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Beta-blockers and 1-year clinical outcomes in hospitalized heart failure patients with atrial fibrillation

Fu-Wei XING, Li-Hua ZHANG, Hai-Bo ZHANG, Xue-Ke BAI, Dan-Li HU, Xin ZHENG✉, Jing LI✉

National Clinical Research Center for Cardiovascular Diseases, NHC Key Laboratory of Clinical Research for Cardiovascular Medications, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center for Cardiovascular Diseases, Beijing, China
✉ Correspondence to: jing.li@fwoxford.org; xin.zheng@fwoxford.org
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ABSTRACT

OBJECTIVE To assess the association between beta-blockers and 1-year clinical outcomes in heart failure (HF) patients with atrial fibrillation (AF), and further explore this association that differs by left ventricular ejection fraction (LVEF) level.

METHODS We enrolled hospitalized HF patients with AF from China Patient-centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study. COX proportional hazard regression models were employed to calculate hazard ratio of beta-blockers. The primary outcome was all-cause death.

RESULTS Among 1762 HF patients with AF (756 women [41.4%]), 1041 (56%) received beta-blockers at discharge and 1272 (72.2%) had an LVEF > 40%. During one year follow up, all-cause death occurred in 305 (17.3%), cardiovascular death occurred in 203 patients (11.5%), and rehospitalizations for HF occurred in 622 patients (35.2%). After adjusting for demographic characteristics, social economic status, smoking status, medical history, anthropometric characteristics, and medications used at discharge, the use of beta-blockers at discharge was not associated with all-cause death [hazard ratio (HR): 0.86; 95% Confidence Interval (CI): 0.65–1.12; P = 0.256], cardiovascular death (HR: 0.76, 95% CI: 0.52–1.11; P = 0.160), or the composite outcome of all-cause death and HF rehospitalization (HR: 0.97, 95% CI: 0.82–1.14; P = 0.687) in the entire cohort. There were no significant interactions between use of beta-blockers at discharge and LVEF with respect to all-cause death, cardiovascular death, or composite outcome. In the adjusted models, the use of beta-blockers at discharge was not associated with all-cause death, cardiovascular death, or composite outcome across the different levels of LVEF: reduced (< 40%), mid-range (40%–49%), or preserved LVEF (≥ 50%).

CONCLUSION Among HF patients with AF, the use of beta-blockers at discharge was not associated with 1-year clinical outcomes, regardless of LVEF.

Heart failure (HF) is a leading cause of death and there are approximately 64.3 million patients with HF worldwide.[1] Among them, atrial fibrillation (AF) is the most common arrhythmia and presents in up to half of HF patients; its prevalence is even higher in those with preserved left ventricular ejection fraction (LVEF).[2] Given the association between AF and worse prognosis in HF patients,[3] we need to consider the presence of AF in the treatment of such patients.

Beta-blockers are important medications to improve outcomes in HF patients with reduced ejection fraction (HFrEF).[4] However, an individual-level meta-analysis suggested beta-blockers did not improve survival of HFrEF patients with concomitant AF.[5] Moreover, current trials have not found sufficient evidence of survival benefits of beta-blockers in HF patients with preserved ejection fraction (HFpEF).[6,7] But the use of beta-blockers was common in HFpEF patients,[8,9] partly because the treatment for complications, such as AF.[4,10] Whether beta-blockers would appear to be ineffective in long-term prognosis in HFrEF patients with AF, and whether this also holds true in those with preserved LVEF are uncertain. The individual-level meta-analysis of 11 randomized controlled trials mainly con-

sisted of HFrEF patients with AF, and only included 73 HFpEF patients with AF, which could make it difficult to draw a reliable conclusion.[6] Despite lack of evidence, the current guidelines recommend beta-blockers as first-line heart rate control treatment in HFrEF/HFpEF patients with AF. [4,10]

To fill these knowledge gaps, we explored the association between use of beta-blockers at discharge and 1-year clinical outcomes in a large prospective cohort study of hospitalized HF patients with AF, and further explored this association that differs by LVEF level.

METHODS

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.[11] 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 study and their geographical locations. Patients were screened and enrolled from August 2016 to May 2018. The ethics committee of 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 (NCT02878811).

