Discharge heart rate and 1-year clinical outcomes in heart failure patients with atrial fibrillation

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Abstract

Background: The association between heart rate and 1-year clinical outcomes in heart failure (HF) patients with atrial fibrillation (AF), and whether this association depends on left ventricular ejection fraction (LVEF), are unclear. We investigated the relationship between discharge heart rate and 1-year clinical outcomes after discharge among hospitalized HF patients with AF, and further explored this association that differ by LVEF level.

Methods: In this analysis, we enrolled 1760 hospitalized HF patients with AF from the China Patient-centered Evaluative Assessment of Cardiac Events Prospective Heart Failure study from August 2016 to May 2018. Patients were categorized into three groups with low (<65 beats per minute [bpm]), moderate (65–85 bpm), and high (≥86 bpm) heart rate measured at discharge. *Cox* proportional hazard models were employed to explore the association between heart rate and 1-year primary outcome, which was defined as a composite outcome of all-cause death and HF rehospitalization.

Results: Among 1760 patients, 723 (41.1%) were women, the median age was 69 (interquartile range [IQR]: 60–77) years, median discharge heart rate was 75 (IQR: 69–84) bpm, and 934 (53.1%) had an LVEF <50%. During 1-year follow-up, a total of 792 (45.0%) individuals died or had at least one HF hospitalization. After adjusting for demographic characteristics, smoking status, medical history, anthropometric characteristics, and medications used at discharge, the groups with low (hazard ratio [HR]: 1.32, 95% confidence interval [CI]: 1.05–1.68, $P = 0.020$) and high (HR: 1.34, 95% CI: 1.07–1.67, $P = 0.009$) heart rate were associated with a higher risk of 1-year primary outcome compared with the moderate group. A significant interaction between discharge heart rate and LVEF for the primary outcome was observed (P for interaction was 0.045). Among the patients with LVEF ≥50%, only those with high heart rate were associated with a higher risk of primary outcome compared with the group with moderate heart rate (HR: 1.38, 95% CI: 1.01–1.89, $P = 0.046$), whereas there was no difference between the groups with low and moderate heart rate. Among the patients with LVEF <50%, only those with low heart rate were associated with a higher risk of primary outcome compared with the group with moderate heart rate (HR: 1.46, 95% CI: 1.09–1.96, $P = 0.012$), whereas there was no difference between the groups with high and moderate heart rate.

Conclusions: Among the overall HF patients with AF, both low (<65 bpm) and high (≥86 bpm) heart rates were associated with poorer outcomes as compared with moderate (65–85 bpm) heart rate. Among patients with LVEF ≥50%, only a high heart rate was associated with higher risk; while among those with LVEF <50%, only a low heart rate was associated with higher risk as compared with the group with moderate heart rate.

Trail Registration: Clinicaltrials.gov; NCT02878811.

Keywords: Atrial fibrillation; Heart failure; Heart rate; Left ventricular ejection fraction

Introduction

Heart failure (HF) is a major health burden, and there are approximately 64.3 million adults with HF worldwide.[1] Among them, atrial fibrillation (AF) is the most common arrhythmia, presenting in up to approximately 40% of hospitalized HF patients,[2,3] and has been shown to be associated with worse clinical outcomes.[4]

A lower heart rate has been shown to be associated with a lower risk of clinical outcomes in HF patients with sinus rhythm[5]; however, whether this association persists in HF patients with AF remains uncertain. Some studies did not support the prognostic significance of heart rate among the HF patients with AF,[6-9] whereas others suggested that lower heart rate was associated with worse outcomes.[10-13] According to the current European Society of Cardiology (ESC) and Chinese clinical guidelines, heart

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rate control is one of the most important treatments in HF patients with AF. A wide range of 60 to 100 beats per minute (bpm) is recommended (class II a, level B); however, the evidence is insufficient.[14-16] Subgroup analysis of HF patients in Race Control Efficacy in Permanent Atrial Fibrillation (RACE) II trial suggested that strict rate control (<80 bpm) did not bring more survival benefits than lenient rate control (<110 bpm) in those with AF, but this finding was not conclusive due to the small sample size. Besides, HF patients in RACE II were underrepresented as they excluded part of patients with reduced left ventricular ejection fraction (LVEF), and their results may be ungeneralizable to those with reduced LVEF. More importantly, they did not provide subgroup analysis according to LVEF.[17,18] Although the current guideline suggested the optimal heart rate control target should be varied according to heart function, they did not offer a specific recommendation.[16] Whether the association between heart rate and prognosis varies across different LVEF levels has not been well studied.

To fill the knowledge gaps in these areas, using the data from a prospective cohort study, we examined the association between heart rate at hospital discharge and the risk of 1-year death or HF rehospitalization after discharge among HF patients with AF and further explored this association stratified by LVEF level.

Methods

Ethical approval

The local Ethics Committees of all collaborating hospitals approved this study. All participants provided written informed consents before enrollment. The study was registered on www.clinicaltrials.gov (No. NCT02878811).

Study design and participants

The design and details of the China Patient-centered Evaluative Assessment of Cardiac Events Prospective Heart Failure study were published previously.[19] In brief, it was a large nationwide prospective cohort study that consecutively recruited patients from 52 hospitals throughout 20 provinces in China. The participating hospitals were selected based on their capacity to conduct the cohort study and their geographical locations. Patients were screened and enrolled from August 2016 to May 2018.

