ORIGINAL ARTICLE

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The effect of beta-blockers in acute heart failure according to heart rate

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Background/Aims: Beta-blockers (BBs) have been shown to improve clinical outcomes in heart failure (HF) patients. We evaluated the prescribing status of BBs in patients with HF with reduced ejection fraction (HFrEF) at discharge according to the presence or not of bradycardia, and its effect on prognosis.

Methods: Study data were obtained from a multicenter cohort of 3,200 patients hospitalized for HF. Patients were classified into four groups according to the presence of bradycardia and use of BBs at discharge. The primary outcome was the incidence of all-cause death during follow-up.

Results: Of 1,584 patients with HFrEF, 281 patients died during follow-up (median 523 days, mean 578.5 ± 429.7 days). In patients with bradycardia, the all-cause death rate did not significantly differ according to the use of BBs, but in those patients without bradycardia, the incidence of all-cause death was significantly lower in the BBs group than the no BBs group. Among these four groups, patients with heart rate (HR) ≥ 60 beats/min with no BBs group had the lowest cumulative death-free survival rate. In addition, HR ≥ 60 beats/min with BBs use was independently associated with a 31% reduced risk of all-cause death in patients with HFrEF.

Conclusions: BBs had a beneficial effect on clinical prognosis only in those HFrEF patients without bradycardia. Therefore, BBs should be given by clinicians to HF patients without bradycardia to improve their clinical outcomes.

Keywords: Beta-blocker; Heart failure; Ejection fraction, ventricular; Bradycardia

INTRODUCTION

A consistently elevated heart rate (HR) is a strong predictor of cardiovascular mortality and morbidity, especially in patients with heart failure (HF) [1-3]. Beta-blockers (BBs) whose effects include reduction of HR have been shown to improve clinical outcomes in patients with HF with a reduced ejection fraction (HFrEF) and

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in current guidelines are recommended for the treatment of these patients [4,5]. The degree of HR reduction is statistically significantly associated with the survival benefit of the use of BBs in HF [6], so the concept of targeting HR reduction in HFrEF treatment has become important. However, in actual clinical practice, patients with HFrEF tend not to receive appropriate BBs as part of guideline-directed medical therapy (GDMT), mainly due to their low blood pressure or low HR [7,8]. Therefore, the rate of BBs use in GDMT remains uncertain in actual practice. In addition, there is controversy over whether the BBs clinically benefit HFrEF patients who already have bradycardia.

To our knowledge, the effect of BBs on long-term clinical outcomes in HFrEF patients either with or without bradycardia has rarely been the subject of study. In this study, we evaluated the status of BBs in patients with HF at hospital discharge according to the presence of bradycardia, and its effect on long-term prognosis in patients with HFrEF.

METHODS

Study design and setting

We obtained our study data from a national Korean Heart Failure (KorHF) registry, which is a prospective multicenter cohort that includes patients admitted to hospital with acute HF. From June 2004 to April 2009, 3200 patients from 24 hospitals in Korea diagnosed with acute HF according to the Framingham criteria at the time of admission were included [9,10]. The diagnosis of HF was confirmed at the time of discharge. At least 1 year of follow-up was strongly recommended to all the patients, and the outcome data, including death and re-hospitalization due to HF, were obtained from medical records and telephone interviews and prospectively recorded. Of the 3,200 HF patients initially enrolled, there was available data on left ventricular ejection fraction (LVEF) from echocardiography on 2,841 patients. Among the patients with LVEF confirmed, it was possible to determine in 2,831 patients whether or not they received BBs at discharge. Of these 2,831 patients, there were 2,770 patients for whom there was also information about their initial HR at hospitalization, and they were finally included in the study. Of these, there were 1,584 patients with HFrEF whose LVEF was < 40% and 1,176 patients with HF mid-range ejection fraction or HF preserved ejection fraction whose LVEF was ≥ 40% according to HF classification [4]. We defined bradycardia as a HR < 60 beats/min according to 2018 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guideline [11]. The patients were then classified according to presence or not of bradycardia at the time of admission, so that finally there were four groups as follows: 'HR < 60 beats/min with BBs group,' 'HR ≥ 60 beats/min with BBs group,' 'HR < 60 beats/min with no BBs group,' and 'HR ≥ 60/ beats min with no BBs group.'

