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ORIGINAL RESEARCH

Lower In-Hospital Mortality With Beta-Blocker Use at Admission in Patients With Acute Decompensated Heart Failure

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BACKGROUND: It remains unclear whether beta-blocker use at hospital admission is associated with better in-hospital outcomes in patients with acute decompensated heart failure.

METHODS AND RESULTS: We evaluated the factors independently associated with beta-blocker use at admission, and the effect of beta-blocker use at admission on in-hospital mortality in 3817 patients with acute decompensated heart failure enrolled in the Kyoto Congestive Heart Failure registry. There were 1512 patients (39.7%) receiving, and 2305 patients (60.3%) not receiving beta-blockers at admission for the index acute decompensated heart failure hospitalization. Factors independently associated with beta-blocker use at admission were previous heart failure hospitalization, history of myocardial infarction, atrial fibrillation, cardiomyopathy, and estimated glomerular filtration rate <30 mL/min per 1.73 m^2. Factors independently associated with no beta-blocker use were asthma, chronic obstructive pulmonary disease, lower body mass index, dementia, older age, and left ventricular ejection fraction <40%. Patients on beta-blockers had significantly lower in-hospital mortality rates (4.4% versus 7.6%, $P<0.001$). Even after adjusting for confounders, beta-blocker use at admission remained significantly associated with lower in-hospital mortality risk (odds ratio, 0.41; 95% CI, 0.27–0.60, $P<0.001$). Furthermore, beta-blocker use at admission was significantly associated with both lower cardiovascular mortality risk and lower noncardiovascular mortality risk. The association of beta-blocker use with lower in-hospital mortality risk was relatively more prominent in patients receiving high dose beta-blockers. The magnitude of the effect of beta-blocker use was greater in patients with previous heart failure hospitalization than in patients without (P for interaction 0.04).

CONCLUSIONS: Beta-blocker use at admission was associated with lower in-hospital mortality in patients with acute decompensated heart failure.

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Key Words: acute decompensated heart failure ■ beta-blocker ■ cohort study

Beta-blockers are guideline-directed medical therapies for heart failure with reduced ejection fraction (HFrEF).[1,2] Previous large clinical trials have consistently shown that beta-blockers reduce mortality and heart failure (HF) hospitalization in patients with chronic HFrEF.[3–5] One of the beneficial effects

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CLINICAL PERSPECTIVE

What Is New?

- In a contemporary acute decompensated heart failure (ADHF) registry, beta-blocker use at admission was significantly associated with lower in-hospital mortality regardless of ischemic etiology and left ventricular ejection fraction.
- This study highlights the beneficial role of beta-blockers in patients hospitalized for ADHF.

What Are the Clinical Implications?

- Prescribing beta-blockers for patients with a high risk of ADHF or a history of heart failure hospitalization might reduce pump failure deaths once they suffer from ADHF.
- The mechanisms of the beneficial effects of beta-blockers at the time of ADHF need to be further investigated.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
ADHF	acute decompensated heart failure
HFrEF	heart failure with reduced ejection fraction
KCHF registry	Kyoto Congestive Heart Failure registry
NYHA	New York Heart Association
SCD	sudden cardiac death

of beta-blockers is reverse remodeling and subsequent improvement in left ventricular ejection fraction (LVEF).[6] Beta-blockers also reduce sudden cardiac death (SCD).[3–5] The discontinuation of beta-blockers in patients admitted with acute decompensated heart failure (ADHF) has been reported to be associated with significantly increased in-hospital and short-term mortality,[7,8] possibly due to activation of the sympathetic nervous system by abrupt discontinuation of beta-blockers.

However, there is a scarcity of data on the effects of beta-blocker use at admission for ADHF on in-hospital outcomes. In ADHF settings, there is a concern about using beta-blockers at hospitalization for their negative inotropic effect to disrupt the compensation of the heart. Therefore, the purpose of this study was to investigate the effect of beta-blocker use at admission for ADHF on in-hospital outcomes in patients with ADHF.

METHODS

Study Population

The KCHF (Kyoto Congestive Heart Failure) registry is a physician-initiated, prospective, observational, multicenter cohort study that enrolled consecutive patients admitted with ADHF for the first time between October 2014 and March 2016 in 19 secondary and tertiary hospitals in Japan. The overall design of the study has been previously described in detail.[9] Briefly, we enrolled patients who presented with ADHF as defined by the modified Framingham criteria, were admitted to the participating centers, and underwent HF-specific treatment involving intravenous drugs within 24 hours after hospital presentation. Among 4056 patients registered in the KCHF registry, the current study population consisted of 3817 patients after excluding patients with the acute coronary syndrome (ACS). Patients were divided into 2 groups according to beta-blocker use at the time of hospital admission. The use of beta-blockers was confirmed by attending physicians and pharmacists.

The investigation conforms with the principles outlined in the Declaration of Helsinki.[10] The study was approved by the institutional review boards of Kyoto University Graduate School of Medicine (approval number: E2311), Shiga General Hospital (approval number: 20141120-01), Tenri Hospital (approval number: 640), Kobe City Medical Center General Hospital (approval number: 14094), Hyogo Prefectural Amagasaki General Medical Center (approval number: Rinri 26-32), National Hospital Organization Kyoto Medical Center (approval number: 14-080), Mitsubishi Kyoto Hospital (approved 11/12/2014), Okamoto Memorial Hospital (approval number: 201503), Japanese Red Cross Otsu Hospital (approval number: 318), Hikone Municipal Hospital (approval number: 26-17), Japanese Red Cross Osaka Hospital (approval number: 392), Shimabara Hospital (approval number: E2311), Kishiwada City Hospital (approval number: 12), Kansai Electric Power Hospital (approval number: 26-59), Shizuoka General Hospital (approval number: Rin14-11-47), Kurashiki Central Hospital (approval number: 1719), Kokura Memorial Hospital (approval number: 14111202), Kitano Hospital (approval number: P14-11-012), and Japanese Red Cross Wakayama Medical Center (approval number: 328). This study was registered with University Hospital Medical Information Network (UMIN) (UMIN identifier: UMIN000015238). A waiver of written informed consent from each patient was granted by the institutional review boards of Kyoto University and each participating center, because the study met the conditions of the Japanese ethical guidelines for Medical and Health Research Involving Human Subjects.[11] We disclosed the present study's details to the public as an opt-out method, and the notice informed patients of their right to refuse enrollment. The data that support the findings

of this study are available from the corresponding author upon reasonable request.

Data Collection and Definitions

The attending physicians or research assistants at each participating hospital collected comprehensive data on patient demographics, medical history, underlying heart disease, pre-hospital activities, socioeconomic status, signs, symptoms, laboratory tests, electrocardiogram, echocardiography, acute management in the emergency room, medications, and clinical events during the index hospitalization.

Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 at admission, calculated using the equation for the Japanese population.[12] Chronic lung disease was defined as asthma or chronic obstructive pulmonary disease. Living status was classified into living with family, living alone, and living in an institution for the aged or in a hospital. Daily life activities were classified into ambulatory, use of wheelchair (outdoor only), use of wheelchair (outdoor and indoor), and bedridden. Hyponatremia was defined as a serum sodium concentration of <135 mmol/L. Anemia was defined as a hemoglobin level <12 g/dL for women and <13 g/dL for men following World Health Organization Criteria.