Patients aged 18 years or above were eligible if they were hospitalized for new-onset HF or decompensation of chronic HF, which were assessed by the local physician. Patients were excluded if they died or withdrew from treatment because of the terminal status at discharge ($n = 55$), did not complete 1-year follow-up after discharge ($n = 9$), were not diagnosed as AF ($n = 3081$), or had no data of discharge heart rate ($n = 2$). The diagnosis of AF was based on at least one 12-lead electrocardiogram performed during hospitalization or discharge diagnosis. In total, 1760 HF patients with AF were included in our analysis [Supplementary Figure 1, http://links.lww.com/CM9/A771]. According to current guidelines, patients with duration of AF <7 days were categorized as paroxysmal AF, and those who had a duration of AF ≥7 days were categorized as persistent AF.[14]

We centrally abstracted data from the inpatient medical chart of the index hospitalization. Each abstractor was trained and qualified before they performed the abstraction. The data accuracy was ensured by clinicians at the coordinating center randomly selecting medical charts for quality check. And we did a face-to-face interview during hospitalization, at 1, 6 months, and 1 year after discharge. Heart rate at discharge was measured by local physicians and documented in the medical record. We also collected blood samples within 48 h of admission for central laboratory analysis of high sensitivity cardiac troponin T, N-terminal brain natriuretic peptide precursor, and creatine. In this study, we trained local experienced physicians to do echocardiography to measure LVEF according to standard operating procedure. LVEF was obtained from apical 2- and 4-chamber views and calculated with the Simpson method. We categorized patients into two LVEF groups: HF with reduced and mid-range LVEF (<50%), and HF with preserved (≥50%) LVEF.[15]

Outcomes

The primary outcome in our study was a composite of 1-year all-cause death and HF rehospitalization. The secondary outcomes included 1-year all-cause death, 1-year HF rehospitalization, and a composite of 1-year all-cause death and all-cause rehospitalization. If there were multiple rehospitalization records, only the first rehospitalization was analyzed. We collected patient outcomes after their index hospitalization via regular follow-up at the local hospitals. Besides, telephone follow-up, medical records in the health information system of local hospitals, and outcome information from the National Center for Disease Control and Prevention were used if patients could not attend regular follow-up visits. We further confirmed vital status according to the cause mentioned in the national database of death. Clinicians at the coordinating center adjudicated all outcome events.

Sample size

According to previous studies, the rate of 1-year composite outcome of all-cause death and HF rehospitalization among low, moderate, and high heart rate groups of HF patients with AF were 34.5%, 27.5%, and 41.4%, respectively.[20] This study set two sides $\alpha = 0.05$, and the power of the test was 80%. The total sample size of the three heart rate groups was 676 using PASS software (version 15.0.6, NCSS, LLC. Kaysville, Utah, USA). Considering the loss of follow-up which was calculated by 10%, a total of 752 patients were finally required. A total of 1760 HF patients with AF were included in this study, and thus there was a sufficient sample size to test the research hypothesis.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and analyzed using χ^2 tests; continuous

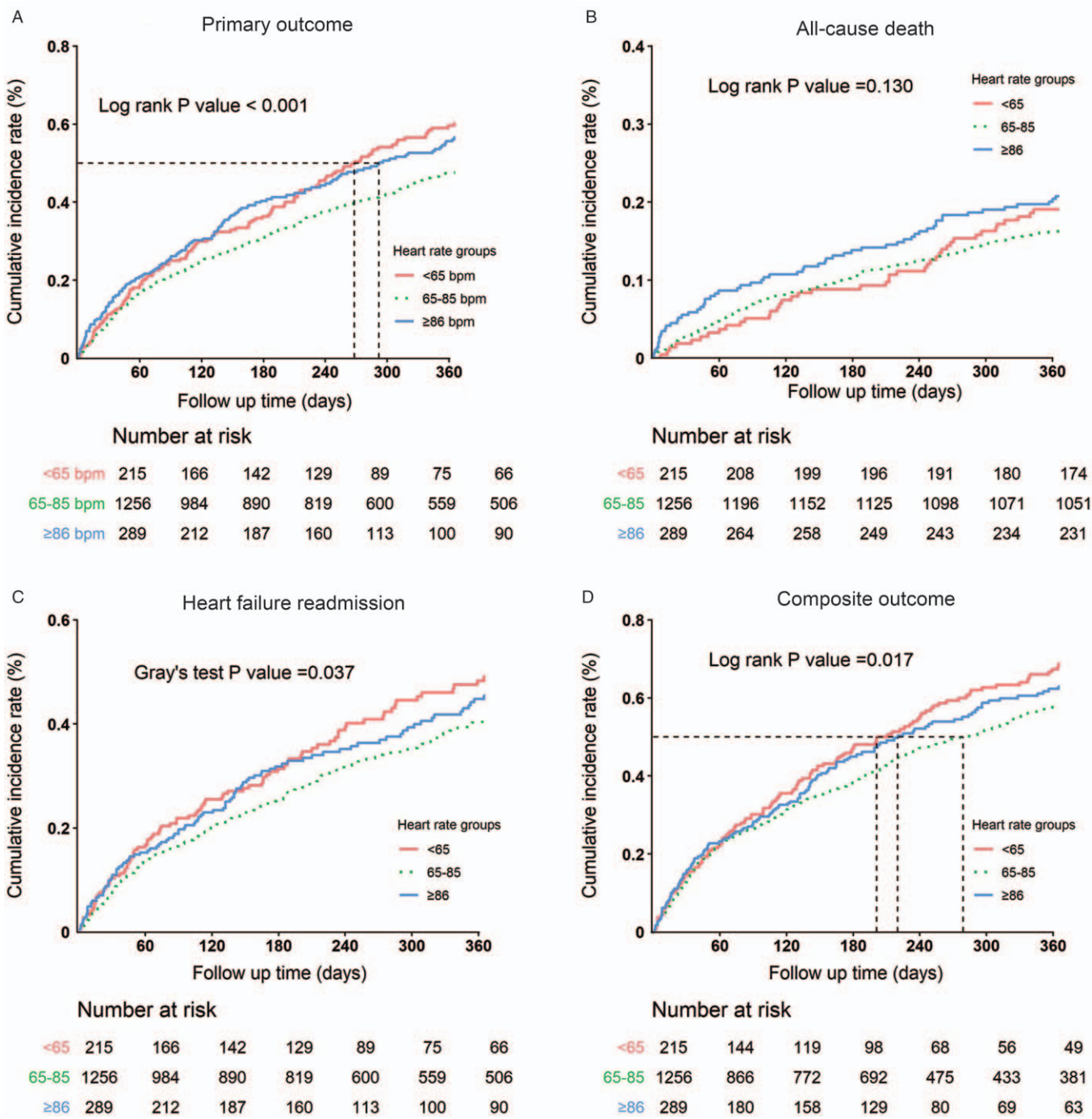

Figure 1: Unadjusted cumulative incidence of 1-year clinical outcomes according to discharge heart rate groups. (A) The primary outcome, which was defined as a composite outcome of all-cause death and HF rehospitalization; (B) all-cause death; (C) heart failure rehospitalization; (D) composite outcome of all-cause death and all-cause rehospitalization. Bpm: Beats per minute; HF: Heart failure.

variables were expressed as medians and interquartile ranges (IQR) and analyzed by the Kruskal-Wallis test.