The study protocol complied with the Declaration of Helsinki and was reviewed and approved by the Institutional Review Board of Hallym University Sacred Heart Hospital and each participating hospital (Hallym University Sacred Heart Hospital IRB no.2002-S2005). All patients provided written informed consent prior to participation in the study.

Data collection

Patients' demographic and clinical characteristics were collected via a web-based electronic data capture system that included electronic case report forms from the KorHF registry database. Baseline characteristics and traditional cardiovascular risk factors were extracted from data. Key laboratory findings relating to HF prognostic factors were also obtained. LVEF was calculated to evaluate left ventricular (LV) systolic function, and LVEF was measured using a modified Simpson's biplane method in apical-four and apical-two chamber views. Where this method was not applicable, the M-mode was used to measure LVEF. LV end-diastolic and end-systolic dimensions were also obtained from echocardiographic parameters. In addition, the discharge medications were identified, and information about the types of BBs taken was also obtained.

Study outcomes

The primary outcome was the incidence of all-cause death identified through a review of the medical records or telephone interview with family during follow-up (median 523 days, mean 578.5 ± 429.7 days). Incidences of composite events including all-cause death or HF readmission during follow-up were also obtained. The

HF readmission was defined as rehospitalization due to worsening of HF.

Statistical analyses

All categorical data are presented as frequencies and percentages, and statistics for continuous variables are displayed as means and standard deviations. Student's *t* test was used to compare consecutive variables of normal distribution, and the Mann-Whitney *U* test was used for consecutive variables of non-normal distribution. Pearson's chi-square test was used to compare categorical variables. Kaplan-Meier survival analyses and log-rank tests were used to compare the death-free survival rate according to use of BBs and depending on the presence of bradycardia in patients with HFrEF. In addition, univariate followed by multivariate Cox proportional hazards regression analyses were performed to evaluate the predictors for all-cause death in the HFrEF group after adjusting for individual risk factors. Variables that were identified as carrying predictive significance ($p < 0.05$) in the univariate analysis were included in the regression model. A $p < 0.05$ was considered significant. All analyses were performed with SPSS version 21.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

Among 2,760 patients suffering from acute HF for whom there was information available about their initial HR at the time of hospitalization, 1,584 patients had HFrEF and were analyzed in our study. Of these, 674 patients were prescribed BBs at discharge and 910 were not prescribed BBs. Of the patients who used BBs, 17 (2.5%) patients had bradycardia (HR < 60 beats/min) initially at hospitalization and 657 (97.5%) patients did not have bradycardia (HR ≥ 60 beats/min). Of those patients who didn't use BBs, 40 (4.4%) patients had bradycardia and 870 (95.6%) patients had no bradycardia at the time of admission. The patients' baseline characteristics according to their use (or not) of BBs at discharge and types of BBs are outlined in Table 1.

Clinical outcomes according to beta-blocker use

A total of 281 patients (17.7%) died during follow-up (mean 578.5 ± 429.7 days) in patients with HFrEF (n = 1,584). Among them, 83 patients (12.3%) died in the BBs group (n = 674) and 198 patients (21.8%) died in the no BBs group (n = 910). The two groups had significantly different probabilities of all-cause death in HFrEF patients according to the prescribing pattern of BBs at discharge, with patients in the BBs group having a significantly higher cumulative death-free survival rate than those in the no BBs group (long-rank test p for trend < 0.001) (Supplementary Fig. 1).