Beta-blocker doses were converted into carvedilol equivalent doses according to a previous report.[13] The carvedilol equivalent dose was 5 times the dose of bisoprolol, one-fifth of the dose of metoprolol tartrate, and one-third of atenolol dose. Patients receiving beta-blockers other than carvedilol, bisoprolol, metoprolol, and atenolol were excluded from the analysis of beta-blocker doses. Since the maximum approved dose of carvedilol in Japan is 20 mg, carvedilol equivalent dose ≥50% of the maximum approved dose, 10 mg, was defined as a high dose, while a carvedilol equivalent dose of <10 mg was defined as a low dose.

The primary outcome measure was all-cause death during the index hospitalization. Secondary outcome measures were cardiovascular death, noncardiovascular death, and SCD during the index hospitalization. Death was considered cardiovascular in origin unless obvious noncardiovascular causes were identified. Cardiovascular death included death related to HF, death related to stroke, sudden death, and death from other cardiovascular causes. Sudden cardiac death was defined as an instantaneous, unexpected death in a previously stable patient.

Statistical Analysis

Categorical variables are presented as numbers (%). Continuous variables are presented as mean±standard deviation or median with interquartile range (IQR). Comparisons between patients with and without beta-blockers were performed using the chi-squared test for categorical variables and Student *t* test or Wilcoxon rank-sum test for continuous variables. To identify clinical characteristics associated with beta-blocker use at admission, we developed a multivariable logistic regression model in which we chose 20 clinically relevant factors potentially affecting beta-blocker use, as shown in Table 1.

We also developed 2 multivariable logistic regression models to explore the effects of beta-blocker use at admission on in-hospital events. In model 1, we used 23 clinically relevant factors to adjust for baseline clinical characteristics. Twenty factors were consistent with our previous reports,[14] and we added 3 more factors relevant to the present analysis (New York Heart Association [NYHA] functional class IV, the use of intravenous inotropic agents, and the prior use of angiotensin-converting enzyme inhibitors [ACEI]/angiotensin II receptor blockers [ARB]), as listed in Table 1. In model 2, we replaced systolic blood pressure <90 mm Hg, eGFR <30 mL/min per 1.73 m^2, and NYHA functional class IV with ADHERE (Acute Decompensated Heart Failure National Registry) risk model.[15] Other variables are the same as in model 1. In the multivariable logistic regression model, we presented the effects of beta-blocker use at hospitalization on in-hospital death, cardiovascular death, noncardiovascular death, and SCD as adjusted odds ratios (ORs) with their 95% CIs.

We also evaluated the effects of high- and low-dose beta-blockers relative to no beta-blocker use in the same multivariable logistic regression model with dummy variables. When assessing the dose status on the outcomes, we used the same multivariable logistic regression model and performed the test for trend, including beta-blocker use as continuous variables (0, no beta-blocker use; 1, low dose; 2, high dose).

For the post hoc subgroup analyses, we selected those subgroups related to the formal indications for beta-blocker use, such as LVEF <40%, myocardial infarction, and history of atrial fibrillation because clinical benefits were assumed to be present in these subgroups, and these subgroup factors might be appropriate for evaluating the consistency of effects of beta-blocker use. We assessed the interactions between the subgroup factors and the effect of beta-blocker use in multivariate logistic models.

All statistical analyses were conducted with JMP 11.2.1 (SAS Institute, Cary, NC). A two-tailed $P<0.05$ was considered statistically significant.

RESULTS

Baseline Clinical Characteristics and Medications at Admission

Among 3817 patients without ACS included in this study, 1512 patients were receiving beta-blockers at

Table 1. Baseline Characteristics

	Entire Study Population (n=3817)	With BBs (n=1512)	Without BBs (n=2305)	*P* Value	No. of Patients Analyzed
Demographics					
Age, y	81 (72–86)	80 (71–85)	81 (73–87)	<0.001	3817
Age ≥80 y*,†	2049 (53.7)	767 (50.7)	1282 (55.6)	0.003	
Women*,†	1731 (45.4)	664 (43.9)	1067 (46.3)	0.15	3817
BMI, kg/m^2	22.8±4.5	23.1±4.5	22.5±4.5	<0.001	3611
BMI <22 kg/m^2*,†	1710 (47.4)	629 (43.3)	1081 (50.1)	<0.001	
Medical history					
Prior hospitalization due to HF*,†	1409 (37.7)	822 (55.2)	587 (26.1)	<0.001	3817
Atrial fibrillation/flutter*,†	1649 (43.2)	769 (50.9)	880 (38.2)	<0.001	3817
Hypertension*,†	2735 (71.7)	1106 (73.2)	1629 (70.7)	0.10	3817
Diabetes mellitus*,†	1385 (36.3)	615 (40.7)	770 (33.4)	<0.001	3817
Dyslipidemia	1428 (37.4)	689 (45.6)	739 (32.1)	<0.001	3817
Prior myocardial infarction*,†	848 (22.2)	469 (31.0)	379 (16.4)	<0.001	3817
Current smoking*	430 (11.5)	158 (10.6)	272 (12.1)	0.18	3817
Prior stroke*	625 (16.4)	246 (16.3)	379 (16.4)	0.89	3817
Ventricular tachycardia/ fibrillation†	160 (4.2)	121 (8.0)	39 (1.7)	<0.001	3817
Chronic kidney disease‡	1707 (44.7)	776 (51.3)	931 (40.4)	<0.001	3817
On chronic hemodialysis	33 (0.9)	15 (1.0)	18 (0.8)	0.49	3817
Malignancy	554 (14.5)	216 (14.3)	338 (14.7)	0.75	3817
COPD†	320 (8.4)	112 (7.4)	208 (9.0)	0.08	3817
Asthma†	232 (6.1)	70 (4.6)	162 (7.0)	0.002	3817
Chronic lung disease*	518 (13.6)	172 (11.4)	346 (15.0)	0.001	3817
Dementia†	733 (19.2)	250 (16.5)	483 (21.0)	<0.001	3817
Prior catheter ablation	136 (3.6)	97 (6.4)	39 (1.7)	<0.001	3817
Prior pacemaker implantation	250 (6.6)	118 (7.8)	132 (5.7)	0.01	3817
Prior ICD implantation	123 (3.2)	104 (6.9)	19 (0.8)	<0.001	3817
Prior CRT implantation	82 (2.2)	68 (4.5)	14 (0.6)	<0.001	3817
Social backgrounds					
With occupation	457 (12.0)	172 (11.4)	285 (12.4)	0.36	3817
Public assistance	225 (5.9)	89 (5.9)	136 (5.9)	0.99	3817
Living alone*	815 (21.4)	326 (21.6)	489 (21.2)	0.80	3817
Institution for aged or hospital	268 (7.0)	83 (5.5)	185 (8.0)	0.002	3817
Daily life activities					3778
Ambulatory*,†	2947 (78.0)	1190 (79.2)	1757 (77.2)	0.01	
Use of wheelchair (outdoor only)	295 (7.8)	125 (8.3)	170 (7.5)		
Use of wheelchair (outdoor and indoor)	372 (9.9)	141 (9.4)	231 (10.2)		
Bedridden	164 (4.3)	47 (3.1)	117 (5.1)		
Underlying heart disease				<0.001	3817
Coronary artery disease	1088 (28.5)	549 (36.3)	539 (23.4)		
Valvular heart disease	819 (21.5)	267 (17.7)	552 (24.0)		
Hypertensive heart disease	985 (25.8)	348 (23.0)	637 (27.6)		
Cardiomyopathy†	520 (13.6)	240 (15.9)	280 (12.2)		
Other	405 (10.6)	108 (7.1)	297 (12.9)		
LVEF, %	46.3±16.4	45.6±16.5	46.8±16.4	0.03	3681