Patients aged 18 years and above were eligible if they were hospitalized primarily for new-onset HF or decompensation of chronic HF, which were assessed by the local physician (n = 4 907). 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), or were not diagnosed as AF (n = 3081). The diagnosis of AF was based on 12-lead electrocardiograms performed during hospitalization or discharge diagnosis. In total, 1 762 HF patients with AF were included in our analysis. Our cohort included any types of AF (paroxysmal, persistent, and permanent). According to current guidelines on AF, patients with a 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.[10] According to current guidelines on HF, patients were categorized into three LVEF groups: HFrEF (< 40%), HF with mid-range LVEF (40%–49%), and HFpEF (≥ 50%).[4]

We centrally abstracted data from inpatient medical chart of the index hospitalization and in-person interviews during 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. 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 creatinine. In this study, we trained local experienced physicians to do echocardiography to measure LVEF according to standard operation procedure. LVEF was obtained from apical 2- and 4-chamber views and calculated with the Simpson method. Some of the variables in the medical history were defined in the appendix. And we did face-to-face interview during hospitalization, at 1 month, 6 months, and 1 year after discharge.

Outcomes

The primary outcome in our study was an all-cause death within 1-year after discharge. The secondary outcome was a cardiovascular death and a composite outcome of all-cause death and HF rehospitalization within 1-year after discharge. All-cause deaths were classified into three categories: cardiovascular death, non-cardiovascular death, and unknown cause of death. Cardiovascular deaths included sudden cardiac death, death due to HF, stroke, acute myocardial infarction, or other cardiovascular cause.[12] Death was considered non-cardiovascular death if an unequivocal and documented non-cardiovascular cause could be established as the primary cause of death. If there were multiple HF rehospitalization records, only the first HF 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 health information system of local hospitals, and outcome information from National Center for Disease Con-

trol and Prevention were used if patients could not attend regular follow up visits. We further confirmed vital status according to the national database of death cause. Clinicians at coordinating center adjudicated all outcome events and the cause of death or rehospitalization.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages and analyzed using x^2 tests; continuous variables were described as medians and interquartile ranges (IQR) and analyzed by the Wilcoxon test.

We investigated the association between use of beta-blockers at discharge and clinical outcomes in HF patients with AF. We plotted cumulative incidence curves and compared using the log-rank test. Multivariable COX proportional hazards models were employed to calculate the adjusted hazard ratios (HRs) of the use of beta-blockers at discharge.

In the minimally adjusted model, we corrected for age, sex, social economic status (married status, educational level), smoking status, and medical history (coronary heart disease, non-ischemic cardiomyopathy, stroke, diabetes, chronic obstructive pulmonary disease, valvular heart disease, and implantation of pacemaker). In the fully adjusted model, New York Heart Association class, LVEF, systolic blood pressure at discharge, heart rate at discharge, laboratory tests (serum creatinine, and N-terminal pro-brain natriuretic peptide), and medication use at discharge (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, aldosterone antagonists, diuretic, and digoxin) were added to the minimally adjusted model. Adjustment variables were selected based on their potential role in the association with clinical outcomes.

We then examined the variable effects of beta-blockers on clinical outcomes according to LVEF. LVEF was analyzed as a continuous variable to model interactions with outcomes. When stratified by LVEF, we adjusted for the same variables as described above, but LVEF was removed from the model. We then examined whether the effects of beta-blockers on outcomes were consistent in different classifications of AF.

To examine whether the results of primary cohort were consistent, we employed four sensitivity analyses. In the first analysis, we excluded patients whose beta-blocker status was changed during follow-up visit (n = 472). In the second analysis, we excluded patients who had no classification of AF (n = 118) and those who were paroxysmal AF (n = 406). In the third analysis, we excluded patients who had antiarrhythmic agents (including amiodarone, sotalol, and propafenone) or radiofrequency ablation for AF during hospitalization or at discharge (n = 182). In the last analysis, we excluded patients without documented heart rhythm at discharge (n = 63) and those who had sinus rhythm or paced rhythm at discharge (n = 354). In these four sensitivity cohorts, we calculated HRs of beta-blockers using the COX model for clinical outcomes overall and in the LVEF subgroups.

We further investigated whether the effect of beta-blockers on clinical outcomes was dose-dependent or not. According to Chinese guidelines on HF, the doses of beta-blockers at discharge were calculated as a percentage target dose of each beta-blocker, which was 190, 150, 10, and 50 mg for metoprolol succinate, metoprolol tartrate tablets, bisoprolol, and carvedilol, respectively.[13] Under stratification according to discharge beta-blocker doses, patients were grouped into four groups: patients receiving low (< 25% of target dose), medium (25%–49% of target dose), and high (≥ 50% of target dose) dose of beta-blockers and those not receiving beta-blockers. We then used adjusted model to calculate HRs of beta-blocker doses. This analysis excluded 15 patients who had no document of doses of beta-blockers.

