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ARTICLE

Heart rate determines the beneficial effects of beta-blockers on cardiovascular outcomes in patients with heart failure and atrial fibrillation

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Abstract

Beta-blockers are recommended as a standard therapy for patients with heart failure (HF). However, beta-blockers are reportedly less effective in HF patients with atrial fibrillation (Af) compared with those with sinus rhythm (SR). Here, we investigated whether HR at discharge determined the cardiovascular outcomes in HF patients with Af treated with beta-blockers. In this analysis, we enrolled 97 HF patients with concomitant Af. These patients were divided into 6 groups according to beta-blocker use and tertiles of discharge HR: lowest <60 beats per minute (bpm), middle 61–70 bpm and highest >71 bpm. The primary endpoint was defined as a composite of rehospitalization due to worsening of HF and all-cause mortality. During a median follow-up of 772 days after discharge, the composite cardiovascular outcome occurred in 37 (61%) and 25 (69%) patients with or without beta-blockers, respectively. In the Cox proportional hazard analysis, the lowest HR tertile in patients with beta-blockers was associated with an increased risk of the composite outcome compared with the middle and highest tertiles in both the unadjusted model (hazard ratio: 2.568, 95% confidence interval (CI): 1.089–6.057, $p = 0.031$; hazard ratio: 2.024, 95% CI: 0.921–4.447, $p = 0.079$, respectively) and the model adjusted for potential confounders (hazard ratio: 2.631, 95% CI: 1.078–6.421, $p = 0.034$; hazard ratio: 2.876, 95% CI: 1.147–7.207, $p = 0.024$, respectively). In patients with HF and Af receiving beta-blockers, low HR adversely increased the risk of cardiovascular events. This fact may blunt the beneficial effects of beta-blockers in patients with HF and Af.

Keywords heart rate · heart failure · atrial fibrillation · beta-blockers

Introduction

Atrial fibrillation (Af) is closely related to the increased risk of mortality or rehospitalization in patients with heart failure (HF) [1–3]. The severity of HF is correlated with the prevalence of Af, ranging from 4% in NYHA class I–II to 50% in NYHA class III–IV [4]. In Japan, more than one-third of hospitalized patients with HF have Af [5]. Although several studies have shown relatively lower hospital admission rates in Japanese patients with HF complicated with Af compared with Westerners [6], we need to take into account the existence of Af when we treat such patients, considering the deleterious effects of Af in HF patients [5].

On the other hand, beta-blockers are widely used as a recommended therapy for rate-control in HF patients with Af [7]. Although beta-blockers are known to be effective for HF with reduced ejection fraction (HFrEF), such beneficial effects are limited to HF patients with sinus rhythm (SR), and beta-blockers seem to be less effective in patients with coexisting Af [8]. These conflicting results led us to consider the underlying mechanisms. One likely explanation for the reduced effect of beta-blockers in HF patients with Af is the differences in the background characteristics of the study populations or the study designs [9]. Another explanation depends on the complex relationship between beta-blockers and heart rate (HR) in HF patients, particularly in

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those with Af. A study showed that beta-blockers decreased the risk of mortality regardless of HR in HFrEF patients with SR but not in those with Af [10]. Importantly, tight HR control was correlated with poor survival in patients with advanced chronic HF with Af [11], and a J-curve relationship may exist between HR and clinical outcomes in Af patients [12]. These lines of evidence support the idea that basal HR may determine whether there are beneficial effects of beta-blockers in HF patients with Af.

To test this idea, we investigated the association between HR at discharge following the occurrence of acute decompensated heart failure (ADHF) and cardiovascular outcomes in HF patients with Af treated with beta-blockers.

Methods

Study population

In total, 253 patients with ADHF were admitted to our hospital from 2005 to 2008. After excluding patients who were lost to follow up ($n = 15$) and patients with SR ($n = 141$), 97 patients with both HF and Af were eligible for analysis (Fig. 1). Af was confirmed by an expert team of cardiologists based on standard 12-lead electrocardiography performed at the time of hospital admission for ADHF. In this study, Af was defined as atrial fibrillation or atrial flutter. We retrospectively collected HR data from the medical records for the day of discharge. We then divided patients according to beta-blocker use at discharge into groups with or without beta-blockers. Furthermore, these groups were stratified based on the tertiles of discharge HR: HR ≤ 60 beats per minute (bpm), HR 61–70 bpm, and HR ≥ 71 bpm. The rationale for this categorization is as follows. Both the AFFIRM [13] and J-RHYTHM [14] studies targeted HR at rest for 60–80 bpm as the rate-control arms, so we categorized the patients with HRs less than 60 bpm as the bradycardia group. Second, the other patients were divided into two groups by the median value of 70 bpm for HR. The patients admitted to our hospital had strictly controlled, so the maximum HR at discharge was no more than 90 bpm. The estimated glomerular filtration rate (eGFR) was derived from the following equation used for the Japanese population: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ for females). Left ventricular end-diastolic volume and end-systolic volume were obtained using the Teichholz formulae.