We employed *Cox* proportional hazard additive model (with additive hazard function) to capture the possible non-linear effects of discharge heart rate on outcomes, with restricted cubic spline as smoother and 25th, 50th (reference), and 75th quantiles of discharge heart rate as knots. Based on the results of the *Cox* additive model and previous studies, we categorized the discharge heart rate into three groups (<65 bpm, 65–85 bpm used as the reference, and ≥86 bpm).[21]

For composite outcome or death, we used a log-rank test to compare the cumulative incidence of these groups, and multivariable *Cox* proportional hazards models were employed to calculate the adjusted hazard ratios (HRs) and 95% confidence interval (CI) of discharge heart rate groups. For HF readmissions, we performed a competing risk analysis using the Fine-Gray model, given that the

mortality occurring in the absence of readmissions is the competing risk.[22]

The scaled Schoenfeld residuals from the models were investigated to detect the violations to the proportional hazards' assumptions. These assumptions were satisfied for the primary outcome, HF readmission, and composite outcome of all-cause death and all-cause readmission ($P > 0.100$), but not for all-cause death ($P = 0.049$). HR of death was assessed separately during the first 250 days and after 250 days of follow-up.

In the multivariable Cox and Fine-Gray models, we corrected 18 baseline characteristics, which included age, sex, smoking status, medical history (coronary artery disease, non-ischemic cardiomyopathy, stroke, diabetes, valvular heart disease, and chronic obstructive pulmonary disease), LVEF, QRS duration, laboratory tests (creatinine and N-terminal pro-brain natriuretic peptide [NT-proBNP]), New York Heart Association classifications, systolic blood pressure (SBP) at discharge, and medication use at discharge (beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and aldosterone antagonists). Adjustment variables were selected based on their potential role in the association with clinical outcomes.

To examine whether the results of the primary cohort were consistent, we employed several sensitivity analyses. In the first three analyses, to avoid possible influence of heart rhythm, as the association between heart rate and clinical outcomes may differ according to underlying rhythm, we excluded patients who had sinus rhythm or paced rhythm at discharge, who were paroxysmal AF, or who had rhythm control treatment during hospitalization or at discharge, respectively. In the fourth analysis, to avoid possible measurement errors of heart rate and influence of clinical instability of acute HF patients, we excluded patients who had unstable discharge heart rate, defined as differences between heart rate of first electrocardiogram and discharge heart rate >20 bpm.[23] The first electrocardiogram was performed within 24 h of admission. In these four sensitivity cohorts, we investigated the associations between discharge heart rate and 1-year primary outcome in multivariable *Cox* models, respectively.

To further adjust potential confounders, we employed a fifth sensitivity analysis. The association between discharge heart rate and the 1-year primary outcome was investigated by inverse probability of treatment weighting (IPTW)-weighted *Cox* regression analysis. Propensity scores were obtained using multinomial logistic regression, with discharge heart rate groups (low, moderate, and high) as the outcome, and with 32 baseline characteristics, such as age, sex, smoking status, medical history, anthropometric characteristics, and medications used at discharge, as pretreatment covariates. Then, we calculated IPTW based on the propensity score. We used standardized mean differences to evaluate the difference between discharge heart rate groups of the baseline characteristics in the IPTW-weighted population, with a difference <0.1 considered as a small difference. Some covariates were added into the IPTW-weighted *Cox* model, if their standardized mean difference was ≥0.1.

For the effects of LVEF, interaction tests between discharge heart rate and LVEF were added into the multivariable *Cox* and Fine-Gray models. We examined whether the effects of discharge heart rate on outcomes were consistent in different LVEF groups using the cut-off (<50% *vs.* ≥50%). When stratified by LVEF, we adjusted for the same variables as we described in the multivariable *Cox* and Fine-Gray models, but LVEF was removed from the model. Proportional hazards' assumptions were assessed again and satisfied for each clinical outcome both in patients with LVEF <50% and in those with LVEF ≥50% ($P > 0.100$).

In total, 15 (0.9%) of discharge SBP and 90 (5.1%) of LVEF data were missing. Levels of missing data among laboratory tests ranged from 0% to 3.5%. Assuming that these data were missing at random, multiple imputation was utilized to account for missingness.

All *P* values were two tailed, and $P < 0.050$ was used to determine statistical significance. Analyses were performed on SAS software (version 9.4, SAS Institute, Cary, NC, USA) and R software (version 3.6.2, R Core Team, Vienna, Austria). The *Cox* proportional hazard additive model was performed using R Package "rms," Version 5.1-4. The IPTW analysis was performed using R Package "twang," Version 2.0. Other statistical analyses were performed using SAS software.

Results

Patient characteristics

A total of 1760 patients were included in the study [Table 1 and Supplementary Figure 1, http://links.lww.com/CM9/A771]. The median age was 69 (IQR: 60–77) years; 723 (41.1%) were female. The median LVEF was 48.0% (IQR: 38.0–58.0%), and the median discharge heart rate was 75 (IQR: 69–84) bpm. The distribution of discharge heart rate is shown in Supplementary Figure 2, http://links.lww.com/CM9/A771. Compared with patients with moderate discharge heart rate, those with lower or higher discharge heart rate were more likely to have higher NT-proBNP or lower LVEF.