(*Continued*)

Table 1. Continued

	Entire Study Population (n=3817)	With BBs (n=1512)	Without BBs (n=2305)	*P* Value	No. of Patients Analyzed
LVEF <40%*,†	1441 (37.9)	593 (39.3)	848 (37.0)	0.15	
Vital signs at presentation					
HR, bpm	96±28	92±25	98±29	<0.001	3787
HR <60 bpm*	313 (8.3)	124 (8.3)	189 (8.3)	1.00	
SBP, mm Hg	148±35	143±35	151±35	<0.001	3804
SBP <90 mm Hg*	108 (2.8)	64 (4.3)	44 (1.9)	<0.001	
DBP, mm Hg	85±24	82±22	86±25	<0.001	
Atrial fibrillation/flutter	1422 (37.3)	592 (39.2)	830 (36.1)	0.049	3810
NYHA functional class IV*	1798 (47.3)	688 (45.6)	1110 (48.5)	0.07	3798
Cold profile	662 (17.6)	289 (19.3)	373 (16.4)	0.02	3772
Admission laboratory values					
BNP, pg/mL	721.4 (403.5–1295.7)	749.0 (435.0–1292.0)	708.4 (386.2–1300.8)	0.07	3373
Creatinine, mg/dL	1.48±1.23	1.59±1.27	1.40±1.19	<0.001	3811
eGFR, mL/min per 1.73 m^2	45.7±23.5	42.0±21.3	48.2±24.5	<0.001	3811
eGFR <30 mL/min per 1.73 $m^{2*,†}$	1056 (27.7)	492 (32.6)	564 (24.5)	<0.001	
Blood urea nitrogen, mg/dL	29.3±17.1	30.7±17.3	28.4±16.9	<0.001	3807
Sodium, mmol/L	139±4	139±4	139±4	0.64	3805
Hyponatremia*	481 (12.6)	172 (11.4)	309 (13.5)	0.06	
Hemoglobin, g/dL	11.5±2.3	11.4±2.2	11.5±2.4	0.26	3810
Anemia*	2585 (67.9)	1055 (69.9)	1530 (66.5)	0.03	
Albumin, g/dL	3.5±0.5	3.5±0.5	3.4±0.5	0.001	3700
Albumin <3.0 g/dL	535 (14.5)	193 (13.2)	342 (15.3)	0.09	
Therapy					
NPPV	833 (21.8)	330 (21.8)	503 (21.8)	1.00	3817
Intubation	123 (3.2)	33 (2.2)	90 (3.9)	0.003	3817
Intravenous inotropic use*	746 (19.5)	315 (20.8)	431 (18.7)	0.10	3817
Medications at admission					
ACEI	466 (12.2)	295 (19.5)	171 (7.4)	<0.001	3817
ARB	1322 (34.6)	604 (40.0)	718 (31.2)	<0.001	3817
ACEI or ARB*,†	1743 (45.7)	875 (57.9)	868 (37.7)	<0.001	3817
MRA†	720 (18.9)	392 (25.9)	328 (14.2)	<0.001	3817
Loop diuretics	1927 (50.5)	1042 (68.9)	885 (38.4)	<0.001	3817
Pimobendan†	116 (3.0)	86 (5.7)	30 (1.3)	<0.001	3817
Digitalis†	258 (6.8)	106 (7.0)	152 (6.6)	0.62	3817
Amiodarone	170 (4.5)	124 (8.2)	46 (2.0)	<0.001	3817

Continuous variables are shown as mean±SD or median (interquartile range) and categorical variables are shown as number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; BMI, body mass index; BNP, B-type natriuretic peptide; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NPPV, noninvasive positive pressure ventilation; NYHA, New York Heart Association; and SBP, systolic blood pressure.

*The multivariable logistic regression models for in-hospital events.

†The multivariable logistic regression model for beta-blocker use at admission.

‡Chronic kidney disease was defined as eGFR <60 mL/min per 1.73 m^2 at admission.

admission for the index ADHF hospitalization, while 2305 patients were not. (Table 1, Figure 1) Patients receiving beta-blockers at admission were slightly but significantly younger, had higher body mass index, and more often had a history of HF hospitalization, atrial fibrillation or flutter, diabetes mellitus, myocardial infarction, ventricular arrhythmia, and chronic kidney disease than those not receiving beta-blockers at admission. Patients receiving beta-blockers less often had bronchial asthma or dementia than those not

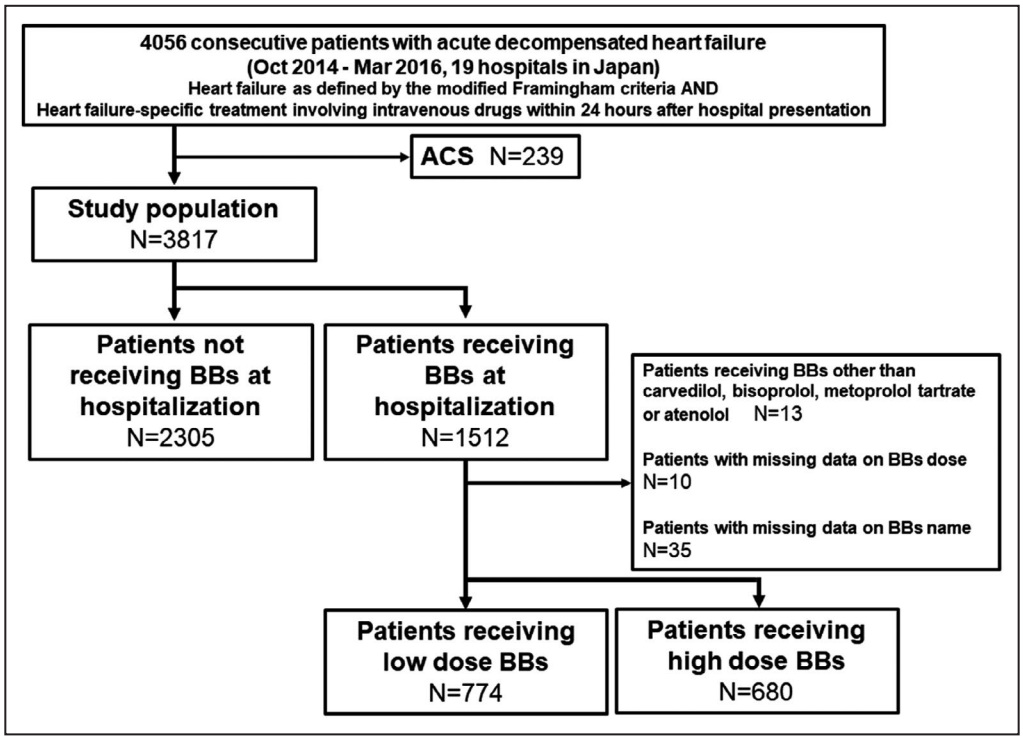

Figure 1. Flow diagram of study patients.
High-dose BBs were defined as carvedilol equivalent doses ≥10 mg, while low-dose BBs were defined as carvedilol equivalent doses <10 mg. The carvedilol-equivalent dose was 5 times the dose of bisoprolol, one-fifth of the dose of metoprolol tartrate, and one-third of atenolol dose. ACS indicates acute coronary syndrome; and BB, beta-blocker.