In total, 2 (0.1%) of discharge heart rate, 16 (0.9%) of discharge systolic blood pressure 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-sided, and $P < 0.05$ was used to determine statistical significance. The forest plots and log-rank tests were performed using R software (version 3.6.3). Other statistical analyses were performed using SAS software (version 9.4).

RESULTS

Patient Characteristics

A total of 1762 patients (756 women [41.4%]) were

included in the study (Figure 1). The median discharge heart rate was 75 (IQR: 68–84) beats/min, and the median of LVEF was 48% (IQR: 38%–58%). Compared to patients discharged without beta-blockers, those with beta-blockers were younger, more likely to be male, had lower LVEF or higher discharge heart rate, or more likely to discharged with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or aldosterone antagonists (Table 1).

Prognostic Value of the Use of Beta-blockers at Discharge

During 1-year follow-up after discharge, all-cause death occurred in 305 patients (17.3%), cardiovascular death occurred in 203 patients (11.5%), and re-hospitalizations for HF occurred in 622 patients (35.2%). Figure 2 showed the cumulative event curves related to use of beta-blockers at discharge, and the log-rank test result suggested the use of beta-blockers was associated with reduced risk of all-cause death (P = 0.016). In the fully adjusted models, the use of beta-blockers was not associated with risk of all-cause death (HR: 0.86; 95% CI: 0.65–1.12; P = 0.256) (Figure 3).

Subgroup Analyses

Supplemental Figures S1–S3 showed the cumulative event curves related to use of beta-blockers, while stratified by LVEF. And the log-rank test results suggested the use of beta-blockers was associated with reduced risk of all-cause death in those with an LVEF of 40%–49% (P = 0.001), but not in those with an LVEF < 40% or ≥ 50%. Fully adjusted COX model suggested the use of beta-blockers was not associated with the risk of all-cause death in patients with reduced, mid-range, or preserved LVEF (Figure 4). There was no significant interaction between use of beta-blockers and LVEF with respect to all-cause death (P for interaction was 0.571).

There was no significant interaction between use of beta-blockers at discharge and classification of AF with respect to all-cause death (P for interaction was 0.889). The use of beta-blockers was not associated with the risk of all-cause death in patients with paroxysmal AF, or persistent/permanent AF (Supplemental Figure S4).