In addition to the comparison of the BBs and no BBs groups, a further investigation of the clinical outcomes according to the presence (or not) of bradycardia is shown in Table 2. In patients with HR below 60 beats/min, the all-cause death rate did not significantly differ according to the use of BBs or not, and the composite events rate of HF readmission or all-cause death also showed no significant difference. However, in patients with HR above 60 beats/min, the incidence of all-cause death was significantly lower in the BBs group compared with the no BBs group (12.3% vs. 22.1%, $p < 0.001$). Moreover, the incidence of composite events was significantly lower in the BBs group (32.9% vs. 42.6%, $p < 0.001$). Among these four groups, HFrEF patients with HR ≥ 60 beats/min with no BBs group had (significantly) the lowest cumulative death-free survival rate (log-rank test p for trend < 0.001) (Fig. 1).

Moreover, Supplementary Table 1 showed the comparison of clinical outcomes according to the presence (or not) of bradycardia and BBs use in HFrEF patients caused by ischemic heart disease and valvular heart disease. Only BBs group of HFrEF patients caused by ischemic heart disease with HR above 60 beats/min had significantly lower incidences of all-cause death, and composite events compared with the no BBs group.

Subgroup analysis according to heart rhythm

Of those patients with HFrEF, 1,051 had sinus rhythm and 284 patients had atrial fibrillation at the time of hospital admission. In the BBs group, compared to the no BBs group, there was a significantly lower incidence of all-cause death in patients with sinus rhythm (10.9% vs. 23.4%, $p < 0.001$) and also in patients with atrial fibrillation (10.9% vs. 20.8%, $p = 0.026$) (Supplementary Table 2). Moreover, in patients with HR ≥ 60 beats/min, there was a significantly lower incidence of all-cause death in the

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Table 1. Baseline characteristics

Characteristic	All (n = 1,584)	BBs group (n = 674)	No BBs group (n = 910)	*p* value
Age, yr	65.8 ± 14.9	64.5 ± 14.6	66.7 ± 15.0	0.005
Male sex	896 (56.6)	389 (57.7)	507 (55.7)	0.427
BMI (> 23 kg/m^2)	687 (48.2)	304 (49.7)	383 (47.1)	0.327
SBP, mmHg	128.6 ± 28.5	131.5 ± 29.8	126.5 ± 27.3	0.001
DBP, mmHg	78.3 ± 18.1	80.1 ± 19.3	77.0 ± 17.0	0.001
Heart rate, beats/min	93.5 ± 23.6	92.5 ± 22.	94.2 ± 24.4	0.148
Previous medical history				
Heart failure	431 (30.4)	139 (24.5)	292 (34.4)	< 0.001
Hypertension	670 (42.3)	298 (44.2)	372 (40.9)	0.190
Diabetes	486 (30.7)	201 (29.8)	285 (31.4)	0.514
Chronic kidney disease	139 (8.8)	62 (9.2)	77 (8.5)	0.613
Myocardial infarction	251 (15.9)	105 (15.6)	146 (16.1)	0.795
Cause of heart failure				
Ischemic heart disease	609 (39.4)	293 (43.7)	316 (36.2)	0.003
Valvular heart disease	147 (9.5)	53 (7.9)	94 (10.8)	0.057
Laboratory findings				
Hemoglobin, g/dL	12.8 ± 2.3	12.9 ± 2.3	12.7 ± 2.3	0.033
Creatinine, mg/dL	1.5 ± 1.2	1.5 ± 1.3	1.5 ± 1.1	0.919
MDRD GFR, mL/min/1.73 m^2	61.8 ± 38.9	64.2 ± 50.8	60.1 ± 27.0	0.042
Serum sodium, mEq/L	138.1 ± 5.2	138.7 ± 5.1	137.8 ± 5.2	0.002
CRP, mg/dL	2.6 ± 4.7	1.9 ± 3.9	3.1 ± 5.1	< 0.001
NT-proBNP, pg/mL	9,334.0 ± 9,897.1	8,992.4 ± 9,418.9	9,600.0 ± 10,254.2	0.325
Echocardiographic findings				
LVEDD, mm	61.1 ± 9.6	60.2 ± 9.6	61.7 ± 9.6	0.003
LVESD, mm	51.5 ± 10.2	50.8 ± 10.3	52.0 ± 10.0	0.022
LVEF, %	27.2 ± 7.2	27.7 ± 7.3	26.8 ± 7.1	0.020
Medication at discharge				
ACEi or ARB	1,095 (69.1)	575 (85.3)	520 (57.1)	< 0.001
Type of BB				-
Carvedilol	438 (27.7)	438 (27.7)	-	
Bisoprolol	38 (2.4)	38 (2.4)	-	
Metoprolol	6 (0.4)	6 (0.4)	-	
Propranolol	1 (0.1)	1 (0.1)	-	
Atenolol	17 (1.1)	17 (1.1)	-	
Unknown	174 (11.0)	174 (11.0)	-	
Aldosterone antagonist	668 (42.2)	351 (52.1)	317 (34.8)	< 0.001