receiving beta-blockers at admission. The living status and daily life activities did not differ between the 2 groups. The prevalence of patients with LVEF <40% was comparable in the 2 groups. However, LVEF was slightly but significantly lower in patients receiving beta-blockers than those not receiving beta-blockers at admission. Patients receiving beta-blockers at admission more often presented with a cold profile and significantly lower blood pressure and heart rate than those not receiving beta-blockers at admission, although the prevalence of NYHA functional class IV was not different between them. The level of B-type natriuretic peptides on admission was comparable in the 2 groups (Figure S1). Patients receiving beta-blockers at admission had worse renal function as indicated by higher serum creatinine, lower eGFR, and higher blood urea nitrogen than those not receiving beta-blockers at admission. The prevalence of noninvasive positive pressure ventilation use and intravenous inotropic use were comparable in the 2 groups, while patients not receiving beta-blockers at admission more often had undergone endotracheal intubation than those receiving beta-blockers at admission. To compare the severity of the disease in each group, patients were stratified with ADHERE risk model[15] (Table S1). Less patients with beta-blockers at admission were classified as low risk than patients without beta-blockers (63.4% versus 73.4%, $P<0.001$). Patients receiving beta-blockers at admission more often had received ACEI or ARB, mineralocorticoid receptor antagonists, loop diuretics, pimobendan, and amiodarone than those not receiving beta-blockers at admission.

Details of Beta-Blockers Used

Among the 1512 patients receiving beta-blockers at admission, 58.7% were receiving carvedilol (median daily total dose: 5 mg [IQR: 2.5–10 mg]) and 33.5% were receiving bisoprolol (median daily total dose: 2.5 mg [IQR: 1.25–5 mg]) (Table 2). Thus, more than 90% of beta-blockers were evidence-based beta-blockers. As maximum approved dose of carvedilol is 20 mg and that of bisoprolol is 5 mg in Japan,[16] daily total dose was much lower than doses used in other studies conducted outside Japan. After excluding 58 patients with missing a beta-blocker dose or beta-blockers unconvertible to carvedilol equivalent doses, 774 patients received low-dose beta-blockers, and 680 patients received high dose beta-blockers (Figure 2 and Table S2). We had no data regarding beta-blocker withdrawal during hospitalization. However, among 1445 patients receiving beta-blockers at admission and were discharged alive, 1289 patients (89.2%) received beta-blockers at discharge

Table 2. Beta-Blockers Used at Hospitalization

	No. of Patients (%)	Daily Total Dose (mg)
Carvedilol	888 (58.7)	5 (2.5–10)
Bisoprolol	507 (33.5)	2.5 (1.25–5)
Atenolol	35 (2.3)	50 (25–50)
Metoprolol tartrate	34 (2.2)	40 (20–60)
Others	13 (0.9)	
Names missing	35 (2.3)	

Beta-blocker dose was expressed as median (interquartile range). Others included arotinolol, betaxolol, propranolol, nipradilol, pindolol, and celiprolol. The beta-blocker dose was missing in 10 patients (carvedilol: 3 patients, bisoprolol: 5 patients, and metoprolol: 1 patient).

(Table S3). Among the 2130 patients not receiving beta-blockers at admission and were discharged alive, 1057 patients (49.6%) received beta-blockers at discharge. Beta-blockers were started on the fifth hospital day as median (IQR 2–10 days).

Factors Associated With the Use of Beta-Blockers at Admission

Among the 20 clinically relevant variables derived from the baseline characteristics and medications, factors independently associated with beta-blocker use at admission were previous HF hospitalization, history of ventricular tachyarrhythmias, use of pimobendan, history of myocardial infarction, use of ACEI or ARB, history of atrial fibrillation, cardiomyopathy, use of mineralocorticoid receptor antagonist, and eGFR <30 mL/min per 1.73 m^2. In contrast, factors independently associated with no beta-blockers use were asthma, chronic obstructive pulmonary disease, lower body mass index, dementia, older age, and LVEF <40% (Table 3).

In-Hospital Outcomes

Patients receiving beta-blockers at admission had a significantly lower incidence of in-hospital death than those not receiving beta-blockers at admission (4.4% versus 7.6%, P<0.001) (Table 4). Even after adjusting for confounders, the excess risk of patients receiving beta-blockers at admission relative to those not receiving beta-blockers at admission remained significant for in-hospital death (adjusted OR, 0.41, 95% CI, 0.27–0.60 in model 1, adjusted OR, 0.42, 95% CI, 0.28–0.61 in model 2). Patients receiving beta-blockers at admission had a significantly lower incidence of both cardiovascular and noncardiovascular deaths (3.4% versus 5.4%, P=0.003, and 1.1% versus 2.2%, P=0.008, respectively) and a numerically lower incidence of sudden cardiac death (0.2% versus 0.43%, P=0.21) than those not receiving beta-blockers at admission. After adjusting for confounders, the lower risks of patients receiving beta-blockers at admission relative to those not receiving beta-blockers at admission were significant for cardiovascular death (adjusted OR, 0.43; 95% CI, 0.26–0.66 in model 1; adjusted OR, 0.41; 95% CI, 0.26–0.65 in model 2) and noncardiovascular death (adjusted OR, 0.44; 95% CI, 0.21–0.86 in model 1; adjusted OR, 0.49; 95% CI 0.24–0.94 in model 2) (Table 4). Details of causes of noncardiovascular death were shown in Table S4.

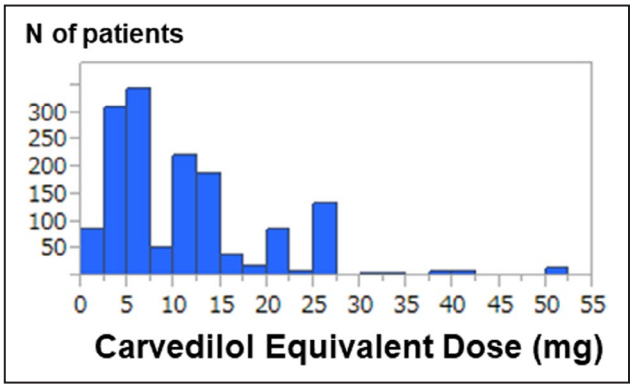

Figure 2. Distribution of the doses of BBs.
The doses of BBs were indicated as the carvedilol equivalent doses. BB indicates beta-blocker.