Sensitivity Analyses

Among those not changing beta-blocker status

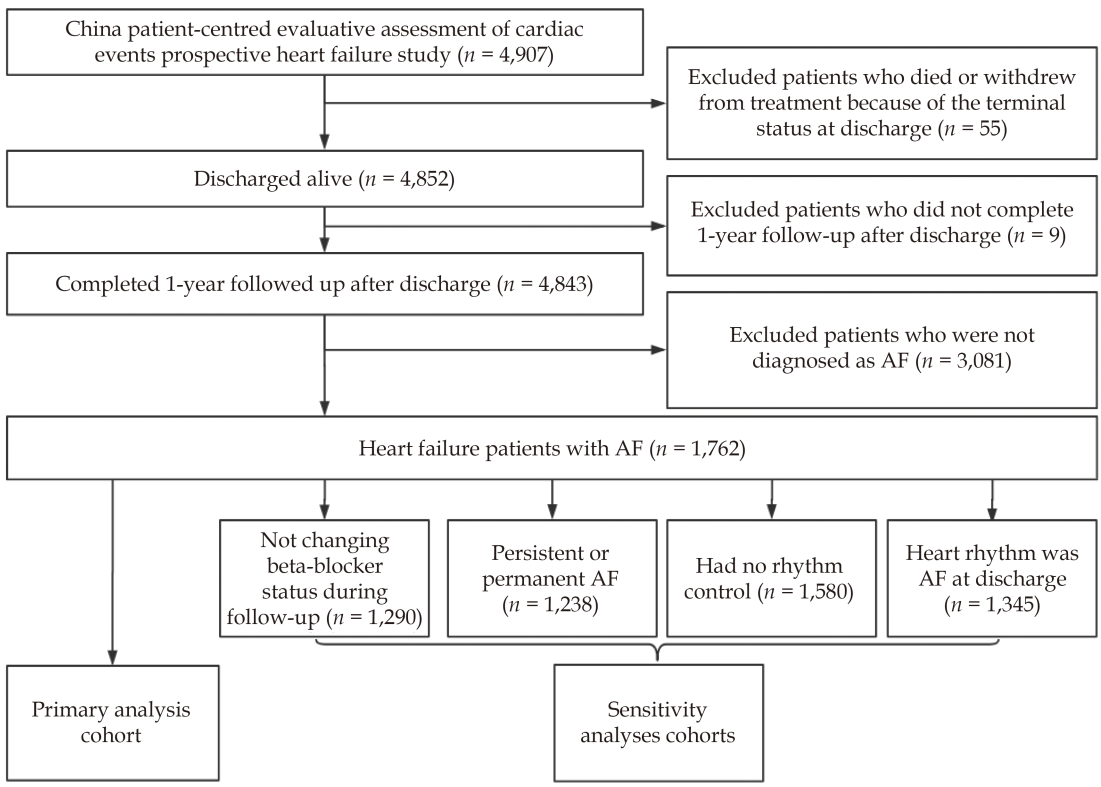

Figure 1 Flow chart of study cohorts. AF: atrial fibrillation.

Table 1 Baseline characteristics according to use of beta-blockers at discharge.

	Total (*n* = 1762)	Beta-blocker (*n* = 1041)	Non-beta-blocker (*n* = 721)	*P*-value
Demographic factors				
Age, yrs	69 (60, 77)	68 (59, 75)	70 (63, 78)	< 0.001
Female	724 (41.1%)	405 (38.9%)	319 (44.2%)	0.025
Social economic status				
Married	1357 (77.0%)	831 (79.8%)	526 (73.0%)	<0.001
High-school education or above	481 (27.3%)	300 (28.8%)	181 (25.1%)	0.008
Current smoking	378 (21.5%)	239 (23.0%)	139 (19.3%)	0.064
Medical history				
Implantation of pacemaker	93 (5.3%)	52 (5.0%)	41 (5.7%)	0.523
Coronary artery disease	927 (52.6%)	541 (52.0%)	386 (53.5%)	0.517
Myocardial infarction	227 (12.9%)	135 (13.0%)	92 (12.8%)	0.898
Non-ischemic cardiomyopathy	344 (19.5%)	257 (24.7%)	87 (12.1%)	< 0.001
Stroke	426 (24.2%)	247 (23.7%)	179 (24.8%)	0.596
Hypertension	971 (55.1%)	576 (55.3%)	395 (54.8%)	0.821
LDL-C elevation	204 (11.6%)	128 (12.3%)	76 (10.5%)	0.203
Diabetes mellitus	484 (27.5%)	297 (28.5%)	187 (25.9%)	0.230
Reduced renal function	479 (27.2%)	282 (27.1%)	197 (27.3%)	0.334
Valvular heart disease	442 (25.1%)	234 (22.5%)	208 (28.8%)	0.002
COPD	345 (19.6%)	188 (18.1%)	157 (21.8%)	0.053
Anemia	394 (22.4%)	209 (20.1%)	185 (25.7%)	0.006
Peripheral vascular disease	241 (13.7%)	139 (13.4%)	102 (14.1%)	0.633
Pericardial disease	444 (25.2%)	226 (21.7%)	218 (30.2%)	< 0.001
Cancer	74 (4.2%)	40 (3.8%)	34 (4.7%)	0.369
LVEF	48% (38%, 58%)	47% (37%, 57%)	50% (40%, 59.7%)	< 0.001
< 40%	490 (27.8%)	312 (30%)	178 (24.7%)	0.003
40%–49%	445 (25.3%)	275 (26.4%)	170 (23.6%)	
≥ 50%	827 (46.9%)	454 (43.6%)	373 (51.7%)	
QRS duration, ms	100 (90, 116)	100 (90, 114)	100 (90, 118)	0.124
Laboratory tests				
Serum potassium, mmol/L	4.14 (3.85, 4.5)	4.11 (3.84, 4.46)	4.17 (3.88, 4.53)	0.069
Serum sodium, mmol/L	139.6 (137, 142)	140 (137.5, 142)	139 (136.7, 141.45)	< 0.001
Troponin T, ng/L	19.19 (11.97, 33.19)	18.35 (11.61, 30.01)	20.46 (12.44, 38.54)	< 0.001
Creatinine, μmol/L	93.16 (78.32, 108.97)	93.17 (79.33, 109.33)	93.14 (77.74, 108.45)	0.420
NT-proBNP, pg/mL	1487 (730.5, 3132)	1476.5 (723.3, 3044)	1504 (736.9, 3274)	0.510
NYHA class III-IV	1411 (80.1%)	827 (79.4%)	584 (81.0%)	< 0.001
SBP at discharge, mmHg	120 (110, 130)	120 (110, 130)	120 (110, 130)	0.094
DBP at discharge, mmHg	70 (65, 80)	70 (66, 80)	70 (65, 80)	0.020
Heart rate at discharge, beats/min	75 (69, 84)	76 (70, 84)	75 (68, 82)	0.009
Heart rhythm at discharge	1345 (76.3%)	823 (79.1%)	522 (72.4%)	0.004
Rhythm control in hospital				
Radiofrequency ablation for AF	11 (0.6%)	3 (0.3%)	8 (1.1%)	0.031
Antiarrhythmic agents*	174 (9.9%)	102 (9.8%)	72 (10%)	0.897