Values are presented as mean ± SD or number (%).
BB, beta-blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDRD GFR, modification of diet in renal disease glomerular filtration rate; CRP, C-reactive protein; NT-proBNP, NT-pro-brain-type natriuretic peptide; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2. Study outcomes

Variable	HR < 60 beats/min				HR ≥ 60 beats/min			
	All (n = 57)	BBs (n = 17)	No BBs (n = 40)	*p* value	All (n= 1,527)	BBs (n = 657)	No BBs (n = 870)	*p* value
All-cause death	8 (14.0)	2 (11.8)	6 (15.0)	1.00	273 (17.9)	81 (12.3)	192 (22.1)	< 0.001
Composite events of HF readmission or all-cause death	22 (38.6)	5 (29.4)	17 (42.5)	0.391	586 (38.4)	216 (32.9)	370 (42.6)	< 0.001

Values are presented as number (%).
HR, heart rate; BB, beta-blocker; HF, heart failure.

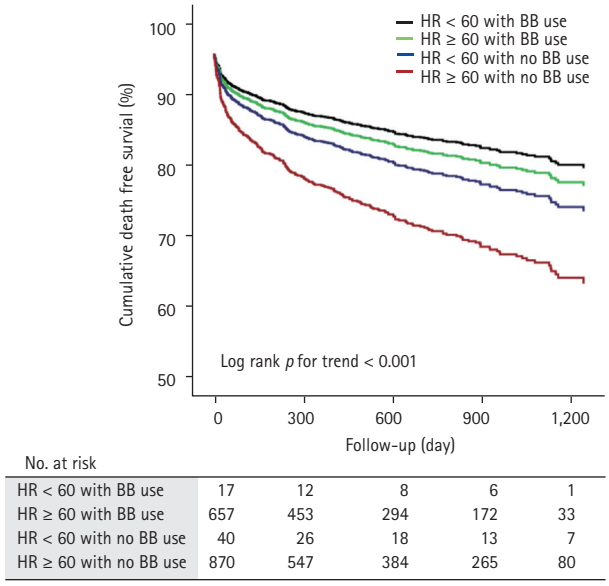

Figure 1. Cumulative death-free survival rate according to bradycardia and beta-blocker (BB) use. Heart rate (HR) ≥ 60 beats/min with no BB group was significantly lowest death-free survival rates in heart failure with reduced ejection fraction patients.

BBs group compared with the no BBs group in both patients with sinus rhythm (10.9% vs. 23.2%, $p < 0.001$) and those with atrial fibrillation (11.5% vs. 21.7%, $p = 0.030$). However, in patients with HR < 60 beats/min, there was no significant difference of incidence of all-cause death between the BBs group and the no BBs group in patients with sinus rhythm and with atrial fibrillation, and also there was no difference in the incidence of composite events of HF readmission or all-cause death.

Effects in HFrEF patients of BBs according to presence of bradycardia on long-term clinical outcomes

Among the HFrEF patients in the four groups, only HR ≥ 60 beats/min with BBs use significantly decreased long-term mortality after univariate analysis (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.417 to 0.702; $p < 0.001$) (Table 3). After adjusting for confounding factors, Cox regression analysis also showed that HR ≥ 60 beats/min with BBs use was independently associated with a 31% reduced risk of all-cause death in patients with HFrEF (OR, 0.69; 95% CI, 0.495 to 0.972; $p = 0.034$). However, in patients with HFrEF, neither bradycardia (HR < 60 beats/min) with BBs and without BBs was independently associated with lower all-cause death. Older age, lower levels of serum sodium, elevated C-reactive protein (CRP), and use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) at discharge were also significant independent predictors of all-cause death during long-term follow-up.