Follow-up

The primary endpoint was defined as a composite of rehospitalization due to worsening of HF and all-cause mortality, including death from any cause or left ventricular assist device implantation, whichever occurred first. The secondary endpoint was defined as rehospitalization due to worsening of HF or all-cause mortality.

Ethics

This study was approved by the National Cerebral and Cardiovascular Center Research Ethics Committee. The committee decided that according to the Japanese Clinical Research Guidelines, the acquisition of informed consent from the chosen subjects was not required because it was a retrospective observational study. Instead, a public announcement was made in accordance with the Ethics Committee's request and Japanese Clinical Research Guidelines.

Statistical analysis

For baseline characteristics, continuous variables are expressed as medians (interquartile ranges) and categorical variables as numbers (%). The HR tertiles were compared in each of the without beta-blockers and beta-blockers groups using the chi-square test for categorical variables and analysis of variance or Kruskal–Wallis test for continuous variables, as appropriate.

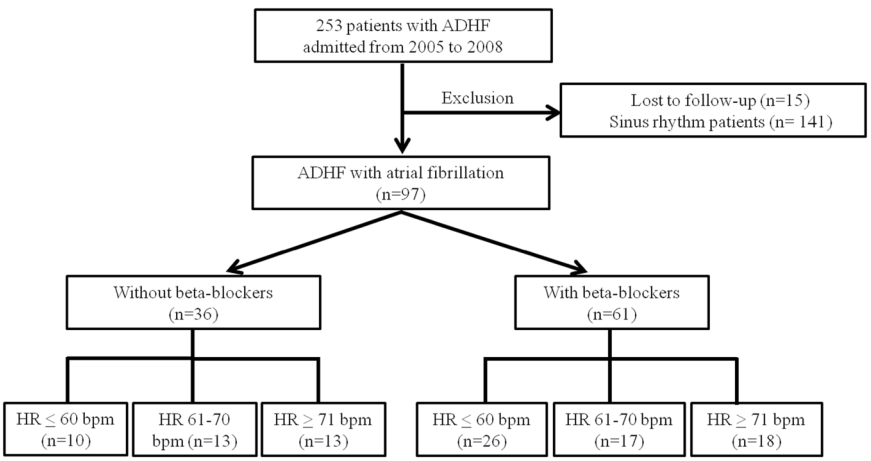

Fig. 1 Flowchart of study design. ADHF, acute decompensated heart failure, HR, heart rate, bpm, beats per minute

Table 1 Baseline characteristics of HF patients coexisting Af without beta-blockers classified into HR tertiles

	≤60 bpm ($n = 26$)	61–70 bpm ($n = 17$)	≥71 bpm ($n = 18$)	p-value
Age, years	67.5 (60–75.3)	68 (60.5–72.5)	63 (49–75.3)	0.757
Male, *n* (%)	19 (73)	7 (41)	12 (67)	0.097
NYHA lll–lV, *n* (%)	22 (85)	12 (71)	13 (72)	0.477
Medical Hitory				
DM, *n* (%)	8 (31)	2 (12)	2 (11)	0.171
Hypertension, *n* (%)	14 (54)	7 (41)	10 (56)	0.641
Hyperlipidemia, *n* (%)	6 (23)	2 (12)	4 (22)	0.626
CVD, *n* (%)	8 (31)	2 (12)	2 (11)	0.171
COPD, *n* (%)	1 (4)	0 (0)	1 (6)	0.639
Underlying heart disease				
Cardiomyopathy, *n* (%)	9 (35)	5 (29)	8 (44)	0.638
lHD, *n* (%)	4 (15)	1 (6)	1 (6)	0.455
HHD, *n* (%)	3 (12)	3 (18)	3 (17)	0.827
Valvular Disease, *n* (%)	5 (19)	5 (29)	4 (22)	0.737
Other, *n* (%)	5 (19)	3 (18)	2 (11)	0.764
Procedures				
CRT, *n* (%)	1 (4)	2 (12)	5 (28)	0.068
ICD, *n* (%)	2 (8)	3 (18)	3 (17)	0.555
Pacemaker, *n* (%)	1 (4)	1 (6)	1 (6)	0.945
CABG, *n* (%)	2 (8)	0 (0)	1 (6)	0.516
PCl, *n* (%)	4 (15)	1 (6)	0 (0)	0.173
Discharge parameter				
SBP, mmHg	109 (100–113)	110 (100–121)	110 (100–120)	0.671
DBP, mmHg	60 (58–65.3)	62 (59–66)	65 (60–70)	0.41
BMl, kg/m^2	20.7 (18.8–22.9)	20 (18.5–23.2)	21.2 (17–25.4)	0.975
Hemoglobin, g/dL	12.9 (11.8–14)	13.2 (11.4–13.9)	12.7 (11.8–14.5)	0.941
Sodium, mEq/L	138 (135.7–140)	137 (136–141.5)	137 (132.7–141.3)	0.585
Potassium,mEq/L	4.3 (3.9–4.75)	4.2 (4.1–4.5)	4.4 (4–4.7)	0.639
BNP, pg/ml	219.5 (78–383.9)	170.5 (109–248)	222.7 (132–472)	0.693
eGFR, mL/min/173 m^2	54 (32.2–78)	62 (47–70.5)	59.5 (49.5–74.7)	0.842
Discharge Treatment				
ACEI, *n* (%)	10 (39)	10 (59)	5 (28)	0.165
ARB, *n* (%)	10 (39)	3 (18)	7 (39)	0.293
Diuretics, *n* (%)	25 (96)	0 (0)	17 (94)	0.639
MRA, *n* (%)	14 (54)	8 (47)	11 (61)	0.706
Amiodarone, *n* (%)	6 (23)	1 (6)	5 (28)	0.225
Warfarin, *n* (%)	25 (96)	15 (88)	0 (0)	0.259
Statin, *n* (%)	6 (23)	1 (6)	3 (17)	0.33
Digoxin, *n* (%)	10 (39)	9 (53)	10 (56)	0.467
Echocardiographic data				
LVDd, mm	57.5 (50–67.3)	58 (50–63.5)	56 (46.5–67.3)	0.836
LVDs, mm	45.5 (34.8–56)	46 (35–55)	43 (35–55.7)	0.976
FS, %	20 (16.4–28)	19 (14–30.9)	18.1 (12.7–33.3)	0.813
LVEDV, ml	163.3 (119.6–229.4)	173.3 (125.3–203.0)	153.9 (103.7–212.3)	0.606
LVESV, ml	94.9 (51.8–149.1)	99.8 (64.0–141.5)	83.1 (54.4–147.4)	0.891
SV, ml	64.1 (49.0–96.1)	65.6 (49.9–77.9)	67.2 (49.9–72.6)	0.192

