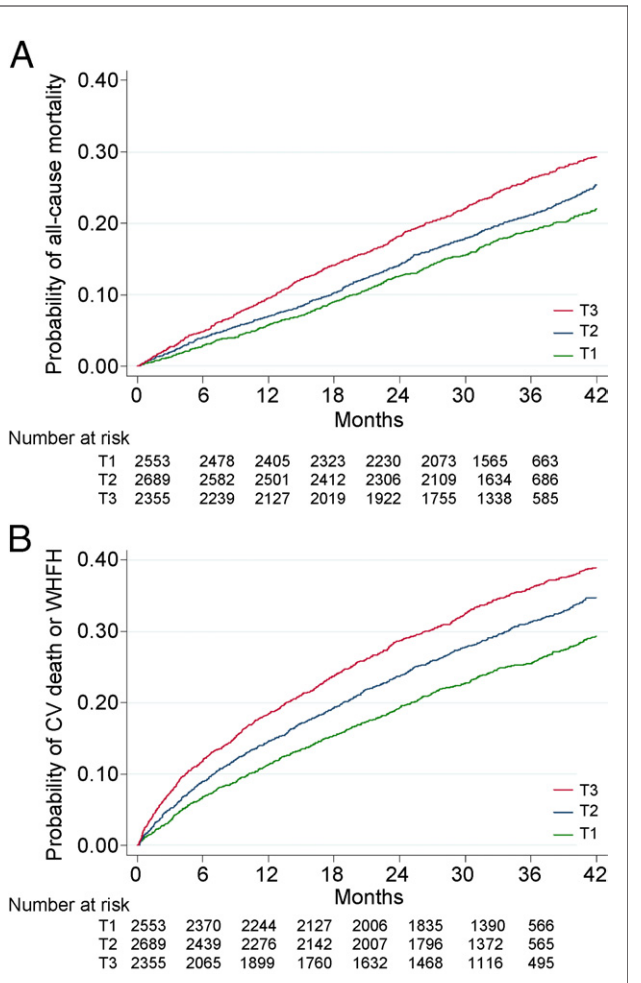

Figure 1 **Kaplan-Meier Survival Analysis According to Baseline Heart Rate**

Event curves for all-cause mortality **(A)** and for the composite outcome of cardiovascular (CV) death or hospital stay for worsening heart failure (WHFH) **(B)** according to tertiles (Ts) of baseline heart rate in the overall CHARM population.

When heart rhythm at randomization was taken into account, the association between higher heart rate and the risk of death was confirmed in patients without AF but not in those with AF at baseline (p for interaction <0.001) (Fig. 5A and Table 4). A 10-beat increase in heart rate was associated with—modeling heart rate as a linear continuous variable—an 8% increase in the risk of death in patients without AF, but no significant increase in risk was observed in patients with AF (Table 4). The association between a higher baseline heart rate and a

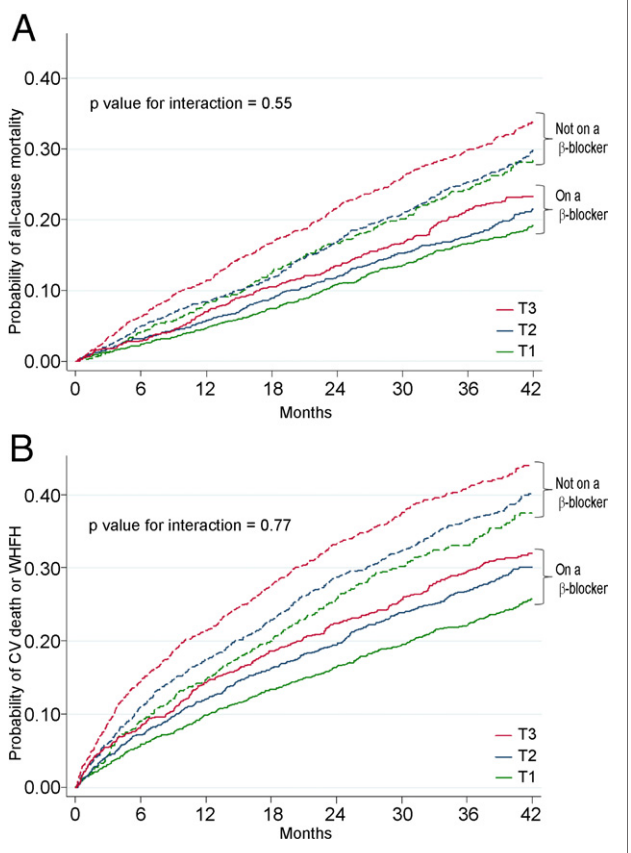

Figure 2 **Kaplan-Meier Survival Analysis According to Baseline Heart Rate, Stratified by Beta-Blocker Use at Baseline**