Continued

	Total (n = 1762)	Beta-blocker (n = 1041)	Non-beta-blocker (n = 721)	P-value
Medications at discharge				
ACEI/ARB	862 (48.9%)	672 (64.6%)	190 (26.4%)	< 0.001
Aldosterone antagonists	1129 (64.1%)	824 (79.2%)	305 (42.3%)	< 0.001
Diuretic	1234 (70.0%)	895 (86.0%)	339 (47.0%)	< 0.001
Digoxin	576 (32.7%)	427 (41.0%)	149 (20.7%)	< 0.001
Calcium channel blocker	225 (12.8%)	146 (14.0%)	79 (11.0%)	0.058
Antiarrhythmic agents*	79 (4.5%)	55 (5.3%)	24 (3.3%)	0.051
Persistent/permanent AF (vs paroxysmal)	1238 (70.3%)	754 (72.4%)	484 (67.1%)	0.050
Length of stay in hospital, days	10 (7, 13)	9 (7, 12)	10 (8, 14)	< 0.001

Data are median (interquartile range) or n (%). ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BPM: beats per minutes; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; 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. *Antiarrhythmic agents including amiodarone, sotalol, and propafenone.

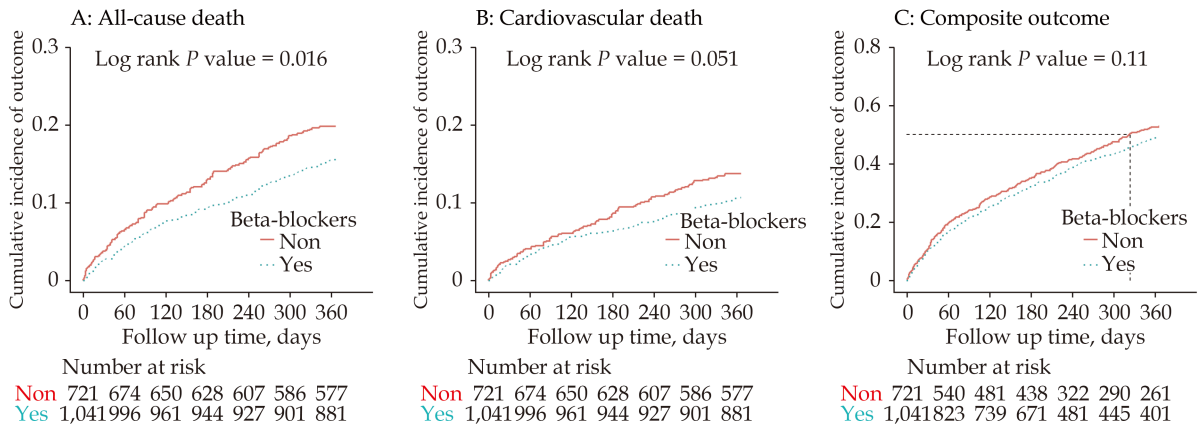

Figure 2 Cumulative incidence of 1-year clinical outcomes by the use of beta-blockers at discharge in entire cohort. (A): all-cause death; (B): cardiovascular death; and (C): composite outcome of all-cause death and heart failure rehospitalization.