Table 1 (continued)

	≤60 bpm ($n = 26$)	61–70 bpm ($n = 17$)	≥71 bpm ($n = 18$)	p-value
lVS, mm	10 (8–12)	10 (8.5–11)	9.5 (8–10.25)	0.737
PW, mm	10 (8–11)	9 (8–11)	9.5 (8–11)	0.601
LAD, mm	50.5 (42–58)	55 (45.5–60)	47 (42.7–57.5)	0.475
MR grade	1 (1.0–2.0)	1 (0.0–1.5)	2 (1.0–3.0)	0.157

Data given as median (interquartile range) and number (%)

HR heart rate, *HF* heart failure, *Af* atrial fibrillation, *bpm* beats per minute, *NYHA* new york heart association functional class, *DM* diabetes mellitus, *CVD* cerebrovascular disease, *COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *HHD* hypertensive heart disease, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter defibrillator, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *BNP* brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotension II receptor blocker, *MRA* mineralocorticoid receptor antagonist, *LVDd* left ventricular end-diastolic diameter, *LVDs* left ventricular end-systolic diameter, *FS* fractional shortening, *LVEDV* left ventricular end-diastolic volume, *LVESV* end-systolic volume, *SV* stroke volume, *IVS* interventricular septum, *PW* posterior wall, *LAD* left atrial diameter, *MR grade* mitral regurgitation grade

We selected potential confounders for inclusion in the multivariate analysis based on clinical judgment and a review of the relevant literature. Six covariates, namely, age, sex, brain natriuretic peptide (BNP) level at discharge, left atrial diameter (LAD), systolic blood pressure at discharge, and the use of cardiac resynchronization therapy, were included in the model. Missing data among baseline covariates were found for potassium level ($n = 1$), BNP level at discharge ($n = 1$) and LAD ($n = 1$).

We performed Kaplan–Meier survival curve analysis and the log-rank test to calculate the estimated event-free rates and to compare event rates between the HR tertiles. The hazard ratios for the primary and secondary endpoints were analyzed using Cox proportional hazard analysis. All of the tests were two-tailed, and $p < 0.05$ was considered statistically significant. We performed the statistical analysis using SPSS version 24.0 (SPSS, Chicago, IL, USA).

Results

The patient characteristics are presented in Tables 1 and 2. The baseline characteristics of the patients in the different HR tertiles at discharge, with or without beta-blockers, were compared. In patients without beta-blockers at discharge, there were significant differences among the tertiles with regard to angiotensin-converting enzyme inhibitor usage, interventricular septum thickness, posterior wall thickness and hemoglobin level. The stroke volume (SV) was significantly higher in the HR < 60 bpm group compared with the other groups (Table 1). Conversely, in patients with beta-blockers at discharge, there were no differences in baseline characteristics among the HR strata (Table 2). Furthermore, there were no differences among the tertiles in terms of the BNP level, left ventricular (LV) end-diastolic diameter, LV end-systolic diameter and fractional shortening in the groups with beta-blockers or without beta-blockers.