Event curves for all-cause mortality **(A)** and for the composite outcome of CV death or WHFH **(B)** according to Ts of baseline heart rate, stratified by beta-blocker use at baseline (**dashed line** = no beta-blocker use at randomization, **solid line** = beta blocker use at randomization) in the overall CHARM population. p value refers to the test for interaction between baseline heart rate and beta-blocker use at baseline. Abbreviations as in Figure 1.

higher risk of death was observed regardless of diabetic and smoking status (p for interaction between heart rate and diabetes = 0.47; p for interaction between heart rate and smoking status = 0.33).

Baseline heart rate and cardiovascular death or hospital stay for worsening HF. Patients with a higher heart rate at baseline had a higher incidence of the composite outcome of cardiovascular death or HF hospital stay (overall log-rank test p value <0.001) (Fig. 1B). The association between higher heart rate and the risk of the composite outcome was observed independently of beta-blocker use at baseline (p for interaction = 0.77) (Fig. 2B). A similar pattern of increase in event rate across heart rate tertiles was seen in both the reduced and preserved LVEF groups (Fig. 3B, Table 4). This finding was confirmed in the univariate and multivariable analysis, where an increase in the risk of cardiovascular death or HF hospital stay was observed with increasing heart rate regardless of baseline LVEF (p for interaction with continuous LVEF = 0.88; p for interaction with categorical LVEF = 0.96) (Fig. 4B, Table 4). Adding baseline treatment, including ACE inhibitors, beta-blockers, diuretic agents, spironolactone and digitalis glycosides, to the multivariable model did not change this finding. With baseline heart rate as a continuous variable, a 10-beat increase in heart rate was associated with a 7% and with a 6% increase in the risk of the composite endpoint in patients with reduced and preserved LVEF, respectively (Table 4).

The prognostic importance of heart rate was confirmed in patients without AF at baseline either modeling heart rate as a categorical (adjusted hazard ratio: 1.28, confidence interval: 1.14 to 1.44 for patients in the highest heart rate tertile) or as a continuous variable (adjusted hazard ratio: 1.10, confidence interval: 1.06 to 1.13 for each 10-beat increase in heart rate). By contrast, in patients with AF at baseline, there was no association between heart rate and the risk of the composite outcome (p value for interaction between heart rate and the presence of AF <0.001) (Fig. 5B, Table 4). This conclusion was not altered by adding

