Int J Heart Fail. 2024 Jul;6(3):119-126
https://doi.org/10.36628/ijhf.2023.0052
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure IJHF

Original Article

Check for updates

Differences in the Effects of Beta-Blockers Depending on Heart Rate at Discharge in Patients With Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation

Young In Kim, MD[1,*], Min-Soo Ahn, MD, PhD[1,*], Byung-Su Yoo, MD, PhD[1], Jang-Young Kim, MD, PhD[1], Jung-Woo Son, MD[1], Young Jun Park, MD[1], Sung Hwa Kim, PhD[2], Dae Ryong Kang, PhD[2], Hae-Young Lee, MD, PhD[3], Seok-Min Kang, MD, PhD[4], and Myeong-Chan Cho, MD, PhD[5]

[1]Division of Cardiology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea
[2]Center of Biomedical Data Science, Yonsei University Wonju College of Medicine, Wonju, Korea
[3]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[4]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[5]Chungbuk National University College of Medicine, Cheongju, Korea

Received: Sep 15, 2023
Revised: Jun 21, 2024
Accepted: Jun 25, 2024
Published online: Jul 3, 2024

Correspondence to
Byung-Su Yoo, MD, PhD
Division of Cardiology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Korea.
Email: yubs@yonsei.ac.kr

*Drs. Min-Soo Ahn and Young In Kim contributed equally to this work and are joint first authors.

ABSTRACT

Background and Objectives: Beta-blockers (BBs) improve prognosis in heart failure (HF), which is mediated by lowering heart rate (HR). However, HR has no prognostic implication in atrial fibrillation (AF) and also BBs have not been shown to improve prognosis in heart failure with preserved ejection fraction (HFpEF) with AF. This study assessed the prognostic implication of BB in HFpEF with AF according to discharge HR.

Methods: From the Korean Acute Heart Failure Registry, 687 patients with HFpEF and AF were selected. Study subjects were divided into 4 groups based on 75 beats per minute (bpm) of HR at discharge and whether or not they were treated with BB at discharge.

Results: Of the 687 patients with HFpEF and AF, 128 (36.1%) were in low HR group and 121 (36.4%) were in high HR group among those treated with BB at discharge. In high HR group, HR at discharge was significantly faster in BB non-users (85.5±9.1 bpm vs. 89.2±12.5 bpm, p=0.005). In the Cox model, BB did not improve 60-day rehospitalization (hazard ratio, 0.93; 95% confidence interval [95% CI], 0.35–2.47) or mortality (hazard ratio, 0.77; 95% CI, 0.22–2.74) in low HR group. However, in high HR group, BB treatment at discharge was associated with 82% reduced 60-day HF rehospitalization (hazard ratio, 0.18; 95% CI, 0.04–0.81), but not with mortality (hazard ratio, 0.77; 95% CI, 0.20–2.98).

Conclusions: In HFpEF with AF, in patients with HR over 75 bpm at discharge, BB treatment at discharge was associated with a reduced 60-day rehospitalization rate.

Keywords: Heart failure; Atrial fibrillation; Heart rate

INTRODUCTION

The prevalence of heart failure (HF) has been increasing in Korea from 0.77% in 2002 to 2.24% in 2018.[1] Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) shared pathophysiological mechanisms, risk factors and comorbidities that predispose to both conditions simultaneously. Once developed, these 2 conditions have the potential to interact with each other in a vicious cycle and are associated with increased morbidity and mortality compared with patients without these diagnoses.[2-5] HFpEF has been proposed to be developed and aggravated in AF because of tachycardia or irregularity-induced cardiomyopathy and loss of atrial systole.[3,6] Treatments for HF that lower mortality and morbidity in cases of heart failure with reduced ejection fraction (HFrEF), such as beta-blockers (BBs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists, do not yield the same results in HFpEF.[7,8] There is a widespread belief that heart rate (HR)-lowering medications in HFpEF patients will benefit from increasing the time of ventricular diastolic filling. However, BB did not improve exercise capacity and symptoms in HFpEF in normal sinus rhythm. HR reduction in HFpEF did not improve symptoms and too low HR might have a deleterious effect in HFpEF.[9,10]

Nevertheless, in addition to the effect of controlling the HR, BBs have various beneficial effects in failing heart.[11] This study aimed to evaluate whether BB has different prognostic implication according to discharge HR after use or non-use of BB in patients with HFpEF and AF.