During a median follow-up of 772 days (197–2062 days) after hospital discharge, the composite outcome occurred in 37 (61%) patients with beta-blockers and 25 (69%) patients without beta-blockers. In the Kaplan–Meier analysis, there were no differences in the event-free rates among the tertiles of HR in patients without beta-blockers (Fig. 2a). In contrast, there were significant differences among the tertiles of HR with beta-blockers (log-rank test: $p = 0.040$) (Fig. 2b). In the secondary endpoint analysis, the event-free rates of rehospitalization due to worsening of HF (Fig. 3a, b) and all-cause mortality (Fig. 3c, d) were not significantly different among the tertiles of HR in HF patients with Af.

In the Cox proportional hazard analysis, there were no differences between the lowest and middle or highest HR tertiles for the composite outcome and secondary endpoints in HF and Af patients without beta-blockers (Table 3). In contrast, the unadjusted model showed that the lowest HR tertile in patients with beta-blockers was associated with an increased risk of the composite outcome compared with the middle and highest tertiles (hazard ratio: 2.568, 95% confidence interval (CI): 1.089–6.057, p = 0.031; hazard ratio: 2.024, 95% CI: 0.921–4.447, $p = 0.079$, respectively). Furthermore, in the adjusted analysis, the lowest HR tertile in patients with beta-blockers remained significantly associated with a higher risk of the composite outcome compared with the middle and highest HR tertiles (hazard ratio: 2.631, 95% CI: 1.078–6.421, $p = 0.034$; hazard ratio: 2.876, 95% CI: 1.147–7.207, $p = 0.024$, respectively).

In addition, in the multivariate analysis of secondary endpoints, the lowest HR tertile in patients with beta-blockers was also associated with an increased risk of rehospitalization due to the worsening of HF compared with the middle and highest tertiles (hazard ratio: 2.322, 95% CI:

Table 2 Baseline characteristics of HF patients coexisting Af with beta-blockers classified into HR tertiles

	≤60 bpm ($n = 10$)	61–70 bpm ($n = 13$)	≥71 bpm ($n = 13$)	*p*-value
Age, years	72.5 (60.7–77.5)	77 (63.5–86.5)	72 (60–80)	0.404
Male, *n* (%)	6 (60)	7 (54)	5 (39)	0.557
NYHA lll–lV, *n* (%)	6 (60)	4 (31)	8 (62)	0.221
Medical hitory				
DM, *n* (%)	3 (30)	1 (8)	2 (15)	0.359
Hypertension, *n* (%)	6 (60)	4 (31)	3 (23)	0.166
Hyperlipidemia, *n* (%)	1 (10)	1 (8)	0 (0)	0.534
CVD, *n* (%)	1 (10)	2 (15)	3 (23)	0.698
COPD, *n* (%)	0 (0)	1 (8)	2 (15)	0.414
Underlying heart disease				
Cardiomyopathy, *n* (%)	2 (20)	1 (8)	0 (0)	0.226
lHD, *n* (%)	0 (0)	0 (0)	0 (0)	—
HHD, *n* (%)	1 (10)	0 (0)	0 (0)	0.263
Valvular Disease, *n* (%)	7 (70)	8 (61)	9 (69)	0.886
Other, *n* (%)	0 (0)	4 (31)	4 (31)	0.138
Procedures				
CRT, *n* (%)	0 (0)	0 (0)	0 (0)	—
ICD, *n* (%)	0 (0)	0 (0)	0 (0)	—
Pacemaker, *n* (%)	0 (0)	1 (8)	3 (23)	0.193
CABG, *n* (%)	0 (0)	0 (0)	0 (0)	—
PCl, *n* (%)	0 (0)	0 (0)	0 (0)	—
Discharge parameter				
SBP, mmHg	121 (102.5–128.5)	114 (109–143)	112 (102–130)	0.652
DBP, mmHg	60 (50–68.5)	60 (57.5–70)	60 (57–67)	0.683
BMl, kg/m^2	19.9 (16.9–20.7)	18.9 (17.5–22.8)	18.6 (15.5–20.5)	0.271
Hemoglobin, g/dL	11.7 (10.1–13.6)	12.6 (11.2–13.4)	11.1 (9.75–11.9)	0.033*
Sodium, mEq/L	138 (136.3–140)	139 (136–140)	136 (133–139)	0.56
Potassium,mEq/L	4.4 (3.7–5)	4.2 (3.8–4.5)	4.2 (4–4.4)	0.848
BNP, pg/ml	171.5 (58.3–259.8)	145.6 (85.2–206.9)	104 (22.8–445.7)	0.797
eGFR, mL/min/173 m^2	51 (41–69.3)	57 (48.5–74)	56 (40.5–62.5)	0.433
Discharge treatment				
ACEI, *n* (%)	7 (70)	6 (46)	2 (15)	0.029*
ARB, *n* (%)	2 (20)	3 (23)	4 (31)	0.823
Diuretics, *n* (%)	0 (0)	11 (85)	12 (92)	0.414
MRA, *n* (%)	5 (50)	8 (62)	10 (77)	0.402
Amiodarone, *n* (%)	0 (0)	0 (0)	0 (0)	—
Warfarin, *n* (%)	0 (0)	11 (85)	11 (85)	0.421
Statin, *n* (%)	0 (0)	1 (8)	0 (0)	0.403
Digoxin, *n* (%)	4 (40)	7 (54)	5 (39)	0.693
Echocardiographic data				
LVDd, mm	58.5 (48–64.7)	48 (41–55.5)	47 (43–52.5)	0.051
LVDs, mm	37 (26.7–53)	33 (25–38)	28 (25.5–37.5)	0.366
FS, %	35.8 (22.8–41.6)	32 (28.7–40.2)	36.8 (23.7–42.6)	0.892
LVEDV, ml	170.3 (118.4–208.5)	104.9 (74.2–147.4)	102.4 (87.7–129.5)	0.051
LVESV, ml	58.2 (32.1–122.3)	42.5 (22.3–62.0)	29.6 (24.6–54.4)	0.311
SV, ml	86.9 (69.2–134.7)	62.7 (51.5–64.4)	67.8 (56.3–77.8)	0.015*

