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Comparative Effects of Carvedilol vs Bisoprolol for Severe Congestive Heart Failure

– Special Reference to Atrial Fibrillation –

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Background: Although carvedilol and bisoprolol are effective medicines for the treatment of patients with heart failure (HF), only a few reports have compared their effects. This study was designed to compare the effects of them in patients with severe HF.

Methods and Results: A total of 655 consecutive patients with HF, categorized as New York Heart Association Class 3 or 4, were retrospectively investigated. Of these patients, 217 were administered β-blockers after admission and were divided into 2 groups (carvedilol, n=110; bisoprolol, n=107). No significant differences were observed in their characteristics between the 2 groups prior to the introduction of the β-blockers. After 18 months of follow-up, there were no significant differences in the survival and cardiac event-free rates between the 2 groups. In contrast, there were several significant differences in patients with atrial fibrillation (AF) (carvedilol, n=40; bisoprolol, n=43). The percent changes in heart rate and brain natriuretic peptide level improved significantly in the bisoprolol group than in the carvedilol group. Furthermore, more patients in the bisoprolol group were defibrillated from AF to sinus rhythm than those in the carvedilol group (48% vs 16%; P=0.03).

Conclusions: Our data suggest that the 2 β-blockers are equally effective in the improvement of severe HF, but bisoprolol shows favorable effects in patients with AF.

Key Words: Atrial fibrillation; Beta-blocker; Heart failure; Japanese

Heart failure (HF) is a serious disease in humans. Several treatments for HF have been developed and assessed in previous studies. For example, in 1975, Waagstein et al reported for the first time that β-blockers are an effective therapy for HF.[1] Following this report, many large-scale trials of β-blockers were conducted and treatment with these agents has been established as the primary therapy for HF.[2,3] Of the β-blocker class of drugs, carvedilol is a non-selective β-adrenergic receptor blocker that also induces α1-adrenergic receptor blockade and has been shown to improve the state of HF patients in many studies.[4–8] Bisoprolol is a highly selective β1-adrenergic receptor blocker and has been shown in many studies to be an effective treatment for HF patients as well.[9–11] Thus, many large-scale trials have confirmed that both these β-blockers are superior to placebo and other β-blockers, although only a few reports have compared their effects. Therefore, this study was designed to compare the effects of carvedilol and bisoprolol in patients with severe congestive HF in a single center.

Methods

Study Population

This study is based on data collected over a 36-month period (January 1, 2005 to January 1, 2008) from 655 consecutive acute decompensated HF (ADHF) patients who were admitted to our hospital with HF categorized as New York Heart Association (NYHA) Class 3 or 4. Patients were excluded from the study if they had acute coronary syndromes (ACS) including acute myocardial infarction, acute pneumonia, severe valvular disease, or end-stage renal disease that required dialysis therapy, and if they had already taken a β-blocker before admission or could not be started on β-blocker treatment until discharge. After discharge, the patients continued treatment with either carvedilol or bisoprolol, with the dose being carefully increased to their tolerance.

Procedures

The study was a retrospective, non-randomized, single center trial. Clinical data were obtained when their hemo-

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Table 1. Baseline Characteristics and Prescriptions on Admission

	Carvedilol (n=110)	Bisoprolol (n=107)	P-value
Sex (Female)	25 (23%)	30 (28%)	0.44
Age	68±12	66±12	0.24
BMI	24.6±5.0	24.8±4.3	0.85
Etiology of HF			
Ischemic	53 (48%)	52 (49%)	1
Non-ischemic	57 (52%)	55 (51%)	1
NYHA class			
Class 3	49 (45%)	47 (44%)	1
Class 4	61 (55%)	60 (56%)	1
AF	40 (36%)	43 (40%)	0.58
CHF	34 (31%)	29 (27%)	0.55
HT	93 (85%)	91 (85%)	1
DM	45 (41%)	38 (36%)	0.49
HL	51 (46%)	53 (50%)	0.68
Smoker	49 (45%)	58 (54%)	0.18
COPD	2 (2%)	3 (3%)	0.68
Digoxin	6 (5%)	5 (5%)	1
Diuretics	104 (95%)	103 (96%)	0.75
CCB	27 (25%)	31 (29%)	0.54
ACEI	31 (28%)	31 (29%)	1
ARB	54 (49%)	50 (47%)	0.79
Nitrate	15 (14%)	17 (16%)	0.70
Statin	27 (25%)	29 (27%)	0.76
Amiodarone	19 (17%)	18 (17%)	1
Aspirin	65 (59%)	66 (62%)	0.78
Ticlopidine	21 (19%)	23 (21%)	0.74
Warfarin	43 (39%)	39 (36%)	0.78
ICD	9 (8%)	6 (6%)	0.60
CRT	2 (2%)	1 (1%)	0.51