METHODS

Study design and population

This study enrolled participants from the Korean Acute Heart Failure (KorAHF) Registry, which gathered data on 5,625 patients hospitalized for acute HF at tertiary medical institutions in Korea between March 2011 and February 2014.[12] Further details regarding this registry can be found in a previous study.[13] For this particular study, individuals with at least one of the following criteria or symptoms of HF were included: lung congestion, objective evidence of left ventricular (LV) systolic dysfunction, or structural heart disease. There were no exclusion criteria except for patients who had withdrawn their consent. Follow-up data was gathered by the participating researchers using a web-based case report form. For patients who could not be reached directly, information was obtained through telephone contact or retrieved from the National Death Records database. All clinical events underwent verification by the Clinical Event Committee, consisting of independent HF experts who were not involved in patient recruitment for this study. The study protocol received approval from the Ethics Committee or Institutional Review Board at each hospital, and a waiver of written informed consent was granted by the Institutional Review Board.

Study variables and definitions

HFpEF was characterized by a left ventricular ejection fraction (LVEF) equal to or greater than 50%.[14] The diagnosis of AF was confirmed through electrocardiography either at admission or during the hospital stay. The study's primary outcomes encompassed all-cause mortality and HF-related rehospitalization within a 60-day follow-up period. BB utilization was evaluated upon discharge, and HR was clinically assessed prior to discharge. Patients who were exclusively prescribed HFrEF management guideline-recommended BB, such as bisoprolol, carvedilol, sustained-release metoprolol succinate, and nebivolol upon discharge, were categorized as BB-treated.[7] The median HR at discharge was 75 beats per minute (bpm). Study subjects were divided into 4 groups based on 75 bpm of HR at discharge and whether or not they were treated with BB at discharge.

Statistical analysis

Data are reported as mean ± standard deviation for continuous variables, numbers and percentages for categorical variables. For comparisons between groups, χ^2 test was used for the categorical variables and unpaired Student's t-test was used for continuous variables. Individual and composite clinical outcomes were analyzed from the time of the first incident. The Kaplan-Meier survival curves and the log-rank test were used to analyze event-free survival according to whether to use BB or not. To assess the relationship between outcomes and BB, Cox proportional hazards regression models were used and adjusted for sex, age, type of HF (de novo vs. acute decompensated HF), diastolic blood pressure, HR at admission, etiology of HF, left atrial volume index and discharge medication including angiotensinogen converting enzyme inhibitor, angiotensin receptor blocker and mineralocorticoid receptor antagonist. In all cases, a p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Version 27.0 (IBM Corp., Armonk, NY, USA).

Ethics statement

The study protocol was approved by the Institutional Review Board at each hospital and the Wonju Christian Hospital, Wonju College of Medicine, Yonsei University (approval No. CR311003), and written informed consent was obtained from each patient or their relative or legal representative.

RESULTS

Baseline characteristics

Of the 5,625 patients in the KorAHF registry, 2,357 HFrEF and 616 HF with mid-range ejection fraction patients were excluded. After exclusion of in-hospital death, 687 patients with HFpEF and AF were analyzed. Based on the median HR 75 bpm, 355 were in low HR group, and 332 were in high HR group. Two hundred forty-nine patients were treated with BB at discharge. One hundred twenty-eight (36.1%) patients were in low HR group and 121 (36.4%) patients in high HR group among those treated with BB at discharge. Baseline characteristics of study population are presented in **Table 1**.

In low HR group, mean discharge HR was 64.7±7.6 bpm. There was no difference in discharge HR according to the treatment of BB (65.0±7.0 bpm in BB untreated vs. 65.0±8.0 bpm in BB treated, p=0.647). Patients treated with BBs at discharge had higher HR and diastolic blood pressure at admission and higher prevalence of de novo HF compared to those not treated with BB. The etiology of HF was often ischemic heart disease and tachycardia induced HF in BB treated group. More than 50% of patients treated with BB at discharge were already taking BBs at admission, a significant difference from patients who were not taking BBs at discharge. Other medications except BBs at discharge were not different between 2 groups (**Table 2**). In high HR group, mean discharge HR was 87.9±11.5 bpm. Discharge HR was significantly faster in BB untreated group compared to BB treated group (85.5±9.1 bpm vs. 89.2±12.5 bpm, p=0.002). The prevalence of hypertension and serum sodium level was higher in BB treated group. Similar to the low HR group, those who were taking BB at discharge were already taking more BB at admission compared to those who were not taking BB. Otherwise, other clinical characteristics including etiology of HF, echocardiographic parameters and discharge medications were not different depending on the treatment of BB.