Table 2 (continued)

	≤60 bpm ($n = 10$)	61–70 bpm ($n = 13$)	≥71 bpm ($n = 13$)	p-value
lVS, mm	11.5 (9.7–12.2)	10 (9–11.5)	8 (8–10)	0.004*
PW, mm	10.5 (10–12)	10 (9–10.5)	9 (8–10)	0.027*
LAD, mm	61 (48.7–63)	58 (42–67.7)	58 (47.3–60)	0.639
MR grade	1 (1.0–2.0)	1 (0.0–1.5)	2 (1.0–3.0)	0.106

Data given as median (interquartile range) and number (%)

HR heart rate, *HF* heart failure, *Af* atrial fibrillation, *bpm* beats per minute, *NYHA* new york heart association functional class, *DM* diabetes mellitus, *CVD* cerebrovascular disease, *COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *HHD* hypertensive heart disease, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter defibrillator, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *BNP* brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotension II receptor blocker, *MRA* mineralocorticoid receptor antagonist, *LVDd* left ventricular end-diastolic diameter, *LVDs* left ventricular end-systolic diameter, *FS* fractional shortening, *LVEDV* left ventricular end-diastolic volume, *LVESV* end-systolic volume, *SV* stroke volume, *IVS* interventricular septum, *PW* posterior wall, *LAD* left atrial diameter, *MR grade* mitral regurgitation grade

*p-value < 0.05

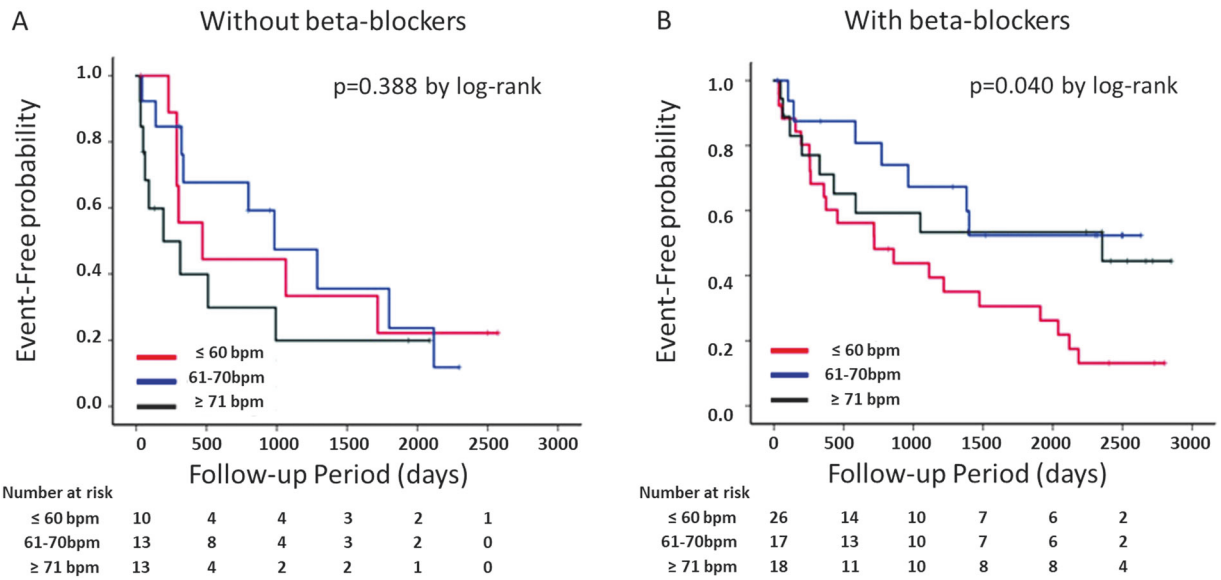

Fig. 2 Kaplan–Meier curves for composite outcome (rehospitalization due to worsening of heart failure (HF) or all-cause mortality) in HF and atrial fibrillation patients without beta-blockers (**a**) or with beta-blockers (**b**). bpm, beats per minute

0.866–6.229, $p = 0.094$; hazard ratio: 2.894, 95% CI: 1.011–8.286, $p = 0.048$, respectively). A similar association between the tertiles of HR and all-cause mortality was also observed (hazard ratio: 2.48, 95% CI: 0.786–7.823, $p = 0.121$; hazard ratio: 3.571, 95% CI: 1.110–11.495, $p = 0.033$, respectively) (Table 4).