Prognostic value of discharge heart rate

During 1-year follow-up after discharge, a total of 792 individuals died or had at least one HF rehospitalization. Figure 1 shows the unadjusted cumulative incidence curves of three heart rate groups. The group with moderate heart rate had a relatively lower rate of the primary outcome (42.5%) than the groups with low (53.0%) and high (49.8%) heart rates ($P < 0.010$). The associations between discharge heart rate and primary outcome calculated by adjusted restricted cubic spline *Cox* regression are shown in Figure 2. We observed a non-linear association (unadjusted and adjusted *P* values of the non-linear test were 0.013 and 0.066, respectively), with the lowest risk at a heart rate of 75 bpm. In the adjusted *Cox* models, the groups with low (HR: 1.32, 95% CI: 1.05–1.68, $P = 0.020$) and high (HR: 1.34, 95% CI: 1.07–1.67, $P = 0.009$) heart rates were associated with higher risks of

Table 1: Baseline characteristics according to discharge heart rate groups.

Characteristics	<65 bpm ($n=215$)	65–85 bpm ($n=1256$)	≥86 bpm ($n=289$)	Statistics	*P* value
Demographic factors					
Age (years)	70 (62, 76)	69 (61, 77)	67 (57, 75)	9.588	0.008
Female	79 (36.7)	535 (42.6)	109 (37.7)	4.233	0.122
Current smoking	43 (20.0)	260 (20.7)	74 (25.6)	3.599	0.161
Medical history					
Implantation of pacemaker	22 (10.2)	67 (5.3)	4 (1.4)	19.327	<0.001
Coronary artery disease	117 (54.4)	652 (51.9)	143 (49.5)	1.212	0.544
Myocardial infarction	39 (18.1)	153 (12.2)	35 (12.1)	6.029	0.050
Non-ischemic cardiomyopathy	52 (24.1)	229 (18.2)	62 (21.5)	4.892	0.082
Stroke	52 (24.2)	313 (24.9)	54 (18.7)	5.000	0.080
Hypertension	127 (59.1)	716 (57.0)	127 (43.9)	17.733	<0.001
LDL-C election	18 (8.4)	152 (12.1)	33 (11.4)	2.699	0.270
Diabetes mellitus	70 (32.6)	351 (27.9)	77 (26.6)	2.339	0.303
Reduced renal function	78 (36.2)	333 (26.5)	67 (23.1)	11.295	0.004
Valvular heart disease	55 (25.6)	316 (25.2)	69 (23.9)	0.278	0.882
COPD	43 (20.0)	254 (20.2)	48 (16.6)	1.942	0.373
LVEF (%)	47.0 (36.0, 57.0)	49.0 (38.7, 59.0)	46.0 (35.0, 56.0)	9.967	0.007
<50%	118 (54.9)	651 (51.8)	165 (57.1)	4.393	0.230
Electrocardiographic results					
QRS duration (ms)	108 (94, 124)	99 (90, 114)	99 (88, 114)	17.900	<0.001
Left bundle branch block	14 (6.5)	58 (4.6)	9 (3.1)	3.247	0.198
Right bundle branch block	23 (10.7)	131 (10.4)	33 (11.4)	0.252	0.886
Atrioventricular block (II–III)	17 (7.9)	19 (1.5)	3 (1.0)	36.919	<0.001
Atrial tachycardia	22 (10.2)	58 (4.6)	5 (1.7)	19.848	<0.001
Ventricular tachycardia	27 (12.6)	105 (8.4)	14 (4.8)	9.633	0.008
Laboratory tests					
Serum sodium (mmol/L)	139.3 (137.0, 142.0)	139.7 (137.0, 142.0)	139.1 (137.0, 142.0)	0.941	0.643
Serum potassium (mmol/L)	4.2 (3.9, 4.6)	4.1 (3.8, 4.5)	4.1 (3.8, 4.5)	5.421	0.067
Troponin T (ng/L)	23.1 (15.0, 42.8)	18.3 (11.6, 30.4)	19.6 (11.8, 38.5)	20.983	<0.001
Creatinine (μmol/L)	99.0 (83.0, 119.3)	92.2 (77.7, 107.7)	94.2 (79.6, 107.6)	15.122	<0.001
NT-proBNP (pg/mL)	1809.0 (738.0, 3354.0)	1399.0 (693.1, 3008.0)	1850.0 (826.2, 3552.0)	8.893	0.012
NYHA classifications (III–IV)	180 (83.7)	985 (78.4)	244 (84.4)	5.528	0.061
SBP at discharge (mmHg)	120 (108, 130)	120 (110, 130)	120 (110, 130)	5.439	0.063
DBP at discharge (mmHg)	70 (60, 75)	70 (67, 80)	72 (67, 80)	32.231	<0.001
Heart rhythm at discharge (AF)	135 (62.8)	961 (76.5)	249 (86.2)	46.269	<0.001
Rhythm control in hospital					
Antiarrhythmic agents*	45 (21.0)	110 (8.8)	18 (6.0)	35.406	<0.001
Radiofrequency ablation for AF	2 (1.0)	6 (1.0)	3 (1.0)	1.562	0.460
Persistent/permanent (*vs.* paroxysmal) AF	123 (57.2)	895 (71.3)	219 (75.8)	44.687	<0.001
Medications at discharge					
Beta-blockers	104 (48.4)	765 (60.9)	171 (59.2)	11.903	0.003
ACEI/ARB	106 (49.3)	642 (51.1)	113 (39.1)	13.585	0.001
Aldosterone antagonists	132 (61.4)	806 (64.2)	190 (65.7)	1.023	0.599
Diuretic	150 (69.8)	878 (69.9)	205 (70.9)	0.135	0.938
Digoxin	60 (28.0)	392 (31.2)	124 (42.9)	17.282	<0.001
Antiarrhythmic agents*	25 (12.0)	44 (4.0)	10 (4.0)	29.187	<0.001
Length of stay in hospital	11 (8, 14)	10 (7, 13)	9 (7, 12)	16.648	<0.001

Data are median (IQR) or *n* (%). The differences of quantitative indexes or categorical variables between the three groups were analyzed using Kruskal-Wallis test or χ^2 test. *Antiarrhythmic agents including amiodarone, sotalol, and propafenone. ACEI: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blocker; Bpm: Beats per minute; COPD: Chronic obstructive pulmonary disease; DBP: Diastolic blood pressure; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; SBP: Systolic blood pressure.

the 1-year primary outcome, when compared with the group with moderate heart rate [Table 2].