Clinical outcomes

Among patients who were prescribed BB at discharge, only 46.4% continued to use them at their 60-day follow-up visit. In contrast, among patients who were not prescribed BB at discharge, 46.3% were subsequently prescribed BB. There was no significant difference in systolic blood pressure and HR at the 60-day follow-up visit based on the use of BB (**Table 3**). In total, there was 64 (9.3%) HF rehospitalizations and 34 deaths (4.9%) during 60-day follow-up. Eighteen patients (5.1%) died in low HR and 16 (4.8%) in high HR (p=0.879) during 60-day follow-up. Thirty-two patients (9.0%) were rehospitalized in low HR and 32 (9.6%) in high HR (p=0.778). There was no difference in clinical outcomes according to discharge HR. Unlike the high HR group, in the low HR group, there was no difference in clinical outcomes between BB treated and untreated, although numerically the event rate was higher in untreated group (**Table 4**). In Kaplan-Meier survival curves, the rates of post-discharge 60-day all-cause mortality and HF rehospitalization did not differ between the groups (**Figure 1**). However, in the high HR group, HF rehospitalization occurred frequently in BB untreated group during 60 days (**Table 4**). In Kaplan-Meier survival curves, HF rehospitalization was significantly lower in BB treated (**Figure 1**). In the Cox model, BB treatment at discharge was associated with 82% reduced 60-day HF rehospitalization in patients with high HR (hazard ratio, 0.182; 95% confidence interval [95% CI], 0.041–0.814; p=0.026) but not in those with low HR (hazard ratio, 0.934; 95% CI, 0.353–2.473; p=0.891). However, BB at discharge was not associated with 60-day mortality in both groups (**Figure 2**).

DISCUSSION

In this study, we evaluated different prognostic implication of BB according to the HR at discharge in patients with HFpEF with AF. We demonstrated that BB at discharge was associated with improved 60-day HF rehospitalization in patients with HR higher than 75 bpm at discharge.

In large-scale epidemiologic studies, resting HR and pharmacological HR lowering were known to be independent prognostic factors for all-cause or cardiovascular mortality in patients with reduced LVEF. However, from the national cohort data of English and Welsh registry, in patients with acute myocardial infarction who did not have HF or LV systolic dysfunction, BBs were not associated with a lower risk of death at any time point up to 1 year (average treatment effect [ATE] coefficient: 0.07; 95% CI: −0.60 to 0.75; p=0.827).[15] In addition, in the Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY), ivabradine to reduce the HR did not improve outcomes in patients who had stable coronary artery disease in patients with normal sinus rhythm and no evidence of clinical HF.[16]

The hemodynamic consequences of reduced HR in HFpEF have not undergone investigation. However, in a study examining the hemodynamic effects of elevated HR in HFpEF patients, there was a remarkable decrease in LV end-diastolic pressure (from 17 to 8 mmHg) during atrial pacing at 120 bpm.[17] Slowing the HR is likely to result in increased filling. When HR is slowed down, the reflected pulse wave returns to the ventricle at a time when it is still in systole, thereby HR lowering results in elevated central blood pressures and augmentation of central systolic pressure

Table 1. Baseline characteristics of patients according to BB treatment and HR at discharge