Discussion

In this study, our investigation revealed that a low HR at discharge was associated with an increased risk of the composite outcome compared with the middle and highest HR tertiles in HF patients with Af who received beta-blockers. In contrast, this association was not observed for those without beta-blockers at discharge. The baseline HR contributes to the beneficial effects of beta-blockers in HF patients with Af.

Beta-blocker therapy in patients with concomitant HR and Af has been extensively investigated, but conclusive evidence is still lacking. A study showed that a reduction in mortality and HF hospitalization could not be achieved by beta-blocker therapy in HFrEF patients with Af [15]. This finding was re-emphasized in the study by Kotecha *et al.*,

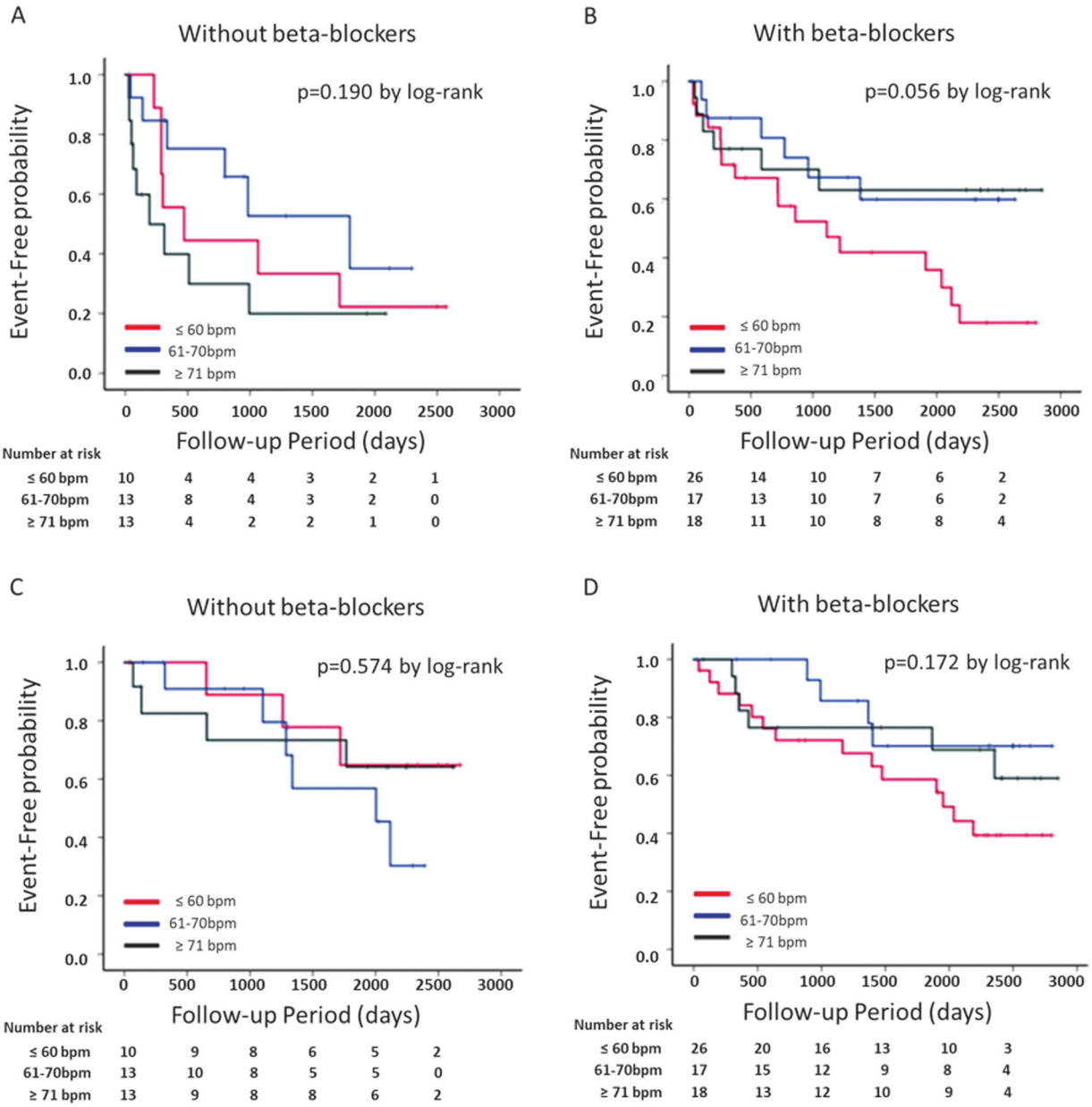

Fig. 3 Kaplan–Meier curves for rehospitalization due to worsening of heart failure (HF) (**a**, **b**) and all-cause mortality (**c**, **d**) in HF and atrial fibrillation patients without or with beta-blockers. bpm, beats per minute