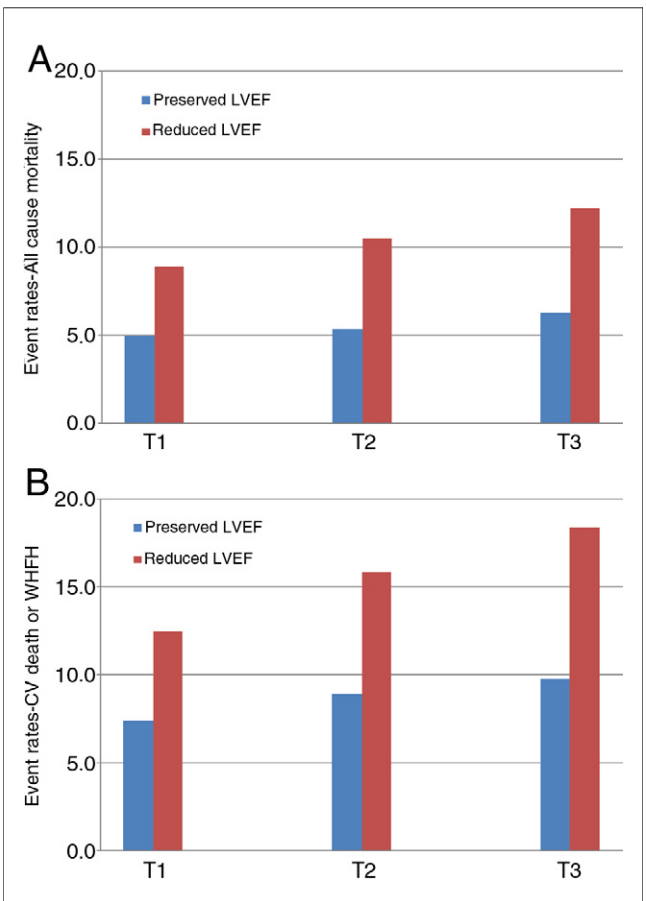

Figure 3 **Event Rates in Patients With Preserved and Reduced LVEF According to Baseline Heart Rate**

All-cause mortality **(A)** and CV death or WHFH **(B)** event rates (per 100-patient years) according to Ts of baseline heart rate in patients with preserved **(blue)** and reduced **(red)** left ventricular ejection fraction (LVEF). Abbreviations as in Figure 1.

Table 4 Event Rates, Adjusted HRs Across Ts of Heart Rate and Adjusted HRs for Each 10-Beats/Min Increase in Baseline Heart Rate for All-Cause Mortality and for CV Death or WHFH

	All-Cause Mortality			CV Death or WHFH		
	Event Rates (95% CI)/ 100 Patient-Yrs	HR (95% CI)*	HR (95% CI)/ 10-Beats/Min Increase*	Event Rates (95% CI)/ 100 Patient-Yrs	HR (95% CI)*	HR (95% CI)/ 10-Beats/Min Increase*
Overall						
T1	7.2 (6.6–7.8)	1.00		10.3 (9.5–11.1)	1.00	
T2	8.3 (7.7–9.0)	1.07 (0.95–1.20)		12.8 (12.0–13.7)	1.11 (1.01–1.23)	
T3	10.2 (9.4–11.0)	1.27 (1.13–1.43)		15.3 (14.3–16.4)	1.23 (1.11–1.36)	
All patients	—	—	1.06 (1.02–1.10)	—	—	1.07 (1.04–1.10)
Reduced LVEF						
T1	8.9 (8.0–9.8)	1.00		12.5 (11.5–13.7)	1.00	
T2	10.5 (9.6–11.5)	1.10 (0.96–1.27)		15.8 (14.6–17.1)	1.15 (1.01–1.30)	
T3	12.2 (11.2–13.3)	1.26 (1.09–1.45)		18.4 (17.0–19.8)	1.25 (1.11–1.42)	
All patients	—	—	1.06 (1.02–1.10)	—	—	1.07 (1.03–1.10)
Preserved LVEF						
T1	5.0 (4.3–5.8)	1.00		7.4 (6.5–8.4)	1.00	
T2	5.2 (4.4–6.1)	1.05 (0.84–1.32)		8.9 (7.8–10.0)	1.14 (0.94–1.37)	
T3	6.3 (5.4–7.3)	1.25 (0.99–1.58)		9.8 (8.6–11.1)	1.14 (0.93–1.38)	
All patients	—	—	1.05 (0.98–1.12)	—	—	1.06 (1.00–1.12)
No AF						
T1	6.7 (6.1–7.4)	1.00		9.4 (8.7–10.2)	1.00	
T2	7.7 (7.0–8.5)	1.08 (0.94–1.23)		12.0 (11.1–13.0)	1.14 (1.02–1.28)	
T3	9.5 (8.8–10.4)	1.26 (1.10–1.43)		15.0 (14.0–16.1)	1.28 (1.14–1.44)	
All patients	—	—	1.08 (1.04–1.12)	—	—	1.10 (1.06–1.13)
AF						
T1	11.6 (9.8–13.6)	1.00		18.3 (15.9–21.1)	1.00	
T2	13.0 (10.9–15.5)	1.15 (0.90–1.48)		17.5 (14.9–20.6)	0.97 (0.78–1.21)	
T3	10.3 (8.4–12.5)	0.97 (0.75–1.26)		14.3 (12.0–17.1)	0.85 (0.67–1.07)	
All patients	—	—	0.97 (0.90–1.05)	—	—	0.95 (0.89–1.02)

*Model is adjusted for age, LVEF, diabetes, body mass index, previous HF hospital stay, sex, NYHA functional class, radiologic cardiomegaly, diastolic blood pressure, randomized treatment, and beta-blocker use at baseline.