DISCUSSION

Results from this national prospective large-scale study showed that only 43.0% of patients with HFrEF received BBs at discharge, even in the absence of bradycardia. A small percentage (29.8%) of HFrEF patients with bradycardia received BBs at discharge. The use of BBs was associated with a significant risk reduction in all-cause death only in HFrEF patients without bradycardia (HR ≥ 60 beats/min). However, initial bradycardia itself did not reduce the risk of all-cause death. These results were consistent regardless of whether the heart rhythm was sinus or atrial fibrillation and independent of the type of BBs.

Current guidelines have recommended the up-titration of BBs until reaching the patient's target HR [4,5],

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Table 3. Independent predictors for long-term mortality in HFrEF

Variable	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
HR ≥ 60 beats/min with no BBs at discharge	Reference			Reference		
HR < 60 beats/min with BBs	0.46	0.114–1.842	0.271	0.41	0.057–2.958	0.376
HR ≥ 60 beats/min with BBs	0.54	0.417–0.702	< 0.001	0.69	0.495–0.972	0.034
HR < 60 beats/min with no BBs	0.66	0.290–1.48	0.307	1.34	0.588–3.069	0.484
Age	1.03	1.020–1.039	< 0.001	1.03	1.015–1.038	< 0.001
History of heart failure	1.79	1.399–2.229	< 0.001	1.45	1.075–1.962	0.015
History of myocardial infarction	1.88	1.438–2.463	< 0.001	1.23	0.868–1.736	0.246
Chronic kidney disease	2.01	1.440–2.814	< 0.001	0.97	0.605–1.550	0.892
Hemoglobin, g/dL	0.86	0.819–0.906	< 0.001	0.94	0.876–1.009	0.088
Serum sodium, mEq/L	0.94	0.925–0.961	< 0.001	0.97	0.946–0.991	0.006
CRP, mg/dL	1.05	1.028–1.073	< 0.001	1.04	1.009–1.061	0.007
Use of ACEis or ARBs at discharge	0.40	0.320–0.511	< 0.001	0.41	0.300–0.547	< 0.001
Use of aldosterone antagonist	0.78	0.609–0.989	0.040	0.90	0.644–1.247	0.516

HFrEF, heart failure with reduced ejection fraction; OR, odds ratio; CI, confidence interval; HR, heart rate; BB, beta-blocker; CRP, C-reactive protein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

with the results of past studies showing that the magnitude of the HR reduction is proportionally associated with better survival rates [2,12,13]. Our KorHF registry study also showed that, in patients with HFrEF, using BBs at discharge had a comparative survival benefit (Supplementary Fig. 1). Despite these demonstrated beneficial effects of BBs, in actual practice only 42.6% of patients with HFrEF are actually prescribed BBs when discharged, with only 43.0% of patients without bradycardia being prescribed BBs and 29.8% of patients with HFrEF with bradycardia (HR < 60 beats/min) taking BBs. In previous HF trials of carvedilol, metoprolol and bisoprolol [14-16], a baseline HR < 68 beats/min was an exclusion criteria but in practice this may not be clinically realistic; our study on the other hand is meaningful in that it takes into account how much BBs are actually used in patients with bradycardia, with real world outcomes. In addition, this study contributes to the knowledge that the use of BBs at discharge had a better prognosis than baseline bradycardia itself in the treatment of HF, and showed that in HFrEF patients with atrial fibrillation, the use of BBs was notable for demonstrating lower all-cause death in patients with HR ≥ 60 beats/min.