which showed a neutral impact of beta-blockers on HFrEF patients with Af, in contrast to their SR counterparts [8]. However, another study reported that beta-blockers were associated with reduced mortality risk but not hospitalizations in patients with HFrEF and coexisting Af [16]. Similarly, a large nationwide cohort study revealed that the use of beta-blockers were associated with an approximately 25% risk reduction in all-cause mortality compared to the lack of the use of beta-blockers in HF patients with Af [17]. Furthermore, the Swedish Heart Failure Registry study also found that beta-blockers were still able to potently diminish the risk of mortality in patients with HFrEF with concomitant Af compared with those who did not receive beta-blockers [18]. Although the effect of beta-blockers on mortality is still incompletely understood in patients with HFrEF and Af, beta-blockers have been widely used to reduce HR [19].

The current study showed that low HR was associated with a worse prognosis in HF patients with Af receiving beta-blockers at discharge. The effect of beta-blockers in HF patients with a lower HR has rarely been evaluated because baseline HR < 60–68 bpm was used as an exclusion criterion in most randomized control trials [20–24] A meta-analysis of beta-blocker trials showed that the median HR at

Table 3 Cox regression analysis for HR discharge in HF and Af patients without beta-blockers

	Unadjusted Hazar ratio (95% CI)	*p*-value	Adjusted Hazar ratio (95% CI)	*p*-value
Composite outcome				
HR ≤ 60/61–70 bpm	1.081 (0.401–2.915)	0.878	0.796 (0.208–3.040)	0.738
HR ≤ 60/ ≥ 71 bpm	0.590 (0.216–1.610)	0.303	0.377 (0.114–1.250)	0.111
Rehospitalization due to Worsening of HF				
HR ≤ 60/61–70 bpm	1.641 (0.549–4.901)	0.375	1.158 (0.284–4.722)	0.838
HR ≤ 60/ ≥ 71 bpm	0.643 (0.238–1.738)	0.384	0.414 (0.127–1.347)	0.143
All-cause mortality				
HR ≤ 60/61–70 bpm	0.516 (0.128–2.075)	0.351	0.490 (0.081–2.961)	0.437
HR ≤ 60/ ≥ 71 bpm	0.851 (0.190–3.815)	0.838	0.664 (0.131–3.376)	0.622

Hazard ratio for composite outcome (rehospitalization due to worsening of HF or all-cause mortality) in HF and Af patients without beta-blockers. Hazard ratio was calculated using Cox proportional hazard analysis and adjusted with age, sex, brain natriuretic peptide at discharge, systolic blood pressure at discharge, cardiac resynchronization therapy, and left atrial diameter

HF heart failure, *Af* atrial fibrillation, *HR* heart rate, *bpm* beats per minute, *CI* confidence interval

Table 4 Cox regression analysis for HR discharge in HF and Af patients with beta-blockers

	Unadjusted Hazar ratio (95% CI)	*p*-value	Adjusted Hazar ratio (95% CI)	*p*-value
Composite outcome				
HR ≤ 60/61–70 bpm	2.568 (1.089–6.057)	0.031*	2.631 (1.078–6.421)	0.034*
HR ≤ 60/ ≥ 71 bpm	2.024 (0.921–4.447)	0.079	2.876 (1.147–7.207)	0.024*
Rehospitalization due to Worsening of HF				
HR ≤ 60/61–70 bpm	2.411 (0.948–6.137)	0.065	2.322 (0.866–6.229)	0.094
HR ≤ 60/ ≥ 71 bpm	2.430 (0.952–6.201)	0.063	2.894 (1.011–8.286)	0.048*
All-cause mortality				
HR ≤ 60/61–70 bpm	2.565 (0.843–7.803)	0.097	2.480 (0.786–7.823)	0.121
HR ≤ 60/ ≥ 71 bpm	1.771 (0.679–4.619)	0.243	3.571 (1.110–11.495)	0.033*

Hazard ratio for composite outcome (rehospitalization due to worsening of HF or all-cause mortality) in HF and Af patients with beta-blockers. Hazard ratio was calculated using Cox proportional hazard analysis and adjusted with age, sex, brain natriuretic peptide at discharge, systolic blood pressure at discharge, cardiac resynchronization therapy, and left atrial diameter

HF heart failure, *Af* atrial fibrillation, *HR* heart rate, *bpm* beats per minute, *CI* confidence interval