BMI, body mass index; HF, heart failure; NYHA, New York Heart Association; AF, atrial fibrillation; CHF, chronic heart failure; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; COPD, chronic obstructive pulmonary disease; CCB, Ca^{2+} entry blocker; ACEI, angiotensin coverting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICD, implantable cardioverter defibrillation; CRT, cardiac resynchronization therapy.
BMI is expressed as weight in kilograms divided by square of height in meters.

Table 2. Baseline Characteristics and Prescriptions of AF Patients on Admission

	Carvedilol (n=40)	Bisoprolol (n=43)	P-value
Type of AF			
Paroxysmal	10 (25%)	10 (23%)	1
Persistent	16 (40%)	18 (42%)	1
Permanent	10 (25%)	11 (26%)	1
Uncertain	4 (10%)	4 (9%)	1
Sex (Female)	8 (20%)	11 (26%)	0.61
Age	66±10	63±13	0.20
BMI	25.1±4.5	24.2±3.6	0.45
Etiology of HF			
Ischemic	21 (53%)	23 (53%)	1
Non-ischemic	19 (48%)	20 (47%)	1
NYHA class			
Class 3	17 (43%)	20 (47%)	0.83
Class 4	23 (58%)	23 (53%)	0.83
CHF	14 (35%)	13 (30%)	0.82
HT	32 (80%)	34 (79%)	1
DM	17 (43%)	18 (42%)	1
HL	21 (53%)	27 (63%)	0.38
Smoker	19 (48%)	22 (51%)	0.83
COPD	0 (0%)	1 (2%)	1
Digoxin	4 (10%)	4 (9%)	1
Diuretics	39 (98%)	42 (98%)	1
CCB	13 (33%)	14 (33%)	1
ACEI	11 (28%)	7 (16%)	0.29
ARB	18 (45%)	20 (47%)	1
Nitrate	4 (10%)	3 (7%)	0.71
Statin	13 (33%)	15 (35%)	1
Amiodarone	8 (20%)	9 (21%)	1
Aspirin	15 (38%)	20 (47%)	0.51
Ticlopidine	4 (10%)	2 (5%)	0.42
Warfarin	30 (75%)	30 (70%)	0.63
ICD	2 (5%)	3 (7%)	1
CRT	1 (3%)	0 (0%)	0.48

Abbreviations see in Table 1.
BMI is expressed as weight in kilograms divided by square of height in meters.

dynamic condition was stabilized before the induction of the β-blockers. The patients enrolled in the study were divided into 2 groups depending on the agent administered after admission: carvedilol (n=110) and bisoprolol (n=107). The choice of these agents was left to the discretion of the attending physician. The diagnosis of HF was made on the basis of the criteria recommended in the Framingham Heart Study. The diagnosis of atrial fibrillation (AF) was made by using Holter monitoring of 24 h. The following assessments were performed: evaluation of clinical symptoms, physical examinations, blood sample analyses, chest X-ray examinations, electrocardiography, and echocardiography. During each echocardiographic study, the left ventricular (LV) diastolic dimension (LVDd), LV systolic dimension (LVDs), interventricular septum thickness (IVST), posterior wall thickness (PWT), and left atrial dimension (LAD) were measured using M-mode in the parasternal long axis view by the leading edge to edge convention. The LV ejection fraction (LVEF) was calculated using a standard method. The deceleration time of the mitral inflow E-wave (DT) and the ratio of the velocity of the mitral inflow E-wave to that of the A-wave (E/A ratio) were measured as markers of diastolic function. After 18 months of treatment, these parameters were re-measured and compared with the initial data. Survival rate was defined as the proportion of patients who had not died from any cause within 18 months of discharge, whereas cardiac event-free rate was defined as the proportion of patients who had no cardiac events, such as ACS and deterioration of ADHF. Defibrillation rate was defined as the proportion of patients who were defibrillated from AF to sinus rhythm after 18 months of treatment. The diagnosis whether patients were defibrillated or not was made by using Holter monitoring of 24 h after 18 months of treatment. No patient in this study was treated with electrical defibrillation after admission.