CI = confidence interval; HR = hazard ratio; WHFH = hospital stay for worsening heart failure; other abbreviations as in Table 1.

digoxin to the multivariable model. Although higher event rates were observed with increasing heart rate, the association between a higher heart rate and a higher risk of cardiovascular death or HF hospital stay seemed stronger in nondiabetic subjects than in diabetic subjects (p for interaction between heart rate and diabetes = 0.01) A possible interaction between heart rate and current smoking was also observed (p = 0.07).

Effect of candesartan and baseline heart rate. Although candesartan did not reduce mortality overall in the CHARM Program, there was a nominally significant interaction between heart rate at baseline and the effect of candesartan on all-cause mortality (p value for interaction = 0.04), with an apparent reduction in mortality only in patients in the highest heart rate-tertile (data not shown). This interaction was not seen for the composite of cardiovascular death or HF hospital stay (p = 0.24), for which there were many more events and which was reduced, overall, by candesartan.

Discussion

The CHARM dataset provided a unique opportunity to examine the relationship between baseline resting heart rate and outcomes in a large cohort of patients with a wide range of LVEF and receiving contemporary management for symptomatic HF. Our analysis confirmed the predictive value of resting heart rate in patients with HF and sinus rhythm, for both the composite outcome of cardiovascular death or HF hospital stay and all-cause mortality. The greater risk of events in patients with higher heart rate was observed across the full spectrum of LVEF and persisted even after adjustment for other recognized predictors of mortality and morbidity. Moreover, the relationship between heart rate and outcomes in patients with sinus rhythm was not modified by the use of beta-blockers at baseline. Interestingly, however, higher heart rate was not related to outcome in patients with AF.

Heart rate as a risk marker in patients with HF. Certain variables previously reported to be associated with worse outcomes in HF (e.g., diabetes, higher NYHA functional class, lower LVEF, and a history of HF hospital stay) were more frequent in patients with a higher heart rate at baseline, but other variables associated with a better outcome were also more common in patients with a higher heart rate (e.g., younger age, female sex, and lower frequency of prior myocardial infarction). The baseline use of beta-blockers was also lower in patients with

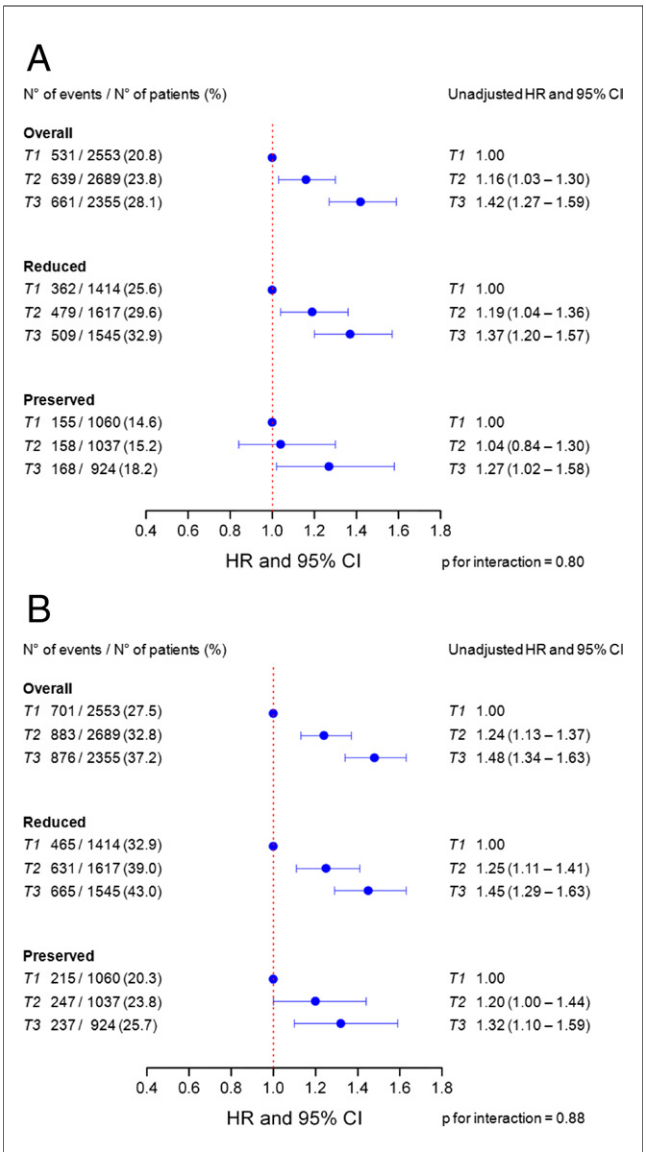

Figure 4 **Association Between Baseline Heart Rate and Outcomes by Subgroups of LVEF**

Unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality **(A)** and for CV death or WHFH **(B)** across Ts of baseline heart rate; p values for interaction between heart rate and LVEF treated as linear continuous variables are shown. Abbreviations as in Figures 1 to 3.

higher heart rate, possibly because these individuals had worse overall clinical status or fewer indications for beta-blockers. In addition, higher heart rate might also reflect unmeasured variance such as neuroendocrine activity, particularly sympathetic activity (or sympathetic-parasympathetic imbalance). However, heart rate remained an independent predictor of outcome in a multivariable analysis taking into account these imbalances, and no interaction between baseline heart rate and beta-blocker use was observed.

Association between heart rate and outcomes across the continuum of LVEF. We found no interaction between resting heart rate and LVEF, indicating that the value of elevated heart rate in predicting worse outcomes was independent of baseline left ventricular systolic function in patients with HF. Despite the epidemiologic importance of HF with preserved LVEF, only 2 other studies have examined the association between baseline heart rate and outcomes in this subgroup of patients. In a post hoc analysis of the DIG (Digitalis Investigation Group) trial, a higher heart rate was associated with a greater risk of HF hospital stay both in patients with reduced and preserved LVEF. However, an association between higher heart rate and higher mortality was only seen in patients with a reduced LVEF (20). The discrepancy between these findings and ours warrants further investigations but might be due to

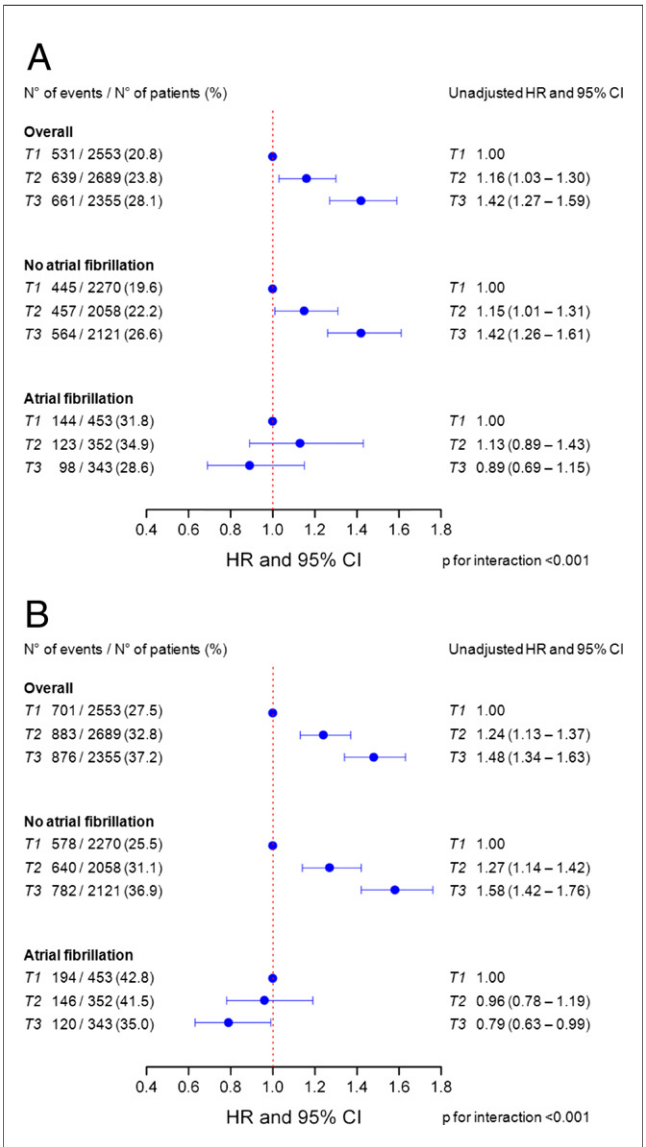

Figure 5 **Association Between Baseline Heart Rate and Outcomes by Baseline Cardiac Rhythm**