The Dose of Beta-Blockers and In-Hospital Death

Both patients receiving low-dose beta-blockers and those receiving high dose beta-blockers had a significantly lower risk of in-hospital death than those not receiving beta-blockers (adjusted OR, 0.43, 95% CI, 0.27–0.68, and adjusted OR, 0.35, 95% CI, 0.19–0.61, respectively) (Table 5). The trend from no beta-blocker use to low dose and high dose on the risk for in-hospital mortality was significant (P<0.001).

Difference Between Evidence-Based Beta-Blockers and Non-Evidence-Based Beta-Blockers

Evidence-based beta-blockers available in Japan are carvedilol and bisoprolol. Among patients receiving beta-blockers at admission, 92.3% of patients received evidence-based beta-blockers. Although number of patients receiving non-evidence-based beta-blockers were limited, there was no significant difference in in-hospital mortality between those with evidence-based beta-blockers and those with non-evidence-based beta-blockers (Table S5).

Post Hoc Subgroup Analysis

In the post hoc subgroup analyses, there was a significant interaction between the subgroup factor of previous HF hospitalization and the effect of

Table 3. Factors Associated With Beta-Blocker Use at Admission

	Adjusted OR	95% CI	*P* Value
Asthma	0.51	0.37–0.71	<0.001
COPD	0.74	0.55–0.97	0.03
BMI <22 kg/m^2	0.75	0.64–0.88	<0.001
Digitalis	0.77	0.57–1.05	0.09
Dementia	0.79	0.63–0.97	0.03
Age ≥80 y	0.81	0.68–0.95	0.01
LVEF <40%	0.81	0.68–0.97	0.02
Diabetes mellitus	0.99	0.84–1.16	0.86
Hypertension	1.06	0.88–1.27	0.55
Ambulatory	1.07	0.88–1.31	0.50
Women	1.08	0.92–1.28	0.33
eGFR <30 mL/min per 1.73 m^2	1.26	1.06–1.49	0.01
MRA use	1.36	1.12–1.66	0.002
Cardiomyopathy	1.58	1.24–2.02	<0.001
History of AF	1.63	1.39–1.90	<0.001
ACEI/ARB use	2.07	1.77–2.42	<0.001
Prior myocardial infarction	2.21	1.83–2.68	<0.001
Pimobendan use	2.22	1.39–3.63	<0.001
History of VT/VF	2.67	1.78–4.07	<0.001
Previous HF hospitalization	2.74	2.33–3.22	<0.001

Multivariable logistic regression analysis was used to identify the factors independently associated with beta-blocker use at admission. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; VF, ventricular fibrillation; and VT, ventricular tachycardia.

beta-blocker use on in-hospital death (Figure 3). The magnitude of the effect of beta-blocker use for in-hospital death was greater in patients with previous HF hospitalization than in patients without previous HF hospitalization. There were no interactions between these subgroup factors other than previous HF hospitalization, and the effect of beta-blocker use on in-hospital death (Figure 3).

DISCUSSION

The main findings of this study were as follows: (1) factors independently associated with beta-blocker use at admission were previous HF hospitalization, history of ventricular tachyarrhythmias, use of pimobendan, history of myocardial infarction, use of ACEI or ARB, history of atrial fibrillation, cardiomyopathy, use of mineralocorticoid receptor antagonist, and eGFR <30 mL/min per 1.73 m^2; and (2) the lower in-hospital mortality risk of patients receiving beta-blockers at admission relative to those not receiving beta-blockers at admission was significant, regardless of ischemic etiology and LVEF.

Few studies have reported the role of beta-blockers at admission in patients with ADHF. In the post hoc analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, which assessed pulmonary artery catheter use among 432 patients admitted with ADHF, in-hospital mortality was 1.5% on admission beta-blocker therapy compared with 2.4% patients not on beta-blocker therapy (*P*=0.48).[17] In the post hoc analysis of the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure), which randomized 949 patients to milrinone or placebo, in-hospital mortality was 2.4% in patients receiving beta-blockers at admission compared with 3.3% in patients not receiving beta-blockers (*P*=0.49).[18] These 2 studies enrolled a small number of patients with extremely low LVEF (around 25%). Therefore, they might not have enough statistical power and generalizability.

Abi Khalil et al reported the results of an extensive HF registry of the middle east,[19] which enrolled 8066 patients admitted with ADHF in a single center. In this registry, the in-hospital mortality rate in patients treated with beta-blockers at admission

Table 4. Primary and Secondary Outcomes

	With BBs No. of Patients With Event/No. of Patients at Risk	Without BBs No. of Patients With Event/No. of Patients at Risk	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI) Model 1	*P* Value	Adjusted OR (95% CI) Model 2	*P* Value
All cause death	67/1512 (4.4%)	175/2305 (7.6%)	0.56 (0.42–0.75)	<0.001	0.41 (0.27–0.60)	<0.001	0.42 (0.28–0.61)	<0.001
Cardiovascular death	51/1512 (3.4%)	125/2305 (5.4%)	0.61 (0.43–0.84)	0.003	0.43 (0.26–0.66)	<0.001	0.41 (0.26–0.65)	<0.001
Noncardiovascular death	16/1512 (1.1%)	50/2305 (2.2%)	0.48 (0.27–0.83)	0.008	0.44 (0.21–0.86)	0.02	0.49 (0.24–0.94)	0.03
Sudden death	3/1512 (0.20%)	10/2305 (0.43%)	0.46 (0.10–1.49)	0.21	0.19 (0.02–0.99)	0.049	0.23 (0.03–1.09)	0.07

Risk adjusting variables in model 1 were shown in Table 1 as variables with *. Risk adjusting variables in model 2 included ADHERE (Acute Decompensated Heart Failure National Registry) risk model instead of Siastolic blood pressure (SBP) <90 mm Hg, glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2, and New York Heart Association (NYHA) class IV. Other variables are the same as in model 1. As for sudden death, the trend was mostly consistent with cardiovascular and noncardiovascular deaths. BB indicates beta-blocker; and OR, odds ratio.

Table 5. BB Dose and In-Hospital Mortality

	No. of Patients With In-Hospital Death/No. of Patients at Risk	BB Dose (mg)	Unadjusted OR (95% CI)	*P* Value	*P* Value for Trend	Adjusted OR (95% CI)	*P* Value	*P* Value for Trend
No BBs	175/2305 (7.6%)	0	1 (reference)		<0.001	1 (reference)		<0.001
Low dose BBs	42/774 (5.4%)	5.0 (2.5–5.0)	0.70 (0.49–0.98)	0.04		0.43 (0.27–0.68)	<0.001	
High dose BBs	22/680 (3.2%)	12.5 (10–20)	0.41 (0.25–0.63)	<0.001		0.35 (0.19–0.61)	<0.001	

Beta-blocker dose was expressed as the carvedilol equivalent dose. Carvedilol equivalent dose ≥10 mg was defined as high dose, while carvedilol equivalent dose <10 mg was defined as low dose. The effects of the high dose and low dose of the BB to no BB were evaluated in the multivariable logistic regression model with dummy variables. Risk-adjusting factors in model 1 were used. When assessing the trend among groups, we used the same multivariable logistic regression model including the status of the beta-blocker use as continuous variables (0, no use; 1, low dose; 2, high dose) to test the incremental impact of the dose of BB on the outcome. BB indicates beta-blocker; and OR, odds ratio.