*p-value < 0.05

baseline in the Af group was 81 bpm, and HR reduction during follow-up was 12 bpm. They showed that HR was not correlated with all-cause mortality in HFrEF patients with Af, regardless of beta-blocker use. However, a careful review of the Kaplan–Meier curve showed that patients with HR ≤ 60 bpm in the beta-blockers group tended to have an increased risk of all-cause mortality compared with those with higher HRs at the interim visit [10]. In this study, the HR ≤ 60 bpm group without beta-blockers showed a significant increase in the SV and a similar incidence of cardiac events. In contrast, the HR ≤ 60 bpm group with beta-blockers showed similar SV and relatively poor prognosis. Cardiac output is determined by SV × HR, which means that the increased SV may compensate for bradycardia in patients with Af. Therefore, the excessive suppression of HR using beta-blockers may lead to the reduction of cardiac output, resulting in an increase in cardiac events. The deleterious effect of low HR in patients with HF with coexisting Af could also be explained through a physiological perspective. The loss of atrial systole in Af impairs LV filling and subsequently decreases cardiac output. Atrial systole can contribute up to 25% of cardiac output and up to 50% in patients with ventricular dysfunction [25]. Therefore, a higher ventricular rate is necessary as a response to the hemodynamic changes to maintain an equivalent cardiac output [4, 26].

Bradycardia is a common side effect during beta-blocker administration [27]. A study showed that the risk of symptomatic bradyarrhythmias in patients taking beta-blockers was associated with age [28]. Moreover, bradycardia is the most common cause of unplanned hospitalization related to the use of beta-blockers and digoxin in elderly patients [29]. Previous studies in the Japanese population have shown that beta-blockers effectively suppress HR in a dose-dependent manner without provoking excessive bradycardia in chronic Af patients [30, 31]. However, patients with chronic HF have sinus node remodeling, characterized by prolonged sinus node recovery and sinoatrial conduction [32], which may increase the likelihood of extreme bradycardia with beta-blocker therapy [27].

In addition to the effect of beta-blockers being partly modulated by HR reduction, beta-blockers also possess an HR-independent mechanism to improve prognosis in patients with HF through the attenuation of sympathetic overactivity, reduction of LV wall stress, exertion of antiarrhythmic effects, facilitation of the recovering of physical capacity and protection against cardiac sudden death [33]. These properties might provide potential benefits if beta-blocker therapy is continued in patients with asymptomatic bradycardia [34]. However, the administration of beta-blockers in Af patients with bradycardia often results in the development of symptomatic bradycardia, requiring pacemaker implantation. A study showed that among patients with Af, a history of HF and permanent Af were associated with threefold increased odds of worsening bradycardia, requiring a permanent pacemaker [35] In addition, a study enrolled in the rate-control arms of AFFIRM and RACE reported that the strict rate-control in Af patients resulted in increased incidences of pacemaker implantations [36]. Thus, clinicians should make individualized decisions concerning beta-blocker usage, considering the risks and benefits, especially in HF patients with low HR.

In the present study, several limitations should be considered. First, this study was a single-center, observational study, which only included a small number of patients, causing low statistical power. Second, information about beta-blocker use was only provided in the discharge period; therefore, this study was conducted under the assumption of full adherence to outpatient beta-blocker therapy or non-modified treatment in the group without beta-blockers at the time of discharge. Third, we did not collect information about the doses of beta-blockers at discharge or during follow-up. Fourth, we did not collect information about changes in HR during the follow-up period. Fifth, despite covariate adjustment, we could not completely exclude measured or unmeasured confounding factors. Sixth, we did not classify the types and duration of Af or stratify HF patients based on the ejection fraction. Despite these limitations, the present study provided clinically insightful results regarding the impact of HR at discharge on cardiovascular outcomes in patients with HF and Af treated with beta-blockers.

In conclusion, in patients with HF and Af receiving beta-blockers, low HR adversely increases the risk of cardiovascular events. Low HR may cause bradycardia that may worsen the severity of HF; therefore, we need to pay attention to HR during the administration of beta-blockers in patients with HF and Af.

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Compliance with ethical standards

Conflict of interest All co-authors of this manuscript have read and approved the submission of the manuscript. All of the authors have made important contributions to the study and are thoroughly familiar with the original data. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest: Dr. Kitakaze reports grants and personal fees from Takeda during the study, grants from the Japanese government, grants from the Japan Heart Foundation, grants from the Japan Cardiovascular Research Foundation, grants and personal fees from Asteras, grants and personal fees from Sanofi, personal fees from Daiichi-sankyo, grants and personal fees from Pfizer, grants and personal fees from Ono, personal fees from Bayer, grants and personal fees from Novartis, personal fees from Bheringer, grants and personal fees from Tanabe-mitubishi, personal fees from Kowa, grants and personal fees from Kyowa-hakko-kirin, personal fees from Dainihon-sumitomo, personal fees from Sawai, personal fees from MSD, grants and personal fees from Abott, grants and personal fees from Otsuka, grants from Calpis, grants from Nihon Kohden, personal fees from Shionogi, personal fees from Astrazeneca, personal fees from Asahikasei Med., personal fees from Novo Nordisk, personal fees from Fuji-film RI, and personal fees from Japan Medical Data, none of which pertained to the submitted work.

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