During 1-year follow-up after discharge, the rates of all-cause death among low, moderate, and high groups were 19.1%, 16.2%, and 20.8%, respectively, and the differences were not significant ($P=0.130$) [Figure 1]. In the adjusted *Cox* models, compared with the group with moderate heart rate, the groups with low and high heart rates were not associated with the risks of the all-cause of death during the first 250 days of follow-up, or after the first 250 days [Table 2].

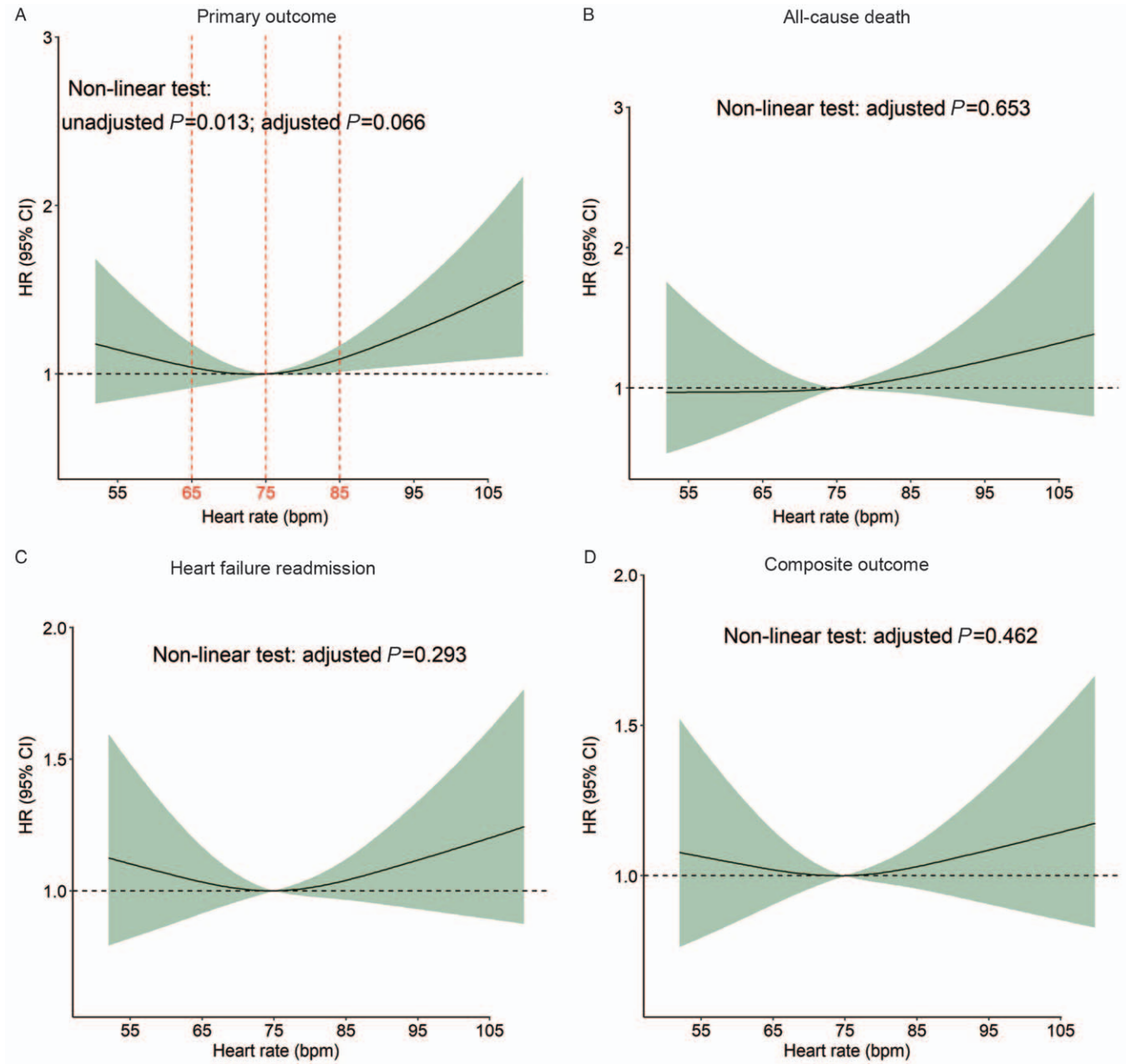

Figure 2: Associations between discharge heart rate and 1-year clinical outcomes in the entire cohort. (A) The primary outcome, which was defined as a composite outcome of all-cause death and HF rehospitalization; (B) all-cause death; (C) HF rehospitalization; (D) composite outcome of all-cause death and all-cause rehospitalization. The analysis used a *Cox* model with restricted cubic splines, corrected for age, sex, smoking status, medical history, LVEF, QRS duration, laboratory tests, NYHA classifications, SBP, and medication use at discharge, and the reference was the median of discharge heart rate (75 bpm). Solid lines represented HRs, and green light shaded areas represented 95% CI. Bpm: Beats per minute; CI: Confidence interval; HR: Hazard ratio; HF: Heart failure; HR: Hazard ratio; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; SBP: Systolic blood pressure.

The group with moderate heart rate had a relatively lower rate of HF rehospitalization (34.0%) than the groups with low (40.9%) and high (36.3%) heart rates ($P = 0.037$) [Figure 1]. In the adjusted Fine-Gray models, compared with the group with moderate heart rate, the groups with low and high heart rates were not associated with the risks of the 1-year HF rehospitalization [Table 2].