Statistical Analyses

All values are expressed as mean±standard deviation and

Table 3. Clinical and Biochemical Characteristics of the 2 Treatment Groups

	Carvedilol (n=110)	Bisoprolol (n=107)	P-value
SBP (mmHg)	138.6±38.8	136.2±24.4	0.59
DBP (mmHg)	81.8±22.6	80.7±19.9	0.70
HR (beats/min)	91.5±24.9	93.6±32.8	0.61
QRSd (ms)	108.4±19.1	109.4±18.8	0.72
LVEF (%)	42.3±13.9	42.4±14.7	0.95
LVDd (mm)	56.8±10.8	55.1±9.6	0.28
LVDs (mm)	45.6±11.4	42.6±11.2	0.10
IVST (mm)	11.5±3.4	11.3±2.8	0.64
PWT (mm)	11.8±3.2	11.3±2.2	0.18
E/A ratio	1.21±0.49	1.22±0.55	0.94
DT (ms)	174.9±63.4	198.9±70.5	0.13
LAD (mm)	44.5±7.9	43.1±7.1	0.28
CTR (%)	56.4±4.5	56.2±5.5	0.74
BNP (pg/ml)	460.7±371.2	445.9±460.8	0.82
CRP (mg/dl)	0.46±0.50	0.41±0.67	0.55
Cre (mg/dl)	1.02±0.35	1.02±0.52	0.92
BUN (mg/dl)	21.0±7.0	19.9±8.5	0.32
eGFR (ml·min^{-1}·m^{-2})	59.9±23.1	61.1±20.4	0.74
Alb (g/dl)	3.9±0.3	3.9±0.3	0.52
Hb (g/dl)	13.3±2.0	13.6±2.0	0.21
CK (IU/L)	134.4±99.1	124.0±86.5	0.44
TnI (ng/ml)	0.21±0.47	0.20±0.44	0.93
TC (mg/dl)	185.6±42.7	191.7±38.9	0.35
LDL-C (mg/dl)	113.7±33.6	111.5±31.5	0.71
HDL-C (mg/dl)	55.0±25.2	56.8±22.9	0.70
HbA_{1c} (%)	6.1±0.9	5.9±0.9	0.27

SBP, systolic blood pressure (BP); DBP, diastolic BP; HR, heart rate; QRSd, QRS duration; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; IVST, interventricular septal thickness; PWT, posterior wall thickness; E/A ratio, a smaller ratio of the mitral inflow E-wave to A-wave; DT, deceleration time of the mitral inflow E-wave; LAD, left atrial diameter; CTR, cardiothoracic ratio; BNP, brain natriuretic peptide; CRP, C-reactive protein; Cre, creatinine; BUN, blood urea nitrogen; eGFR, age-based estimate glomerular filtration rate; Alb, albumin; Hb, hemoglobin concentration; CK, creatine kinase; TnI, troponin-I level; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