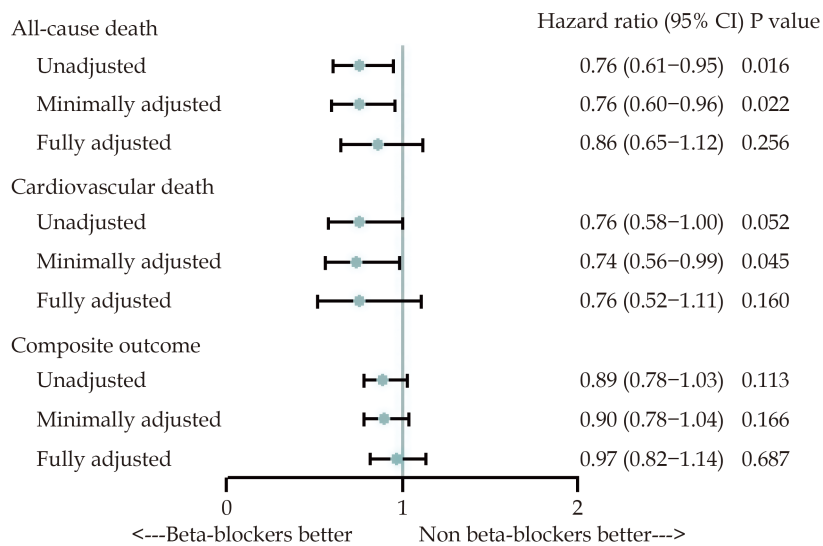

Figure 3 Associations between the use of beta-blockers at discharge and 1-year clinical outcomes in entire cohort. In the minimally adjusted model, we corrected for age, sex, social economic status, smoking status, and medical history. In the fully adjusted model, anthropometric characteristics and medications used at discharge were added to the minimally adjusted model.

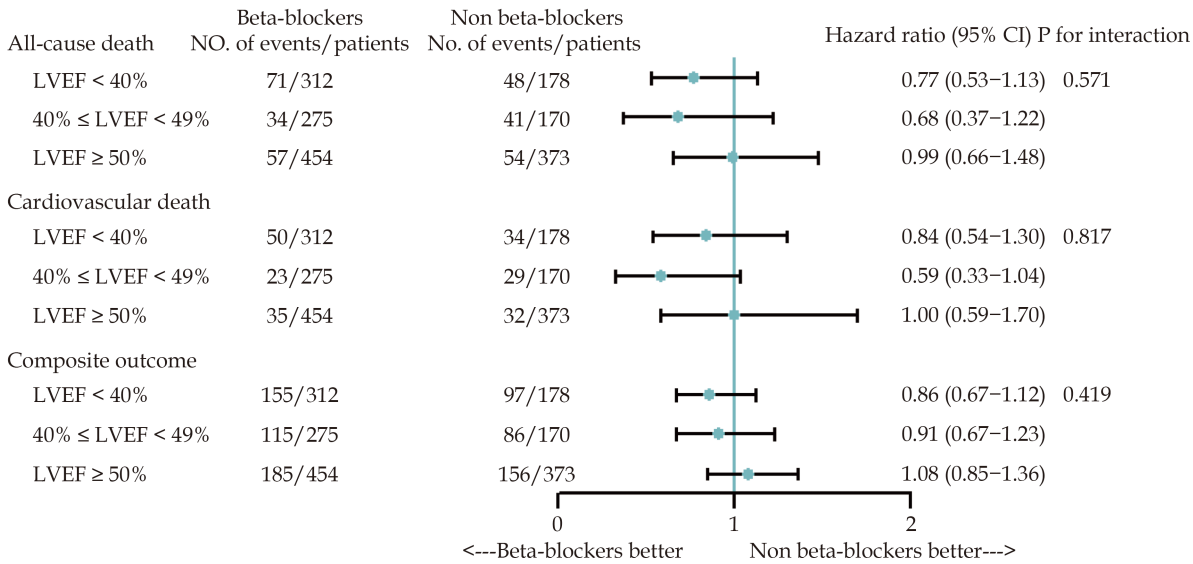

Figure 4 Associations between the use of beta-blockers at discharge and 1-year clinical outcomes according to left ventricular ejection fraction. LVEF: left ventricular ejection fraction.

during follow-up (n = 1 290), those who were persistent/permanent AF (n = 1 238), or those who had no rhythm control treatment (n = 1 579), the use of beta-blockers was not associated with all-cause death, regardless of LVEF (Supplemental Figure S5−S7). Among those whose heart rhythm was AF at discharge (n = 1 345), the use of beta-blockers was not associated with all-cause death, except those with mid-range LVEF (Supplemental Figure S8).