There has been a debate whether the benefits of BB therapy in HFrEF patients are dependent on the BB dose given or the actual HR reduction achieved [17,18]. Indeed, the role of BBs in the prognosis of HFrEF patients with bradycardia has been the subject of considerable debate from an early stage. Ibrahim et al. [19] showed no significant difference in all-cause mortality among four groups divided on the basis of the patient's baseline HR (HR ≥ 70 beats/min vs. < 70 beats/min) and the patient being on at least 50% of the GDMT BB dose (the 100% GDMT BB dose was considered to be 200 mg of metoprolol succinate equivalent daily). However, HF hospitalization was significantly lower in the HR < 70 beats/min group, and a higher risk of HF hospitalization appeared to be more dependent on HR and less dependent on the BB dose. Their definition of bradycardia (HR < 70 beats/min) differed from ours (HR < 60 beats/min) and their patients had a worse LVEF of ≤ 35%, with sinus rhythm. Our study did not exclude patients with atrial fibrillation and we undertook a separate sub-analysis of the patients with atrial fibrillation. In another study, Fiuzat et al. [17] showed that HFrEF patients using low-dose BB (carvedilol < 25 mg/day) who had an elevated HR (≥ 70 beats/min) had the significantly highest incidence of all-cause death and hospitalization among four groups divided on the basis of the patient's resting HR and BB dose. They

also had a different definition of bradycardia than we did, and they analyzed the prognosis according to BB dose and resting HR in patients with a LVEF (< 35%), which excluded atrial fibrillation. By contrast, our results confirmed whether baseline bradycardia itself had a favorable effect on clinical outcomes in HFrEF or the prognosis improved by lowering the high HR using BBs.

In managing patients with HFrEF, not only role of BBs, but role of ACEis or ARBs is also important. The effectiveness of treatment with ACEis or ARBs has been proven in patients with HFrEF and current guidelines recommend these medications for survival benefit [4,11]. We showed that use of ACEis or ARBs at discharge was also independently reduced risk of all-cause death in patients with HFrEF, and this result was consistent with the current guidelines. In addition, we showed that elevated CRP independently increased risk of all-cause death in patients with HFrEF. It is not clear whether CRP directly regulates the HF progression and prognosis. However, it is known that plasma CRP level increase in response to pathophysiological change that cause ventricular remodeling [20]. CRP can stimulate the complement system and cytokine production, and can cause direct inflammation in endothelial cells [21,22]. These multiple mechanisms may make HF worse, thereby promoting ventricular remodeling and dysfunction.

This study has some limitations. Firstly, not being randomized controlled trials, multicenter cohort studies like ours are unable to avoid the inevitable biases that could affect clinical outcomes. Secondly, the definition of bradycardia in our study differed from that of previous HF studies and in addition, the numbers of patients in our study with HR < 60 beats/min was small. However, it may be appropriate to define bradycardia as HR < 60 beats/min when treating HF patients, and the use of BBs at HR < 60 beats/min rather than at HR < 70 beats/min is practically reluctant and is accordingly reflected in the prognosis. Moreover, considering that a patient with bradycardia in acute HF status from the time of hospitalization is rare, our study may reflect real world. Third, although a variability and the extent of reduction of HR due to the effect of BBs are important factors for treating HF patients, HR at discharge or at follow-up visit was not presented in our study. Next, previous medication history including BBs was not shown, which could affect HR at the time of admission. Also, previous medication history in patients with previous HF history was not revealed, which may affect long-term clinical outcomes. Finally, the reasons why BBs was not used, and the type, dose and tolerability of BBs were not presented in our study in detail, which may have affected the outcomes. However, SBP and DBP were significantly lower in no BBs group than BBs group and HR was not different. We assume that the reason why physicians did not use BBs might be patients' low BP rather than low HR.

In conclusion, BBs was associated with beneficial effect on clinical prognosis only in HFrEF patients without bradycardia, but less than half of patients with HFrEF were prescribed BBs at discharge and for even fewer HFrEF patients with bradycardia. Clinicians should actively prescribe BBs to HF patients without bradycardia to improve their clinical outcomes.