Sensitivity analyses

Among those whose heart rhythm was AF at discharge ($n = 1345$), compared with the group with moderate heart rate, the groups with low (HR: 1.39, 95% CI: 1.06–1.81, $P = 0.016$) and high (HR: 1.35, 95% CI: 1.09–1.67, $P = 0.007$) heart rate were associated with higher risks of the primary outcome. Among those who were persistent/permanent AF ($n = 1237$), compared with the group with moderate heart rate, the groups with low (HR: 1.36, 95% CI: 1.02–1.80, $P = 0.038$) and high (HR: 1.29, 95% CI: 1.02–1.63, $P = 0.034$) heart rate were associated with higher risks of the primary outcome. Among those who had no rhythm control treatment ($n = 1579$), compared with the group with moderate heart rate, the group with high heart rate was not associated with a higher risk of the

Table 2: Associations between discharge heart rate groups and 1-year clinical outcomes in the entire cohort.

Outcomes	Event rate (%)	Unadjusted HRs (95% CI)	*P*-value	Adjusted HRs (95% CI)	*P* value
Composite outcome of all-cause death and HF readmission (primary outcome)					
<65 bpm	53.0	1.39 (1.12–1.72)	0.003	1.32 (1.05–1.68)	0.020
65–85 bpm	42.5	1.00 (reference)	NA	1.00 (reference)	NA
≥86 bpm	49.8	1.34 (1.11–1.62)	0.002	1.34 (1.07–1.67)	0.009
All-cause death*					
<65 bpm	19.1	0.98 (0.65, 1.47)	0.924	0.76 (0.50, 1.15)	0.191
65–85 bpm	16.2	1.00 (reference)	NA	1.00 (reference)	NA
≥86 bpm	20.8	1.35 (0.98, 1.87)	0.067	1.14 (0.82, 1.60)	0.433
HF readmission					
<65 bpm	40.9	1.28 (1.02–1.61)	0.033	1.14 (0.88–1.46)	0.327
65–85 bpm	34.0	1.00 (reference)	NA	1.00 (reference)	NA
≥86 bpm	36.3	1.14 (0.92–1.41)	0.232	1.16 (0.91–1.47)	0.238
Composite outcome of all-cause death and all-cause readmission					
<65 bpm	57.7	1.29 (1.06–1.56)	0.010	1.25 (1.02–1.54)	0.034
65–85 bpm	49.4	1.00 (reference)	NA	1.00 (reference)	NA
≥86 bpm	49.8	1.17 (0.97–1.40)	0.093	1.23 (1.01–1.49)	0.044

Proportional hazards assumptions were satisfied for the primary outcome, HF readmission, and composite outcome of all-cause death and all-cause readmission, but not for all-cause death. *HRs for all-cause death pertain to a 250-day follow-up period; all other HRs are based on the entirety of 1-year follow-up. Bpm: Beats per minute; CI: Confidence interval; HR: Hazard ratio; HF: Heart failure.

primary outcome (HR: 1.21, 95% CI: 0.97–1.49, $P = 0.087$), while the group with low heart rate was still associated with higher risks of the primary outcome (HR: 1.38, 95% CI: 1.09–1.76, $P = 0.009$). Among those who had stable discharge heart rate ($n = 1493$), compared with the group with moderate heart rate, the groups with low (HR: 1.33, 95% CI: 1.05–1.68, $P = 0.017$) and high (HR: 1.26, 95% CI: 1.00–1.59, $P = 0.050$) heart rate were associated with higher risks of the primary outcome [Supplementary Tables 1–4, http://links.lww.com/CM9/A771].

In the IPTW-weighted analysis, standardized mean differences between discharge heart rate groups were considerably smaller and <0.1 for all the baseline characteristics, except history of stroke and low-density lipoprotein cholesterol elevation. IPTW-weighted *Cox* regression analysis concluded that the groups with low and high heart rates were associated with higher risks of the primary outcome, compared with the group with moderate heart rate [Supplementary Tables 5, http://links.lww.com/CM9/A771 and 6, http://links.lww.com/CM9/A771].

Subgroup analyses of LVEF

However, the pattern of association between discharge heart rate and primary outcome differed according to the LVEF strata [Figure 3]. There was a significant interaction between discharge heart rate and LVEF with respect to the primary outcome (*P* for interaction was 0.045). Among the patients with LVEF ≥50%, the group with a high heart rate was associated with a higher risk of primary outcome compared with the group with moderate heart rate (HR: 1.38, 95% CI: 1.01–1.89, $P = 0.046$), while there was no difference between the groups with low and moderate heart rate [Table 3]. Among the patients with LVEF <50%, the group with low heart rate was associated with a higher risk of primary outcome compared with the group with moderate heart rate (HR: 1.46, 95% CI: 1.09–1.96, $P = 0.012$), while there was no difference between the groups with high and moderate heart rate [Table 3].

Discussion

We explored the associations between discharge heart rate and 1-year clinical outcomes among HF patients with AF and a wide spectrum of LVEF in this nationwide prospective cohort. For patients with LVEF ≥50%, only high heart rate (≥86 bpm) group was associated with higher risk compared with the moderate group (65–85 bpm); while for patients with LVEF <50%, only low heart rate (<65 bpm) group was associated with higher risk compared with a moderate group (65–85 bpm). The robustness of our results was demonstrated by the use of multiple sensitivity analyses. These findings provided the evidence to refine recommendations in future clinical guidelines to guide the management of heart rate for HF patients with AF.