Dose Analyses

The median of percentage target dose of beta-blockers was 25%. Compared with patients discharged without beta-blockers, those received low (< 25% of target dose), medium (25%-49% of target dose), and high (≥ 50% of target dose) dose of beta-blockers were not associated with 1-year clinical outcomes (Figure 5).

DISCUSSION

In this large prospective cohort study, we investigated the effect of use of beta-blockers at discharge on long-term clinical outcomes in HF patients with AF who had a wide spectrum of LVEF. Although the unadjusted COX model suggested the use of beta-blockers was associated with reduced risk of all-cause death, fully adjusted COX model suggested that the use of beta-blockers was not associated with the risk of all-cause death in HF patients with AF, regardless of LVEF. The robustness of our results was demonstrated by the use of multiple sensitivity analyses.

These findings were consistent with the individual-level meta-analyses conducted by Kotecha and Cleland, *et al.*,[5,6,14] but our studies made three important complements. First, the meta-analyses only included a small number of patients with mid-range and preserved LVEF, therefore, their results may only apply to those with reduced LVEF. By contrast, more than 70% patients in our cohort had an LVEF > 40% (n = 1 272), making our results more generable. Moreover, we conducted the subgroup analysis of LVEF and corroborated the results of the prior meta-analyses. Second, the diagnosis of AF in prior studies was based on a single baseline electrocardiogram, and they may misdiagnose paroxysmal AF as having no AF. As reported previously, AF was present in approximately 40% of HF patients,[2] while it only accounted for 17% of HF patients in the meta-analyses. By contrast, 36.4% HF patients in our cohort had concomitant AF, which was closer to that in the real-world setting. Thus, AF patients in the meta-analyses were likely to be persistent AF. By contrast, up to 30% AF patients in our cohort were paroxysmal AF. The survival benefit of beta-blockers was hypothesized to be modulated by the classification of AF, with less benefit in persistent/permanent AF.[15] We conducted subgroup analyses of classification of AF, and there was no difference

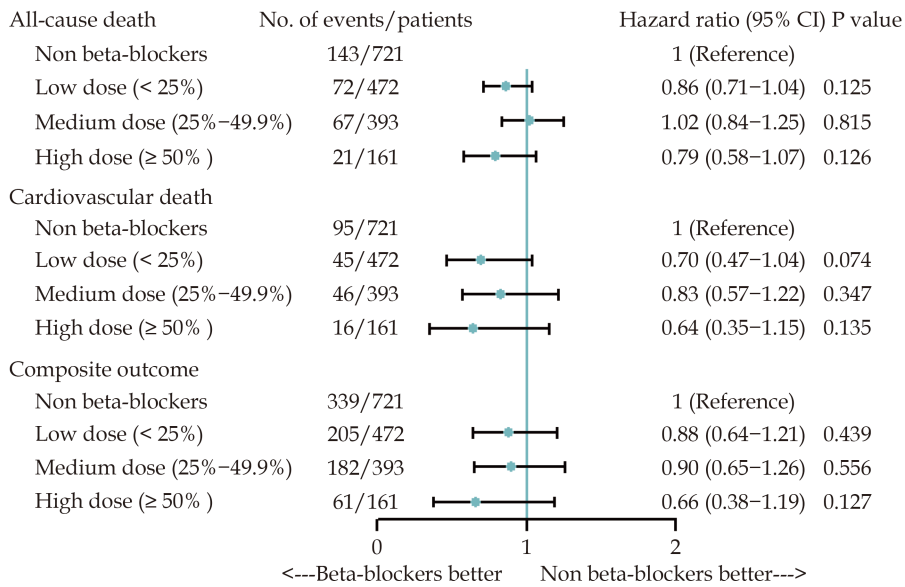

Figure 5 Associations between the use of beta-blockers at discharge and 1-year clinical outcomes according to beta-clockers doses.

in the effect of beta-blockers between paroxysmal and persistent/permanent AF. We further conducted three sensitive analyses, and concluded that the use of beta-blockers was not associated with the risk of all-cause death in those who were persistent/permanent AF, those whose heart rhythm was AF at discharge, or those who had no rhythm control treatment, which are consistent with the primary results of the entire cohort. Last, we investigated whether the effect of beta-blockers was dose-dependent in HF patients with AF, which was not included in the meta-analyses, and concluded that the effect did not vary by dose.