Characteristics	Low HR			High HR		
	BB treated (n=128)	BB untreated (n=227)	p value	BB treated (n=121)	BB untreated (n=211)	p value
Demographic characteristics						
Male	45 (35.2)	84 (37.0)	0.728	48 (39.7)	74 (35.1)	0.403
Age (years)	74.8±11.7	73.6±11.1	0.334	72.8±10.8	73.8±12.6	0.439
Height (cm)	157.4±8.5	157.1±9.63	0.790	157.7±8.8	157.5±9.5	0.853
Weigh (cm)	58.4±12.4	59.2±13.5	0.601	59.8±12.0	57.4±11.5	0.070
BMI (kg/m^2)	23.4±3.9	23.8±4.3	0.411	24.0±4.0	23.1±4.1	0.057
SBP (mmHg)	135.6±27.8	132.6±28.5	0.338	134.2±28.8	133.9±27.6	0.918
DBP (mmHg)	81.5±18.4	75.0±17.7	0.001	81.6±18.9	78.9±19.9	0.237
HR at admission (beats/min)	90.7±25.8	81.8±27.7	0.003	97.9±27.6	96.2±28.2	0.593
HR at discharge (beats/min)	65.0±8.0	65.0±7.0	0.647	85.5±9.1	89.2±12.5	0.002
NYHA functional class			0.870			0.848
Class II	23 (18.0)	40 (17.6)		21 (17.4)	40 (19.0)	
Class III	50 (39.1)	95 (41.9)		44 (36.4)	80 (37.9)	
Class IV	55 (43.0)	92 (40.5)		56 (46.3)	91 (43.1)	
De novo heart failure	69 (53.9)	83 (36.6)	0.002	66 (54.5)	108 (51.2)	0.555
Comorbidity						
Hypertension	98 (76.6)	148 (65.2)	0.026	91 (75.2)	119 (56.4)	0.001
DM	40 (31.3)	66 (29.1)	0.667	41 (33.9)	51 (24.2)	0.057
IHD	26 (20.3)	40 (17.6)	0.531	16 (13.2)	38 (18.0)	0.255
CKD	13 (10.2)	25 (11.0)	0.802	11 (9.1)	13 (6.2)	0.321
COPD	16 (12.5)	32 (14.1)	0.673	12 (9.9)	34 (16.1)	0.116
CHADS-VASc						
Medication at admission						
ACEi	10 (7.8)	16 (7.0)	0.791	5 (4.1)	13 (6.2)	0.432
ARB	43 (33.6)	90 (39.6)	0.258	35 (28.9)	61 (28.9)	0.998
BB	66 (51.6)	55 (24.2)	<0.001	68 (56.2)	45 (21.3)	<0.001
MRA	21 (16.4)	75 (33.0)	0.001	20 (16.5)	41 (19.4)	0.511
Etiology of heart failure			0.001			0.072
IHD	31 (24.2)	27 (11.9)		16 (13.2)	22 (10.4)	
VHD	33 (25.8)	106 (46.7)		29 (24.0)	88 (41.7)	
Cardiomyopathy	11 (8.6)	15 (6.6)		9 (7.4)	7 (3.3)	
HHD	4 (3.1)	7 (3.1)		3 (2.5)	8 (3.8)	
Tachycardia induced	39 (30.5)	42 (18.5)		46 (38.0)	55 (26.1)	
ECG characteristics at admission						
LBBB	0 (0)	4 (1.8)	0.131	0 (0.0)	2 (0.9)	0.283
RBBB	7 (5.5)	25 (11.0)	0.080	8 (6.6)	13 (6.2)	0.871
Laboratory characteristics at admission						
Na^+ (mmol/L)	137.9±4.6	137.0±5.7	0.134	138.1±4.6	136.6±5.8	0.018
K^+ (mmol/L)	4.3±0.6	4.3±0.7	0.833	4.2±0.6	4.3±0.6	0.532
Albumin (g/dL)	3.8±0.5	3.8±0.5	0.810	3.7±0.5	3.6±0.5	0.109
Hemoglobin (g/dL)	12.3±2.0	11.8±2.0	0.012	12.4±1.8	12.1±2.1	0.151
Creatinine (mg/dL)	1.2±0.8	1.3±0.8	0.455	1.1±0.5	1.1±0.5	0.269
hs-CRP (mg/dL)	2.0±4.1	2.4±4.7	0.539	1.7±2.1	1.9±3.6	0.649
NT-proBNP (pg/mL)	5,892.2±7,617.2	5,441.6±6,629.9	0.691	6,573.2±894.5	6,984.7±669.0	0.631
BNP (pg/mL)	914.1±816.4	790.3±1,071.9	0.434	483.1±64.0	686.9±642.2	0.825
CK-MB (ng/mL)	4.8±9.5	5.8±23.3	0.681	5.2±18.9	6.8±39.0	0.700
Troponin I (mg/mL)	1.0±4.5	1.3±8.7	0.817	1.0±4.2	1.2±11.8	0.867
Echocardiographic characteristics						
LVEF (%)	59.0±6.6	58.8±6.1	0.814	58.1±6.5	58.2±6.1	0.947
LVEDV (mL)	98.5±45.1	108.4±43.7	0.107	99.9±48.0	100.6±48.9	0.912
LVEDV index (mL/m^2)	64.3±29.2	69.5±27.5	0.181	63.3±30.1	64.2±29.2	0.841
LVESV (mL)	40.8±21.6	44.4±20.6	0.223	42.8±28.3	42.5±24.4	0.942
LVESV index (mL/m^2)	26.5±13.5	28.5±13.1	0.272	26.9±17.4	27.1±15.5	0.919
LA volume index (mL/m^2)	74.0±37.3	99.0±69.2	0.002	68.2±29.8	89.5±109.6	0.077

Values are number (%) or mean ± standard deviation, unless otherwise indicated.
BB = beta-blocker; HR = heart rate; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; NYHA = New York Heart Association; DM = diabetes mellitus; IHD = ischemic heart disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor II blocker; MRA = mineralocorticoid receptor antagonists; VHD = valvular heart disease; HHD = hypertensive heart disease; ECG = electrocardiography; LBBB = left bundle branch block; RBBB = right bundle branch block; Na = serum sodium; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N terminal-pro B-type natriuretic peptide; BNP = B-type natriuretic peptide, CK-MB = creatine kinase muscle brain; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LA = left atrium.