was significantly lower than that in patients not treated with beta-blockers at admission (3.6% versus 14.4%). After adjusting for confounders, the odds ratio of patients with versus without beta-blockers at admission was 0.18 (95% CI, 0.23–0.61, *P*=0.001) for in-hospital death. However, it was an old and long-lasting registry starting in 1991 and included when beta-blocker therapy was not widely implemented. Therefore, the conclusion might not apply to current patients. Furthermore, one-third of the patients were accompanied by ACS, and the benefit of beta-blockers might be through the reduction of acute ischemia in patients with ACS. Another report from the Italian Survey on Acute Heart Failure revealed the beneficial role of beta-blockers in patients admitted for worsening HF.[20] In-hospital mortality was 2.8% in 362 patients receiving beta-blockers at admission and continuing during hospitalization compared with 10.1% in 811 patients not receiving beta-blockers at admission and not starting during hospitalization. The association between beta-blocker use and lower in-hospital mortality was significant after adjusting for clinical, hemodynamic, and therapeutic variables. Although it was a registry in a real-world setting like the present study, it was performed in 2003 and the enrolled patients were relatively younger. In recent years, HF patients in developed countries have become older with a high prevalence of HF with preserved ejection fraction. Therefore, more studies are needed to evaluate the role of beta-blocker use at admission in the more current population of ADHF.

In the present study, we demonstrated the significantly lower in-hospital mortality risk of patients receiving beta-blockers at admission relative to those not receiving beta-blockers at admission, regardless of ischemic etiology and LVEF, using the current extensive database of ADHF.

In previous large clinical trials of chronic HFrEF, death from pump failure was reduced by beta-blockers in addition to the reduction of SCD. Death from pump failure decreased by 78% in US Carvedilol,[3] by 26% in CIBIS II (Cardiac Insufficiency Bisoprolol Study),[4] and by 49% in MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure).[5] Our findings in patients with HFrEF are in line with previous studies showing the beneficial effects of beta-blockers on pump failure death in the ADHF situation. Also, in the present study, the association of beta-blockers with lower in-hospital mortality was observed in patients with LVEF ≥40%.

We postulate 3 possible underlying mechanisms by which beta-blockers were associated with favorable in-hospital outcomes. First, beta-blockers might suppress the activated sympathetic nervous system in patients with ADHF. Patients receiving beta-blockers at admission presented significantly lower blood pressure and heart rate, suggesting that activation of sympathetic nervous system might have been suppressed. The sympathetic nervous system's activation causes both arteriolar and venous vasoconstriction, thereby increasing both preload and afterload.[21] Increased preload progresses congestion, and increased afterload causes afterload mismatch, leading to rash pulmonary edema. Thus, ADHF worsens in the vicious cycle, which might be attenuated by beta-blockers. Second, prior use of beta-blockers may suppress the occurrence of atrial fibrillation in patients with ADHF. Almost half of the patients taking beta-blockers at admission had a history of atrial fibrillation; however, <40% of them presented with atrial fibrillation at hospital admission. Third, one of the factors associated with the use of beta-blocker included the history of HF hospitalization and ventricular arrhythmias. Thus, the prophylactic effect on SCD might be another mechanism of beta-blockers, although higher use of implantable cardioverter defibrillator in patients receiving beta-blockers might be associated with lower incidence of sudden death.

Unexpectedly, the risk of noncardiovascular death was lower in patients with beta-blockers. As shown in Table S5, the lower risk of noncardiovascular death in patients with beta-blockers derived from death by infection. Previous studies demonstrated the association

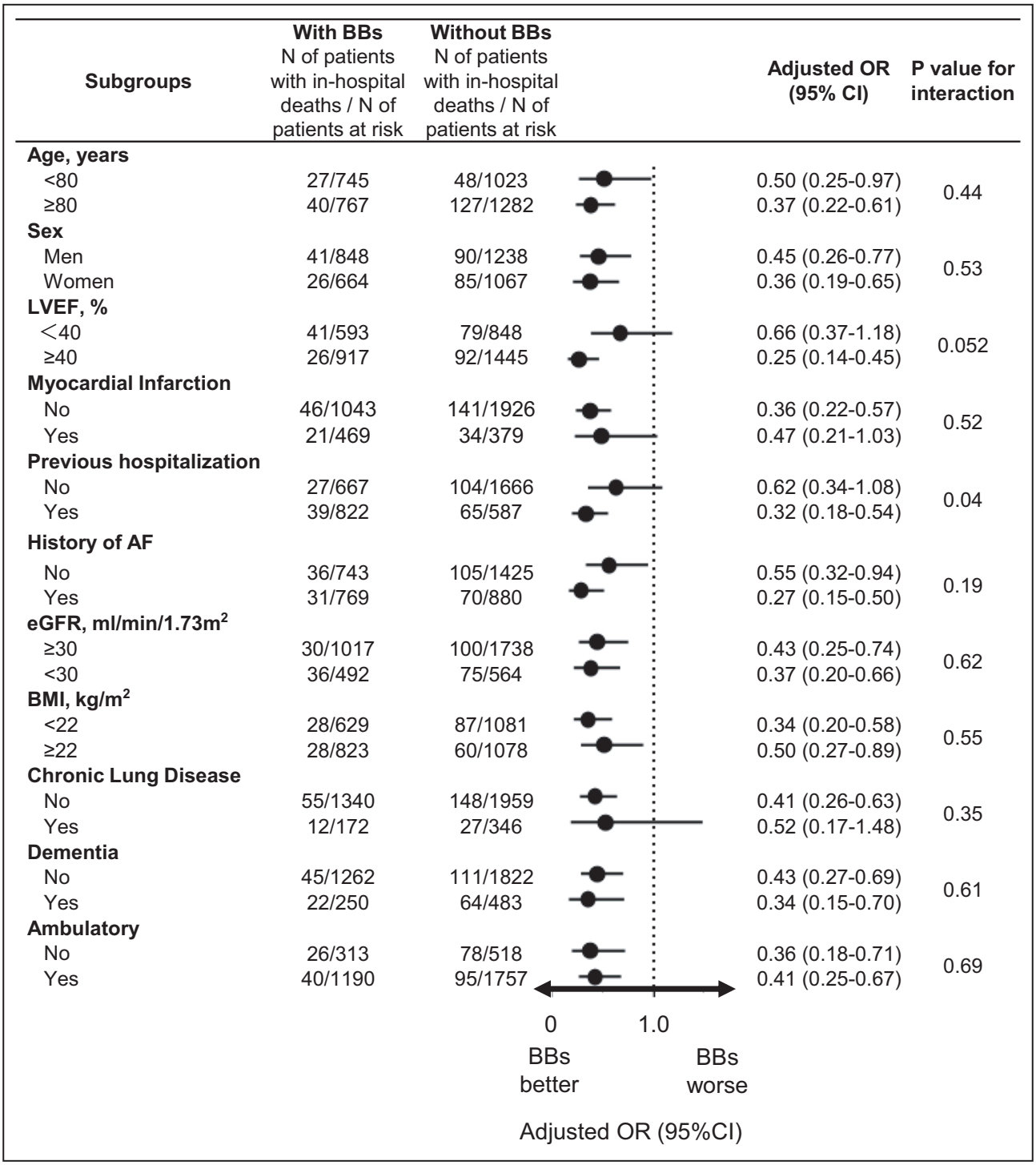

Figure 3. Subgroup analyses.
Risk-adjusting factors in model 1 were used. AF indicates atrial fibrillation; BB, beta-blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and OR, odds ratio.

between premorbid beta-blocker exposure and lower mortality in sepsis.[22] Although the mitigation of catecholamine excess might be beneficial in patients with ADHF and infection, this result may be hypothesis-generating and needs to be evaluated by future clinical and basic studies.