Compared with RACE II, our study is the only randomized controlled trial to investigate strategies of rate control treatment in AF patients[17]; our study made three important complements. First, subgroup HF patients in RACE II were underrepresented as they excluded patients hospitalized for HF in the past 3 months, part of HF patients with reduced LVEF, and severe systolic HF patients.[18] Consequently, their results may be ungeneralizable to these patients. In contrast with them, our cohort entirely consisted of hospitalized HF patients and had a wide spectrum of LVEF. Second, based on the results of RACE II, current guidelines suggest the optimal heart rate target in HF patients with AF is still unclear and could be 60 to 100 bpm.[14,15] Our results suggest that a narrower target for heart rate control (65–85 bpm) than the current guidelines may be beneficial for HF patients with AF. Third, RACE II did not offer subgroup analysis according to LVEF.[18] And the current guidelines did not offer different optimal heart rate targets according to LVEF,

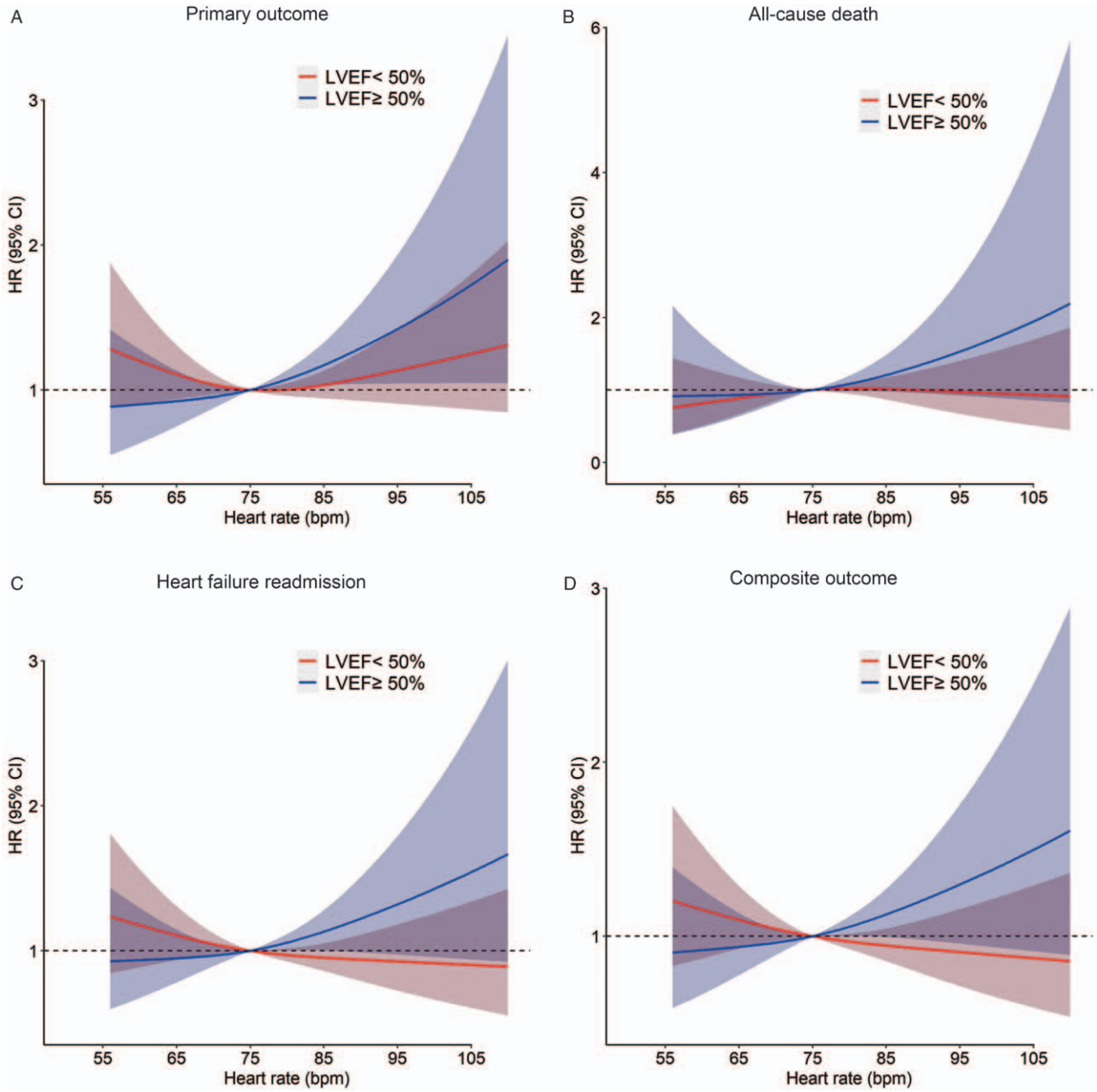

Figure 3: Associations between discharge heart rate and 1-year clinical outcomes in different subgroups of LVEF. (A) The primary outcome, which was defined as a composite outcome of all-cause death and HF rehospitalization; (B) all-cause death; (C) HF rehospitalization; (D) composite outcome of all-cause death and all-cause rehospitalization. The analysis used a *Cox* model with restricted cubic splines, corrected for age, sex, smoking status, medical history, QRS duration, laboratory tests, NYHA classifications, SBP, and medication use at discharge, and the reference was the median of discharge heart rate (75 bpm). Solid lines represented HRs, and light-shaded areas represented 95% CI. Red showed the results of patients with LVEF <50%, and blue showed the results of those with LVEF ≥50%. Bpm: Beats per minute; CI: Confidence interval; HR: Hazard ratio; HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; SBP: Systolic blood pressure.

although they emphasized that the target should be individualized according to heart function.[14,16] We reported a distinguished prognostic value of discharge heart rate in patients with LVEF ≥50% and <50%, which means the impact mechanisms between heart rate and clinical outcomes were partly achieved through different types of cardiac dysfunction.

For HF patients with preserved LVEF and AF, the group with a high (≥86 bpm) heart rate was associated with a higher risk of composite outcome compared with a moderate group. This phenotype of HF is termed diastolic HF. The diastolic function loss suggested the need for lower heart rates to extend diastolic blood perfusion time and increase myocardial oxygen delivery. Otherwise, high heart rates may lead to increased oxygen demand, and induced ischemia, and thus increase the risks of serious arrhythmias and clinical outcomes.[24] In a mouse model of HF with a preserved LVEF, heart rate lowering treatments improved diastolic function[25] and survival rate.[26] However, current trials have not found sufficient evidence of survival benefits of heart rate lowering treatments

Table 3: Associations between discharge heart rate and 1-year clinical outcomes in different subgroups of LVEF.