Table 2. Medications at discharge

Characteristics	Low HR			High HR		
	BB treated (n=128)	BB untreated (n=227)	p value	BB treated (n=121)	BB untreated (n=211)	p value
ACEi or ARB	81 (63.3)	128 (56.4)	0.205	66 (54.5)	100 (47.4)	0.210
ACEi at discharge	29 (22.7)	39 (17.2)	0.208	18 (14.9)	36 (17.1)	0.604
Ramipril equivalent dose (mg)	3.3±2.3	2.6±1.8	0.147	2.5±2.0	2.5±1.9	0.984
ARB at discharge	54 (42.2)	89 (39.2)	0.582	48 (39.7)	64 (30.3)	0.083
Candesartan equivalent dose (mg)	13.1±8.1	12.6±7.4	0.710	10.9±4.8	10.9±5.0	0.942
MRA at discharge	54 (42.2)	115 (50.7)	0.125	48 (39.7)	91 (43.1)	0.539
Loop diuretics	91 (71.1)	171 (75.3)	0.425	90 (74.4)	164 (77.7)	0.375
Amiodarone	10 (7.8)	17 (7.5)	0.902	8 (6.6)	23 (10.9)	0.335
Digoxin	43 (33.6)	75 (33.0)	0.929	43 (35.5)	99 (46.9)	0.085
Anticoagulation	69 (53.9)	132 (58.1)	0.599	56 (46.3)	107 (50.7)	0.633

Values are number (%) or mean ± standard deviation, unless otherwise indicated.
HR = heart rate; BB = beta-blocker; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor II blocker; MRA = mineralocorticoid receptor antagonists.

Table 3. Vital sign and medications at 60-day

Characteristics	Low HR			High HR		
	BB treated (n=128)	BB untreated (n=227)	p value	BB treated (n=121)	BB untreated (n=211)	p value
SBP (mmHg)	111.0±19.2	115.2±20.4	0.104	115.5±19.8	114.6±20.6	0.755
DBP (mmHg)	66.2±11.6	67.9±12.4	0.272	69.3±13.3	67.4±13.0	0.950
HR (bpm)	78.8±16.5	80.9±17.3	0.386	81.7±17.7	78.5±14.6	0.170
BB	47 (43.9)	80 (42.3)	0.815	43 (45.3)	75 (44.1)	0.364
ACEi	30 (28.0)	45 (23.8)	0.569	26 (27.4)	51 (30.0)	0.462
ARB	37 (34.6)	63 (33.3)	0.744	30 (31.6)	50 (29.4)	0.467
MRA at discharge	44 (41.1)	79 (41.8)	0.889	38 (40.0)	68 (40.0)	0.737
Anticoagulation	28 (26.2)	56 (29.6)	0.277	33 (34.7)	55 (32.4)	0.053

Values are number (%) or mean ± standard deviation, unless otherwise indicated.
HR = heart rate; BB = beta-blocker; SBP = systolic blood pressure; DBP = diastolic blood pressure; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor II blocker; MRA = mineralocorticoid receptor antagonists.

Table 4. Clinical outcomes

Characteristics	Low HR			High HR		
	BB treated (n=128)	BB untreated (n=227)	p value	BB treated (n=121)	BB untreated (n=211)	p value
60-day heart failure rehospitalization	10 (7.8)	22 (9.7)	0.553	3 (2.5)	29 (13.7)	0.001
60-day mortality	5 (3.9)	13 (5.7)	0.453	5 (4.1)	11 (5.2)	0.658

Values are number (%), unless otherwise indicated.
HR = heart rate; BB = beta-blocker.

even though peripheral blood pressures can be lower.[18,19] This paradoxically suggests that a low HR is not desirable in patients with HFpEF and that higher resting HR might provide hemodynamic benefits.[20] In the Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and LV function of patients with Diastolic Dysfunction (ELANDD) study, HR was significantly lower after 6 months nebivolol therapy (67±8 bpm vs. 75±13 bpm, p<0.001) and treatment with nebivolol did not improve exercise capacity in patients with HFpEF.[10] In addition, another study showed that the higher level of N-terminal pro-B-type natriuretic peptide and worsening HF symptoms were reported in the study group treated with bisoprolol and carvedilol for HFpEF patients.[21,22]

BBs are strongly recommended for short and long-term rate control in patients with acute and chronic HF with AF.[7] However, there are currently insufficient data to provide treatment recommendations for patients with HFpEF and AF. Patients with AF at baseline demonstrated no consistent benefit on clinical outcomes with BB, regardless of LVEF.[23] In addition, according to previous meta-analysis, patients with HF and AF given BBs had no significant reduction in all-cause mortality, cardiovascular hospital admission, or composite clinical outcomes compared with those receiving placebo. The lack of effect of BB on the prognosis of AF or HFpEF may be explained by the fact that the effect of BB on HR may be different from the effect on HF in patients with HFrEF or normal sinus rhythm.