Limitations

This study was a post hoc analysis, and the status of beta-blocker administration during hospitalization was missing. However, 89.2% of patients taking beta-blockers at admission received beta-blockers at discharge, suggesting that most patients continued to receive beta-blockers in

the acute phase of ADHF. Up to 50% of the patients who were not receiving beta-blockers at admission did receive beta-blockers by the time of discharge. Starting beta-blockers during hospitalization in patients not receiving beta-blockers at admission would diminish the effect of beta-blockers. Nonetheless, beta-blocker-use at admission was significantly associated with lower in-hospital mortality. This might suggest beta-blocker use at very early phase of acute decompensation is crucial. The present study is observational, and there may be an unadjusted bias related to beta-blocker use before admission. Patients receiving beta-blockers at admission also more often received other evidence-based HF medications such as ACEI/ARB, mineralocorticoid receptor antagonist, and loop diuretics than patients not receiving beta-blockers at admission. Therefore, we could not deny the beneficial effect of these HF medications other than beta-blockers, although we included ACEI/ARB as a risk-adjusting variable in the multivariable logistic regression analysis. This study also indicated only an association and not a causal relationship between beta-blocker use and in-hospital mortality. A prospective study on beta-blocker use in specific high-risk groups for HF is warranted to determine beta-blockers' protective roles at the onset of ADHF.

CONCLUSION

Beta-blocker use at admission is associated with lower in-hospital mortality in patients with ADHF.

ARTICLE INFORMATION

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Supplementary Material

Appendix S1
Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

APPENDIX

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Table S1. Risk stratification by ADHERE risk model.

ADHERE Risk Stratification		With BBs (N=1512)	Without BBs (N=2305)	P value
Low risk	BUN<43mg/dl SBP≥115mmHg	958 (63.4%)	1691 (73.4%)	<0.001
Intermediate risk 3	BUN<43mg/dl SBP<115mmHg	246 (16.3%)	233 (10.1%)	
Intermediate risk 2	BUN≥43mg/dl SBP≥115mmHg	209 (13.8%)	274 (11.9%)	
Intermediate risk 1	BUN≥43mg/dl, SBP<115mmHg Cr<2.75mg/dl	66 (4.4%)	64 (2.8%)	
High risk	BUN≥43mg/dl SBP<115mmHg Cr≥2.75mg/dl	22 (1.5%)	31 (1.3%)	

Variables are shown as number (percentage).

ADHERE, Acute Decompensated Heart Failure National Registry; BB, Beta blocker; BUN, Blood Urea Nitrogen; SBP, Systolic Blood Pressure; Cr, Creatinine.

Table S2. Baseline Characteristics according to beta blocker dose.

	No BBs (N=2305)	Low dose BBs (N=774)	High dose BBs (N=680)	P value
Demographics				
Age, years	81 (73-87)	81 (72-86)	79 (71-84)	<0.001
Age ≥80 years *†	1282 (55.6)	416 (53.8)	319 (46.9)	<0.001
Female *†	1067 (46.3)	356 (46.0)	281 (41.3)	0.07
BMI, kg/m^2	22.5 ± 4.5	22.4 ± 4.2	23.9 ± 4.5	<0.001
BMI <22 kg/m^2 *†	1081 (50.1)	366 (49.4)	242 (37.0)	<0.001
Medical history				
Prior hospitalization due to HF *†	587 (26.1)	427(56.1)	373 (55.5)	<0.001
Atrial fibrillation/flutter *†	880 (38.2)	372 (48.1)	369 (54.3)	<0.001
Hypertension *†	1629 (70.7)	542 (70.0)	510 (75.0)	0.06
Diabetes mellitus *†	770 (33.4)	292 (37.7)	302 (44.4)	<0.001
Dyslipidemia	739 (32.1)	355 (45.9)	308 (45.3)	<0.001
Prior myocardial infarction *†	379 (16.4)	273 (35.3)	181 (26.6)	<0.001
Current smoking *	272 (12.1)	77 (10.1)	73 (10.9)	0.31
Stroke *	379 (16.4)	124 (16.0)	111 (16.3)	0.96
VT/VF †	39 (1.7)	51 (6.6)	68 (10.0)	<0.001
Chronic kidney disease #	931 (40.4)	407 (52.6)	340 (50.0)	<0.001
On chronic hemodialysis	18 (0.8)	5 (0.7)	10 (1.5)	0.22
Malignancy	338 (14.7)	117 (15.1)	92 (13.7)	0.72
COPD †	208 (9.0)	59 (7.6)	51 (7.5)	0.29
Asthma †	162 (7.0)	29 (3.8)	37 (5.4)	0.002
Chronic lung disease *	346 (15.0)	81 (10.5)	85 (12.5)	0.003
Dementia †	483 (21.0)	161 (20.8)	77 (11.3)	<0.001
Prior catheter ablation	39 (1.7)	41 (5.3)	55 (8.1)	<0.001
Prior pacemaker implantation	132 (5.7)	69 (8.9)	45 (6.6)	0.01
Prior ICD implantation	19 (0.8)	36 (4.7)	66 (9.7)	<0.001
Prior CRT implantation	14 (0.6)	32 (4.1)	34 (5.0)	<0.001
Social backgrounds				
With occupation	285 (12.4)	68 (8.8)	94 (13.8)	0.005
Public assistance	136 (5.9)	44 (5.7)	45 (6.6)	0.73
Living alone *	489 (21.2)	170 (22.0)	147 (21.6)	0.90
Institution for aged or hospital	185 (8.0)	48 (6.2)	34 (5.0)	0.01
Daily life activities				
Ambulatory *†	1757 (77.2)	592 (77.1)	557 (82.3)	<0.001