Excessive heart rate control may be able to explain our findings, as this side effect may counterbalance the survival benefits of beta-blockers.[16] First, a lower heart rate is associated with reduced risk of clinical outcomes in HF patients with sinus rhythm,[17] while others argued that it may be associated with increased risk of clinical outcomes in HF patients with AF.[18] Subgroup analysis of Race Control Efficacy in Permanent Atrial Fibrillation II trial suggested that strict rate control (< 80 beats/min) did not bring more survival benefits than lenient rate control (< 110 beats/min) in HF patients with AF.[19] Second, the use of high dose of beta-blockers may be related with excessive rate control.[16] Despite the survival benefits of beta-blockers were dose-dependent in HF patients,[7,14] our finding suggested the higher dose of beta-blockers (≥ 50% of target dose) did not bring more survival benefits in those with concomitant AF. For HF patients with AF, the findings from subgroup analyses of randomized controlled trials reported no survival benefit of beta-blockers,[5,14] and those from observational studies were the only ones that indicated survival benefit of beta-blockers.[20,21] As showed in Appendix Table S1, randomized controlled trials had higher doses of beta-blockers and stricter heart rate control than observational studies, and it may partly explain the different findings between these studies. Last, conduction system diseases, including sinus node dysfunction and atrioventricular node dysfunction, were common in AF patients. And they may be further exacerbated by beta-blockers.[16] Devices such as pacemaker and cardiac resynchronization therapy can prevent severe bradyarrhythmia, cardiac arrest, and sudden death in HF patients with AF,[4,10] however, 94.7% patients in our cohort had not been implanted with these devices, and the use of beta-blockers should be careful in those who had a low heart rate.

Although the use of beta-blockers at discharge was not associated with reduced risk of death in hospitalized HF patients with AF, regardless of LVEF, it did not increase the risk of clinical outcomes. Thus, our results do not contradict the guidelines recommending beta-blocker as the first-line heart rate control treatment in HFrEF/HFpEF patients with AF. Our findings should be examined

in future prospective trials.

In the present study, several limitations should be considered. First, given the nature of observational study, residual confounding may still exist, although we collected comprehensive clinical data and adjusted potential confounders. Nevertheless, our results provided the relevant evidence as there were still no randomized controlled trials focusing on investigating the survival benefits of beta-blockers in HF patients with AF. Second, the patient recruitment of this study may not include the most severe patients who were unable to sign the informed consent form within 24 h. Third, excessive heart rate control was not observed in our cohort as approximately half patients had a discharge heart rate > 75 beats/min. And information on the changes in heart rate during follow-up period were not recorded. Thus, we may be unable to investigate whether the effects of beta-blockers were influenced by excessive heart rate control, which should be further tested by future prospective trials. Fourth, information on the changes in heart rhythm or heart rhythm control treatments during follow-up period were not collected. But our sensitive analyses among those whose heart rhythm was AF at discharge, or those who had no rhythm control treatment during hospitalization or at discharge, were consistent with the primary results of the entire cohort, and thus our results are still convincing. Last, although we trained local physicians to perform echocardiography to measure LVEF according to standard operation procedure, the measurement of the LVEF posed challenges in patients with concomitant AF. Thus, our classifications of LVEF may have some overlaps, and some of HF patients with mid-range LVEF may be HFrEF patients. It may partly explain why patients with an LVEF of 40%-49% tended to receive survival benefits from use of beta-blockers at discharge, although the adjusted results suggested that the association between beta-blockers and all-cause death was not significant. Besides, there was no interaction with LVEF, suggesting the effects of beta-blockers were similar between reduced, mid-range, and preserved LVEF. And our results may be particularly reliable for HFpEF patients with AF since the results of primary analysis and sensitive analyses among these patients were stable.

In conclusion, the use of beta-blockers at discharge did not reduce the risk of clinical outcomes in hospitalized HF patients with AF, regardless of LVEF. This effect did not vary by beta-blocker dose. But future randomized controlled trials are warranted to examine the effects of beta-blockers use on the long-term outcomes of HF patients with AF.

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CONFLICT OF INTERESTS

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 assess-

ing 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.

AUTHOR CONTRIBUTIONS

Fuwei Xing: concept, design, literature search, data analysis, statistical analysis, manuscript preparation; Lihua Zhang: concept, design, manuscript preparation, manuscript editing, and manuscript review; Haibo Zhang: concept, design, manuscript preparation, manuscript editing, and manuscript review; Xueke Bai: data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review; Danli Hu: literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review; Xin Zheng: concept, design, manuscript preparation, manuscript editing, and manuscript review; Jing Li: concept, design, manuscript preparation, manuscript editing, and manuscript review.

Trial Registration Number

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