The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison Between Lenient Versus Strict Rate Control II (RACE II trial) demonstrated a more lenient HR control strategy of up to 100 bpm was not inferior to a strict HR control of <80 bpm with a numerical signal towards a better outcomes at higher HR.[24] In patients with HFrEF and AF, the risk of death due to pump failure

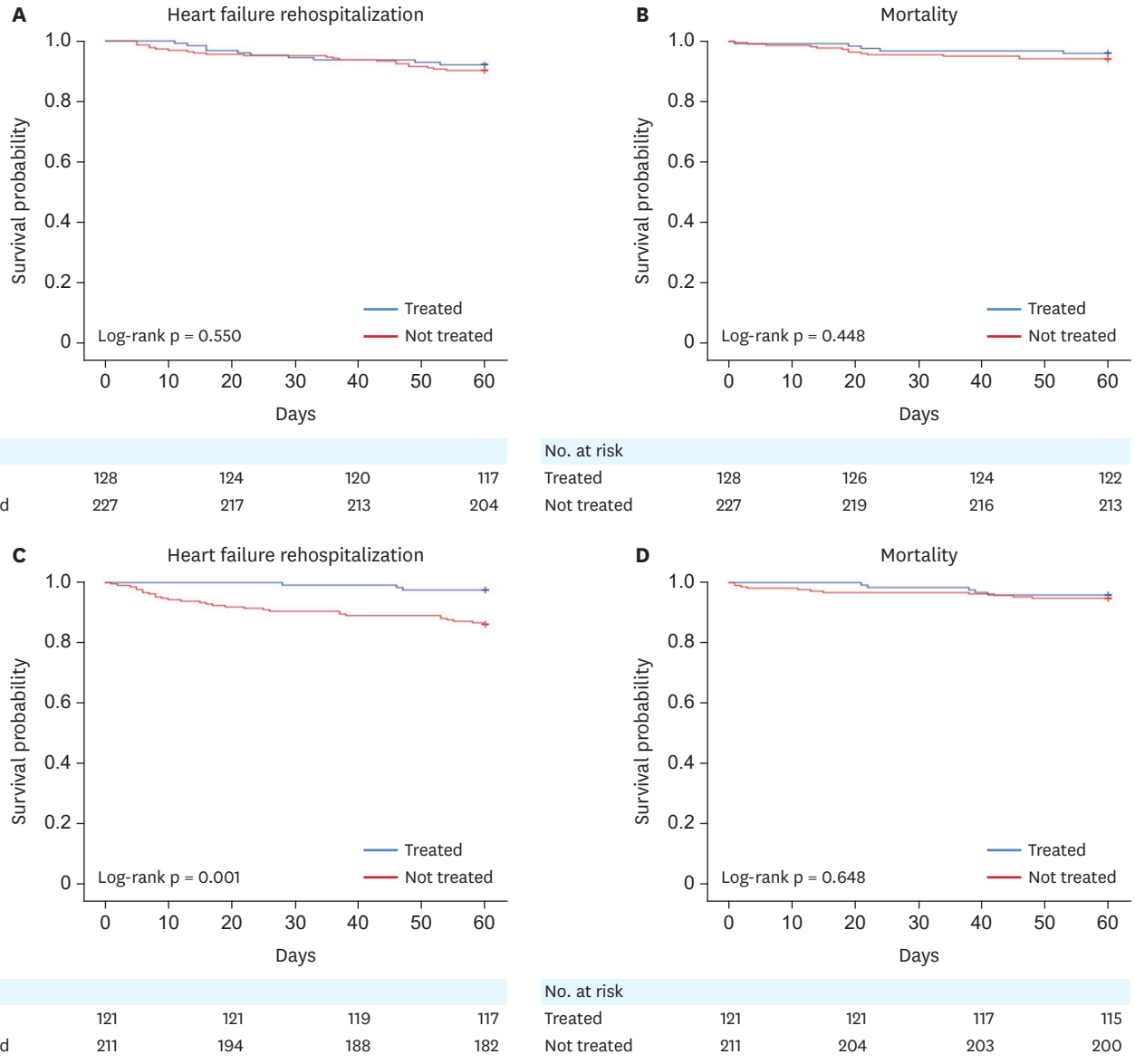

Figure 1. The 60-day event free survival according to the treatment with beta blocker at discharge: (A) heart failure hospitalization, (B) mortality for low heart rate and (C, D) for high heart rate (blue line: beta blocker treated, red line: beta blocker untreated).