Use of wheelchair [outdoor only]	170 (7.5)	67 (8.7)	53 (7.8)	
Use of wheelchair [outdoor and indoor]	231 (10.2)	88 (11.5)	48 (7.1)	
Bedridden	117 (5.1)	21 (2.7)	19 (2.8)	
Underlying heart disease				<0.001
Ischemic heart disease	539 (23.4)	308 (39.8)	226 (33.2)	
Valvular heart disease	552 (24.0)	156 (20.2)	98 (14.4)	
Hypertensive heart disease	637 (27.6)	143 (18.5)	184 (27.1)	
Cardiomyopathy †	280 (12.2)	114 (14.8)	121 (17.8)	
Others	297 (12.9)	53 (6.8)	51 (7.5)	
LVEF, %	46.8 ± 16.4	43.8 ± 16.2	46.9 ± 16.5	<0.001
LVEF<40% *†	848 (37.0)	341 (44.1)	238 (35.0)	<0.001
Vital signs at presentation				
Heart rate (HR), bpm	98 ± 29	94 ± 24	89 ± 26	<0.001
HR<60 bpm *	189 (8.3)	49 (6.4)	70 (10.3)	0.03
Systolic BP (SBP), mmHg	151 ± 35	141 ± 34	145 ± 36	<0.001
SBP<90 mmHg *	44 (1.9)	35 (4.6)	25 (3.7)	<0.001
Diastolic BP, mmHg	86 ± 25	82 ± 22	82 ± 22	<0.001
Atrial fibrillation/flutter	830 (36.1)	292 (37.8)	276 (40.7)	0.09
NYHA functional class IV *	1110 (48.5)	359 (46.4)	301 (44.3)	0.13
Cold Profile	373 (16.4)	160 (20.9)	122 (18.1)	0.02
Admission laboratory values				
BNP, pg/mL	708.4 (386.2-1300.8)	777.4 (441.6-1404.9)	734.8 (427.7-1202.8)	0.054
Creatinine, mg/dL	1.40 ± 1.19	1.57 ± 1.17	1.63 ± 1.39	<0.001
eGFR, mL/min/1.73 m^2	48.2 ± 24.5	41.2 ± 21.0	42.4 ± 21.6	<0.001
eGFR <30 mL/min/1.73 m^2 *†	564 (24.5)	267 (34.6)	214 (31.5)	<0.001
Blood urea nitrogen, mg/dL	28.4 ± 16.9	30.8 ± 16.8	30.9 ± 18.0	<0.001
Sodium, mmol/L	139 ± 4	139 ± 4	139 ± 4	0.88
Hyponatremia *	309 (13.5)	89 (11.5)	78 (11.5)	0.21
Hemoglobin, g/dL	11.5 ± 2.4	11.3 ± 2.2	11.5 ± 2.3	0.06
Anemia *	1530 (66.5)	555 (71.9)	462 (67.9)	0.02
Albumin, g/dl	3.4 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	<0.001
Albumin<3.0g/dl	342 (15.3)	101 (13.4)	84 (12.9)	0.21
Therapy				
NPPV	503 (21.8)	170 (22.0)	143 (21.0)	0.89
Intubation	90 (3.9)	15 (1.9)	16 (2.4)	0.007

Intravenous inotropic use *	431 (18.7)	192 (24.8)	113 (16.6)	<0.001
Medication at admission				
ACE-I	171 (7.4)	164 (21.2)	120 (17.7)	<0.001
ARB	718 (31.2)	265 (34.2)	309 (45.4)	<0.001
ACE-I or ARB *†	868 (37.7)	421 (54.4)	414 (60.9)	<0.001
MRA †	328 (14.2)	216 (27.9)	164 (24.1)	<0.001
Loop diuretics	885 (38.4)	558 (72.1)	451 (66.3)	<0.001
Pimobendan †	30 (1.3)	55 (7.1)	29 (4.3)	<0.001
Digitalis †	152 (6.6)	54 (7.0)	48 (7.1)	0.88
Amiodarone	46 (2.0)	60 (7.8)	60 (8.8)	<0.001

Continuous variables are shown as mean ± SD or median (interquartile range) and categorical variables are shown as number (percentage).

Variables with † were used in the multivariable logistic regression model for beta-blocker use at admission.

Variables with * were used in the multivariable logistic regression models for in-hospital events.

#Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m^2 at admission.

BB, beta blocker; BMI, body mass index; HF, heart failure; VT/VF, ventricular tachycardia/fibrillation; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, B-type natriuretic peptide, eGFR, estimated glomerular filtration rate; NPPV, non-invasive positive pressure ventilation; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.

Table S3. Beta-blocker use at discharge.

	With BBs (N=1512)	Without BBs (N=2305)
In-hospital death	67 (4.4%)	175 (7.6%)
Discharged alive	1445 (95.6%)	2130 (92.4%)
With BBs at discharge	1289/1445 (89.2%)	1057/ 2130 (49.6%)
Without BBs at discharge	156/ 1445 (10.8%)	1073/ 2130 (50.4%)

Variables are shown as number (percentage).

BB, beta blocker.

Table S4. Details of non-Cardiovascular death.

	Entire Study Population (N=3817)	With BBs (N=1512)	Without BBs (N=2305)	P value
All non-CV death	66 (1.7)	16 (1.1)	50 (2.2)	0.008
Infection	35 (0.92)	5 (0.33)	30 (1.3)	0.002
Respiratory failure	15 (0.39)	4 (0.26)	11 (0.48)	0.43
Malignancy	7 (0.18)	2 (0.13)	5 (0.22)	0.71
GI bleeding	5 (0.13)	3 (0.20)	2 (0.087)	0.39
Other non-CV causes	4 (0.10)	2 (0.13)	2 (0.087)	0.65

Variables are shown as number (percentage).

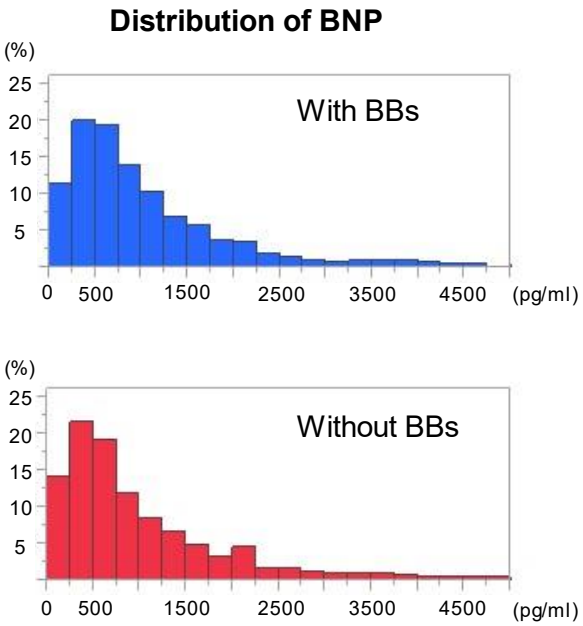
BB, beta blocker; CV, Cardiovascular; GI, Gastrointestinal.

Table S5. Comparison of evidence-based beta-blockers and non-evidence-based beta-blockers.

	With Evidence-based BBs N of patients with event/N of patients at risk	**With Non-Evidence-based BBs** N of patients with event/N of patients at risk	**Unadjusted OR* (95% CI)**	**P value**
All cause death	63/1395 (4.5%)	4/117 (3.4%)	0.74 (0.22-1.86)	0.57
Cardiovascular death	48/1395 (3.4%)	3/117 (2.6%)	0.74 (0.18-2.05)	0.60
Non-Cardiovascular death	15/1395 (1.1%)	1/117 (0.85%)	0.79 (0.04-3.97)	0.82
Sudden death	3/1395 (0.22%)	0/117 (0%)	N.D.	

ORs are expressed as the risk of patients with non-evidence-based BBs relative to those with evidence-based BBs.
Evidence-based BBs are carvedilol and bisoprolol. Non-evidence-based BBs are beta-blockers other than carvedilol and bisoprolol.
BB, Beta-blocker; OR, Odds ratio; CI, Confidence interval, N.D.; not determined.

Figure S1. Distribution of BNP.



BB, beta-blocker.