Outcomes	LVEF <50%		LVEF ≥50%		
	Adjusted HRs (95% CI)	*P*	Adjusted HRs (95% CI)	*P*	*P* value for interaction
Composite outcome of all-cause death and HF readmission (primary outcome)					0.045
<65 bpm (*vs.* 65–85 bpm)	1.46 (1.09–1.96)	0.012	1.11 (0.78–1.59)	0.551	
≥86 bpm (*vs.* 65–85 bpm)	1.24 (0.95–1.62)	0.122	1.38 (1.01–1.89)	0.046	
All-cause death					0.057
<65 bpm (*vs.* 65–85 bpm)	1.21 (0.76–1.93)	0.423	1.15 (0.63–2.11)	0.642	
≥86 bpm (*vs.* 65–85 bpm)	1.27 (0.84–1.94)	0.260	1.44 (0.86–2.43)	0.169	
HF readmission					0.794
<65 bpm (*vs.* 65–85 bpm)	0.98 (0.70–1.38)	0.905	1.22 (0.83–1.80)	0.303	
≥86 bpm (*vs.* 65–85 bpm)	1.03 (0.76–1.41)	0.842	1.31 (0.91–1.88)	0.141	
Composite outcome of all-cause death and all-cause readmission					0.005
<65 bpm (*vs.* 65–85 bpm)	1.37 (1.04–1.80)	0.027	1.08 (0.79–1.47)	0.636	
≥86 bpm (*vs.* 65–85 bpm)	1.08 (0.83–1.41)	0.561	1.49 (1.12–1.98)	0.006	

Proportional hazards assumptions were satisfied for each clinical outcome both in patients with LVEF <50% and in those with LVEF ≥50%. Bpm: Beats per minute; CI: Confidence interval; HR: Hazard ratio; HF; Heart failure; LVEF: Left ventricular ejection fraction.

(including beta-blockers) in HF patients with preserved LVEF,[27] and few studies investigated these treatments in those with concomitant AF. Our result indicated that these treatments could be beneficial, and further prospective trials were warranted to examine these hypotheses.

For HF patients with reduced LVEF and AF, the group with low (<65 bpm) heart rate was associated with a higher risk of composite outcome compared with a moderate group. This phenotype of HF is termed systolic HF. The systolic function loss had reduced cardiac output, which was also caused by the loss of regular atrial contraction.[28] Cardiac output was equal to the stroke volume multiplied by the number of bpm, which implied that higher heart rates can lead to a compensatory increase of the cardiac output.[29,30] Otherwise, a lower heart rate may result in the reduction of cardiac output and thus increase the risk of clinical outcomes.[31] Besides, other pathophysiologic mechanisms may be able to explain the association. A slow ventricular rate might indicate conduction system disease, including sinus node dysfunction and atrioventricular node dysfunction, which may lead to worse outcomes.[21] And chronotropic incompetence was common in the HF population, with a range of 25% to 70%. It may be further exacerbated by pharmacological heart rate lowering.[32] Despite the fact that beta-blockers have been proved to improve survival in HF patients with reduced LVEF, an individual-level mate-analysis concluded that beta-blockers could not improve clinical outcomes in those with concomitant AF.[33] Our findings may be able to explain this unexpected result.

Limitations

In the present study, several limitations should be considered. First, given the nature of the observational study for this analysis, although we employed multivariable *Cox* and Fine-Gray analyses to adjust potential confounders, and conducted several sensitivity analyses to examine the robustness of the results, unmeasured and residual confounding may still exist. But our results could still have the reference value due to a lack of relevant randomized controlled trials. Second, the patient recruitment in this study may not include the most severe patients who were not able to sign the informed consent form within 24 h, but it had limited influence on the relationship between discharge heart rate and clinical outcomes. Third, heart rate at discharge was usually measured by a routine electrocardiogram, rather than by a 24-h Holter electrocardiogram. However, this is a common problem found in previous studies.[23,34,35] To reduce bias due to possible errors in measurement and instability of heart rate in acute HF and AF patients, we investigated the effects of discharge heart rate on clinical outcomes among those who had stable discharge heart rate, defined as differences between the heart rate of the first electrocardiogram and discharge heart rate ≤20 bpm.[23] These results were consistent with the primary results of the entire cohort, and thus our results were still convincing. Last, information on the changes in heart rhythm, heart rate, LVEF, and use of heart rate lowering treatments during the follow-up period was not recorded.

Conclusions

Among the overall HF patients with AF, both low (<65 bpm) and high heart (≥86 bpm) rates were associated with poorer outcomes as compared with moderate heart rate (65–85 bpm). Among patients with LVEF ≥50%, only a high heart rate was associated with higher risk, while among those with LVEF <50%, only a low heart rate was associated with higher risk as compared with the group with moderate heart rate. These findings still await further assessment by randomized controlled trials.

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Conflicts of interest

Dr. Jing Li reported receiving research grants, through Fuwai Hospital, from China for work to improve the management of hypertension and blood lipids and to improve care quality and patient outcomes of cardiovascular disease; receiving research agreements, through the National Center for Cardiovascular Diseases and Fuwai Hospital, from Amgen for a multicenter clinical trial assessing the efficacy and safety of omecamtiv mecarbil and for dyslipidemic patient registration; receiving a research agreement, through Fuwai Hospital, from Sanofi for a multicenter clinical trial on the effects of sotagliflozin; receiving a research agreement, through Fuwai Hospital, with the University of Oxford for a multicenter clinical trial of empagliflozin; receiving a research agreement, through the National Center for Cardiovascular Diseases, from AstraZeneca for clinical research methods training outside the submitted work; and receiving a research agreement, through the National Center for Cardiovascular Diseases, from Lilly for physician training outside the submitted work. No other disclosures were reported.

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