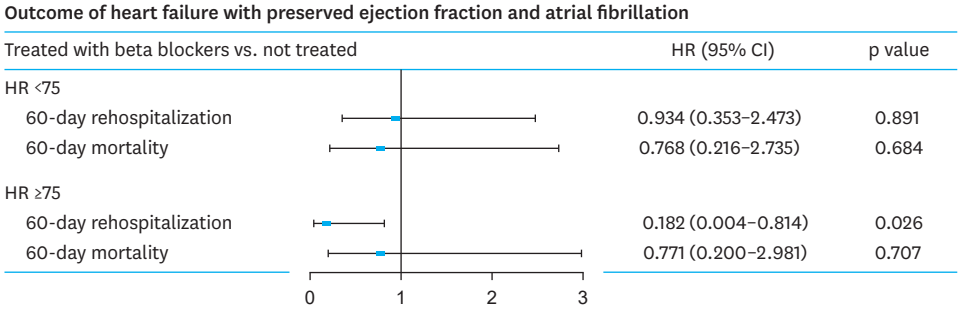

Figure 2. Forest plot of 60-day clinical outcomes adjusted for sex, age, type of HF (de novo vs. acute decompensated HF), diastolic blood pressure, HR at admission, etiology of HF, left atrial volume index and discharge medication including angiotensinogen converting enzyme inhibitor, angiotensin receptor blocker and mineralocorticoid receptor antagonist.
HF = heart failure; HR = heart rate; CI = confidence interval.

varied based on HR, showing a lower risk in the upper 2 tertiles of HR compared to the lowest tertile (T2 unadjusted hazard ratio, 0.67; 95% CI, 0.47–0.97; p=0.035, and T3 unadjusted hazard ratio, 0.67; 95% CI, 0.46–0.96; p=0.031).[25] Due to the absence of the atrial kick and irregular ventricular response during AF, individuals with AF may require a higher HR to sustain a comparable cardiac output, especially in cases of HF.[26] In this study of patients with HFpEF and AF, BB reduced the HF rehospitalization rate compared to those without BBs when HR was kept higher at the time of discharge. There has been no treatment to show convincingly improve prognosis in patients with HFpEF, especially accompanied by AF. The results of this study suggest that BB may be an option for unmet need in patients with HFpEF with AF.

As other previous study of our cohort registry, our study has several limitations. First, the sample size is small, and determining the target HR has been challenging. Therefore, the findings of this study suggest that while using BBs, caution should be needed not to excessively lower the HR. Second, because of the nature of prospective cohort study, there is a possibility of selection bias in treatment decision by physician. Despite the adjustment of for confounding variables that could influence prognosis, this bias may have affected the prognosis. Third, it is limited in information related to AF as AF diagnosis was based on electrocardiography at admission or during admission. There may be underestimation or overestimation according to rhythm changes after discharge. Fourth, we presented cubic spine curve that showed HR dependency of BB effect. However, total number of patients with HR over 100 bpm at discharge was just 26 patients. This cubic spine curve needs to be interpreted cautiously. Fifth, we have no data for the use of non-dihydropyridine calcium channel blocker. The effect of the calcium channel blocker on the prognosis could not be analyzed. Sixth, we presented positive result of 60-day follow-up data. However, BB did not improve 1-year prognosis in our data (**Supplementary Figures 1** and **2**). HF therapy was changed during the follow-up period. After 1-year follow after discharge, 49.7% patients were treated with BB in groups who had not treated with BB at discharge and 50.8% in BB treated group at discharge. This change of treatment pattern may influence the long-term clinical outcomes.

Our study showed that BB reduces 60-day readmission rates in patients with HFpEF and AF, provided that it does not excessively reduce HR in patients with discharge HR higher than 75 bpm. These findings suggest that BB may be an option for unmet need in patients with HFpEF with AF. Further investigation is needed, particularly regarding the optimal therapeutic options for this specific patient subgroup.

ORCID iDs
Young In Kim
https://orcid.org/0000-0003-4823-2698
Min-Soo Ahn
https://orcid.org/0000-0001-7896-8175
Byung-Su Yoo
https://orcid.org/0000-0002-3395-4279
Jang-Young Kim
https://orcid.org/0000-0002-0813-7082
Jung-Woo Son
https://orcid.org/0000-0002-1790-3228
Young Jun Park
https://orcid.org/0000-0002-1461-5597
Sung Hwa Kim
https://orcid.org/0000-0002-5482-1758
Dae Ryong Kang
https://orcid.org/0000-0002-8792-9730
Hae-Young Lee
https://orcid.org/0000-0002-9521-4102
Seok-Min Kang
https://orcid.org/0000-0001-9856-9227
Myeong-Chan Cho
https://orcid.org/0000-0002-0047-0227

Funding
This work was supported by Research of Korea Centers for Disease Control and Prevention (grant No. 2010-E63003-00,2011-E63002-00, 2012-E63005-00, 2013-E63003-00, 2013-E63003-01, 2013-E63003-02, and 2016-ER6303-00) and Gangwon branch of the Korean Society of Cardiology (grant No. GAH2022-02-02).