Unadjusted HRs and 95% CIs for all-cause mortality **(A)** and for CV death or WHFH **(B)** across Ts of baseline heart rate; p values for interaction between heart rate treated as a linear continuous variable and baseline rhythm (sinus rhythm vs. atrial fibrillation) are shown. Abbreviations as in Figures 1 to 4.

differences between the studies. Beta-blockers were not used to treat HF at the time of the DIG trial, and patients in that trial had an LVEF >45% (compared with 40% in CHARM). Perhaps, most importantly, the DIG preserved LVEF ancillary trial was a much smaller than the CHARM-Preserved study, resulting in considerably fewer deaths in this subset of patients in the DIG trial (i.e., 231 vs. 364 in the CHARM-Preserved study) and greater statistical power in the CHARM-Preserved study. Nevertheless, further examination of the relationship between heart rate and outcomes in HF with preserved LVEF is needed before any definitive conclusion can be drawn. Recently, Kapoor et al. (21) reported that high resting heart rate was associated with worse survival among 685 consecutive patients with preserved systolic function (with 278 deaths overall). However, this cohort was unusual in that 97% of the patients were male.

The prognostic value of heart rate according to baseline cardiac rhythm. An interesting finding of our analysis was the lack of predictive value of higher heart rate in patients with AF at baseline. Although the number of patients and events was much smaller in the AF subgroup, the highly significant interaction between heart rhythm and the relationship between heart rate and outcomes suggests that this finding is a true one. Moreover, a similar observation was made in a cohort of patients with acute HF, in which a higher heart rate was associated with a significantly lower all-cause and cardiovascular mortality in those with AF (22). In another study of patients with moderate-to-severe chronic HF and concomitant AF, a lower heart rate at baseline was associated with a worse prognosis (23). The explanation for this apparently paradoxical finding in patients with AF (compared with those in sinus rhythm) is uncertain. Although in patients with HF and in sinus rhythm a higher heart rate could be a marker of greater neurohumoral activation (24) or significant autonomic impairment (25), this might not be so in those with AF. Furthermore, systematic underestimation of the ventricular rate might have occurred in patients with AF when the rate was assessed by palpation or auscultation. Conversely, a true low ventricular rate might indicate conducting system disease, itself a poor prognostic feature. In patients with AF, a higher ventricular rate might be a compensatory response to the reduction in cardiac output due to loss of effective atrial contraction (26).

The prognostic value of heart rate according to diabetic and smoking status. Although both diabetic and nondiabetic patients showed increasing event rates with increasing heart rate, the association between a high heart rate and the risk of the primary composite outcome (cardiovascular death or HF hospital stay) seemed to be stronger in nondiabetic than in diabetic patients. For the same outcome, a similar figure was observed in nonsmokers as compared with current smokers. The imbalance between sympathetic/parasympathetic systems associated with cardiac autonomic neuropathy in diabetic subjects and the increased sympathetic outflow induced by smoking are possible explanations for these findings (27,28). However, multiple interaction tests were conducted with the possibility of a nominally significant interaction occurring by chance alone (29).

Strengths and limitations. One of the main strengths of the present study is the wide spectrum of LVEF across which the prognostic impact of heart rate was investigated. In addition, the modern HF treatment used in the CHARM Program—especially beta-blockers—in more than one-half of the patients makes our results more generalizable to real clinical practice, compared with previous reports (5,20). Some limitations of the present analysis should also be acknowledged. We relied on investigator-reported baseline heart rate, which was probably measured in different ways, at different times of day, and under different circumstances. Estimation of the average ventricular rate in patients with AF was probably less reliable than measurement of heart rate in those in sinus rhythm. Similarly, patients were classified as having AF or no AF according to the investigator interpretation of their baseline ECG. In addition, we did not use serial assessments of heart rate over time for the prediction of risk.

Conclusions

In patients with stable chronic symptomatic HF and without AF, resting heart rate is a powerful predictor of mortality and cardiovascular outcomes, irrespective of LVEF, treatment with beta-blockers, and other important prognostic factors. This easily measured clinical variable could be used in the risk stratification of these patients in everyday clinical practice.

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Key Words: atrial fibrillation ■ ejection fraction ■ heart failure ■ heart rate ■ prognosis.

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