KEY MESSAGE

1. Fewer than half of patients with heart failure with reduced ejection fraction (HFrEF) used beta-blockers (BBs) at discharge.
2. Use of BBs in HFrEF patients without bradycardia reduced risk of all-cause death.
3. Use of BBs conferred no beneficial effect on all-cause death in patients with bradycardia.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Study outcomes according to cause of heart failure

Variable	HR < 60 beats/min				HR ≥ 60 beats/min			
	All (n = 19)	BBs (n = 6)	No BBs (n = 13)	*p* value	All (n= 590)	BBs (n = 287)	No BBs (n = 303)	*p* value
Ischemic heart disease patients								
All-cause death	4 (21.1)	1 (16.7)	3 (23.1)	1.000	130 (22.0)	44 (15.3)	86 (28.4)	< 0.001
Composite events of HF readmission or all-cause death	9 (47.4)	2 (33.3)	7 (63.8)	0.628	257 (43.6)	107 (373)	150 (49.5)	0.003
Valvular heart disease patients								
All-cause death	1 (50.0)	1 (100.0)	0	1.000	32 (22.1)	9 (17.3)	23 (24.7)	0.404
Composite events of HF readmission or all-cause death	2 (100.0)	1 (100.0)	1 (100.0)	-	62 (42.8)	20 (38.5)	42 (45.2)	0.486

Values are presented as number (%).
HR, heart rate; BB, beta-blocker; HF, heart failure.

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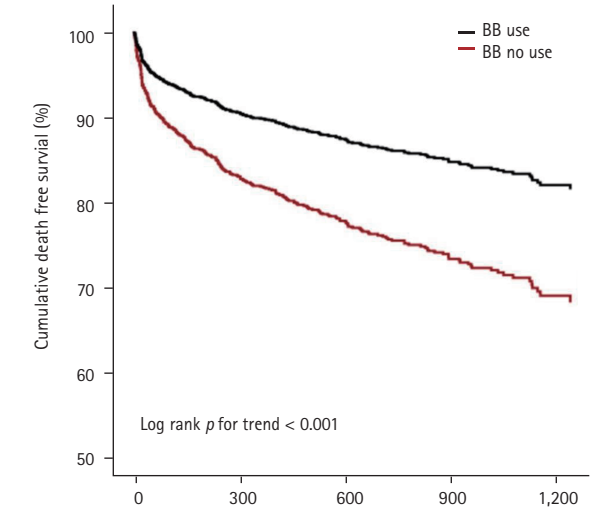
Supplementary Table 2. Study outcomes according to heart rhythm

Variable	Sinus rhythm				Atrial fibrillation rhythm			
	All (n = 1,051)	BB use (n = 432)	No BB (n = 619)	*p* value	All (n= 284)	BB use (n = 137)	No BB (n = 147)	*p* value
All-cause death	192 (18.3)	47 (10.9)	145 (23.4)	< 0.001	51 (18.0)	13 (10.9)	36 (20.8)	0.026
Composite events of HF readmission or all-cause death	410 (39.0)	139 (32.2)	271 (43.8)	< 0.001	104 (35.6)	34 (28.6)	70 (40.5)	0.037
HR ≥ 60 beats/min	986	412	574		270	113	157	
All-cause death	178 (18.1)	45 (10.9)	133 (23.2)	< 0.001	47 (17.4)	13 (11.5)	34 (21.7)	0.030
Composite events of HF readmission or all-cause death	378 (38.3)	131 (31.8)	247 (43.0)	< 0.001	99 (36.7)	34 (30.1)	65 (41.4)	0.057
HR < 60 beats/min	29	8	21		17	5	12	
All-cause death	4 (13.8)	1 (12.5)	3 (14.3)	1.000	1 (5.9)	0	1 (8.3)	1.000
Composite events of HF readmission or all-cause death	11 (37.9)	3 (37.5)	8 (38.1)	1.000	3 (17.6)	0	3 (25.0)	0.218

Values are presented as number (%).
BB, beta-blocker; HF, heart failure; HR, heart rate.



No. at risk					
BB use	674	466	304	180	36
BB no use	910	574	403	278	89

Supplementary Figure 1. Cumulative death-free survival rate according to beta-blocker (BB) use.

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