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Ahn MS, Kim YI, Yoo BS, Kim JY, Son JW, Park YJ. Software: Kim SH, Kang DR. Supervision: Lee HY, Kang SM, Cho MC. Writing - original draft: Ahn MS. Writing - review & editing: Kim YI, Yoo BS.

SUPPLEMENTARY MATERIALS

Supplementary Figure 1
The 1-year event free survival according to the treatment with beta blocker at discharge: (A) heart failure hospitalization, (B) mortality for low heart rate and (C, D) for high heart rate (blue line: beta blocker treated, red line: beta blocker untreated).

Supplementary Figure 2
Forest plot of 1-year clinical outcomes.

REFERENCES

1. Park JJ, Lee CJ, Park SJ, et al. Heart failure statistics in Korea, 2020: a report from the Korean Society of Heart Failure. Int J Heart Fail 2021;3:224-36. PUBMED | CROSSREF

2. Ariyaratnam JP, Lau DH, Sanders P, Kalman JM. Atrial fibrillation and heart failure: epidemiology, pathophysiology, prognosis, and management. Card Electrophysiol Clin 2021;13:47-62. PUBMED | CROSSREF
3. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. J Am Coll Cardiol 2016;68:2217-28. PUBMED | CROSSREF
4. Gangu K, Bobba A, Chela HK, Avula S, Basida S, Yadav N. In-hospital mortality rate and predictors of 30-day readmission in patients with heart failure exacerbation and atrial fibrillation: a cross-sectional study. Int J Heart Fail 2022;4:145-53. PUBMED | CROSSREF
5. Kim YG. Interaction between heart failure and atrial fibrillation. Int J Heart Fail 2022;4:139-41. PUBMED | CROSSREF
6. Ellis ER, Josephson ME. Heart failure and tachycardia-induced cardiomyopathy. Curr Heart Fail Rep 2013;10:296-306. PUBMED | CROSSREF
7. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726. PUBMED | CROSSREF
8. Youn JC, Kim D, Cho JY, et al. Korean Society of Heart Failure guidelines for the management of heart failure: treatment. Int J Heart Fail 2023;5:66-81. PUBMED | CROSSREF
9. Pal N, Sivaswamy N, Mahmod M, et al. Effect of selective heart rate slowing in heart failure with preserved ejection fraction. Circulation 2015;132:1719-25. PUBMED | CROSSREF
10. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail 2012;14:219-25. PUBMED | CROSSREF
11. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. Circulation 2003;107:1570-5. PUBMED | CROSSREF
12. Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. Eur J Heart Fail 2014;16:700-8. PUBMED | CROSSREF
13. Lee SE, Lee HY, Cho HJ, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean Acute Heart Failure Registry (KorAHF). Korean Circ J 2017;47:341-53. PUBMED | CROSSREF
14. Cho JY, Cho DH, Youn JC, et al. Korean Society of Heart Failure guidelines for the management of heart failure: definition and diagnosis. Korean Circ J 2023;53:195-216. PUBMED | CROSSREF
15. Dondo TB, Hall M, West RM, et al. β-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. J Am Coll Cardiol 2017;69:2710-20. PUBMED | CROSSREF
16. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014;371:1091-9. PUBMED | CROSSREF
17. Wachter R, Schmidt-Schweda S, Westermann D, et al. Blunted frequency-dependent upregulation of cardiac output is related to impaired relaxation in diastolic heart failure. Eur Heart J 2009;30:3027-36. PUBMED | CROSSREF
18. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213-25. PUBMED | CROSSREF
19. Rimoldi SF, Messerli FH, Cerny D, et al. Selective heart rate reduction with ivabradine increases central blood pressure in stable coronary artery disease. Hypertension 2016;67:1205-10. PUBMED | CROSSREF
20. Meyer M, LeWinter MM. Heart rate and heart failure with preserved ejection fraction: time to slow β-blocker use? Circ Heart Fail 2019;12:e006213. PUBMED | CROSSREF
21. Bergström A, Andersson B, Edner M, Nylander E, Persson H, Dahlström U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail 2004;6:453-61. PUBMED | CROSSREF
22. Edelmann F, Musial-Bright L, Gelbrich G, et al. Tolerability and feasibility of beta-blocker titration in HFpEF versus HFrEF: insights from the CIBIS-ELD trial. JACC Heart Fail 2016;4:140-9. PUBMED | CROSSREF
23. Cleland JG, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39:26-35. PUBMED | CROSSREF
24. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363-73. PUBMED | CROSSREF
25. Docherty KF, Shen L, Castagno D, et al. Relationship between heart rate and outcomes in patients in sinus rhythm or atrial fibrillation with heart failure and reduced ejection fraction. Eur J Heart Fail 2020;22:528-38. PUBMED | CROSSREF
26. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. Am J Cardiol 1996;78:1433-6. PUBMED | CROSSREF