Table 4. Clinical and Biochemical Characteristics of the AF Patients

	Carvedilol (n=40)	Bisoprolol (n=43)	P-value
SBP (mmHg)	136.6±31.0	132.6±20.3	0.49
DBP (mmHg)	83.7±18.8	82.0±17.2	0.68
HR (beats/min)	96.9±22.0	108.2±36.2	0.09
QRSd (ms)	112.2±21.7	111.4±15.2	0.86
LVEF (%)	42.9±13.2	43.2±13.5	0.92
LVDd (mm)	57.7±9.6	55.7±8.9	0.40
LVDs (mm)	46.1±10.1	42.9±10.3	0.21
IVST (mm)	12.0±2.8	11.5±3.2	0.47
PWT (mm)	11.8±2.9	11.1±2.4	0.25
LAD (mm)	46.4±6.5	46.5±6.2	0.94
CTR (%)	56.9±3.7	57.8±5.7	0.47
BNP (pg/ml)	431.1±372.4	493.5±417.4	0.51
CRP (mg/dl)	0.46±0.45	0.39±0.62	0.61
Cre (mg/dl)	1.09±0.42	1.04±0.56	0.62
BUN (mg/dl)	20.3±7.3	21.8±10.4	0.45
eGFR (ml·min^{-1}·m^{-2})	53.9±21.4	63.7±24.5	0.10
Alb (g/dl)	3.8±0.3	3.8±0.4	0.51
Hb (g/dl)	13.7±1.8	14.2±2.0	0.30
CK (IU/L)	123.7±84.3	159.2±109.3	0.13
TnI (ng/ml)	0.18±0.34	0.18±0.37	0.99
TC (mg/dl)	182.4±38.8	196.1±34.5	0.17
LDL-C (mg/dl)	107.7±34.4	109.5±29.0	0.85
HDL-C (mg/dl)	61.2±36.2	58.7±19.3	0.80
HbA_{1c} (%)	5.9±0.7	5.6±0.7	0.22

Abbreviations see in Tables 1,3.

data of categorical variables are expressed as the number and percentage of patients. Fisher's exact test or the chi-square test was used to compare categorical variables, while mortality, hospitalization rate, relevant serious adverse events, and defibrillation rate were analyzed by the log-rank test. Survival curves were calculated using Kaplan–Meier estimates. Pearson's or Spearman's correlation analysis was used to assess the association between the measured parameters (SPSS software). Differences were considered significant at $P<0.05$.

Results

Clinical Characteristics

As shown in Table 1, there were no significant differences between the 2 groups in terms of age, gender, etiology of HF, and prevalence of AF, chronic HF, hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, and smoking at admission. The percentage of patients classified as either NYHA Class 3 or 4 was also similar in the 2 groups. With regard to cardiac medications, administration of digoxins, diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), nitrates, statins, amiodarone, aspirin, ticlopidine, and warfarin was similar in both groups. In addition, the 2 groups had similar usage of mechanical devices during the initial hospitalization, such as implantation of implantable cardioverter defibrillators and cardio resynchronization therapy using bi-ventricular pacemakers. The number of patients with AF was 40 in the carvedilol group and 43 in the bisoprolol group at admission, with the clinical and demographic characteristics being similar in the 2 groups (Table 2).

Hemodynamics and Blood Analyses

On admission, systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, and QRS duration (QRSd) were similar in both groups (Table 3). There were also no differences between the 2 groups with regard to echocardiographic measurements (LVEF, IVST, PWT, LAD, DT, and E/A ratio); cardiothoracic ratio on chest X-ray; and levels of brain natriuretic peptide (BNP), C-reactive protein, creatinine, blood urea nitrogen, age-based estimate glomerular filtration rate (eGFR), albumin, creatine kinase, troponin-I, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and hemoglobin. Table 4 shows that hemodynamics data and blood analyses were also similar in both groups.

Dose of β-Blockers

In the carvedilol group, patients were first administered a

Table 5. Clinical Outcomes in the Carvedilol Group, Those in the Bisoprolol Group and Changes in Clinical Outcomes After 18 Months of Treatment With Either Carvedilol or Bisoprolol

	Carvedilol (n=110)		P-value	Bisoprolol (n=107)		P-value	Carvedilol (n=110)	Bisoprolol (n=107)	P-value
	Baseline	After 18 months		Baseline	After 18 months		% change	% change	
SBP (mmHg)	138.6±38.8	122.3±17.8	<0.0001	136.2±24.4	124.9±19.1	0.001	−5.6±21.3	−5.5±16.2	0.96
DBP (mmHg)	81.8±22.6	72.0±13.7	0.001	80.7±19.9	73.9±12.3	0.005	−5.1±26.1	−5.8±21.2	0.87
HR (beats/min)	91.5±24.9	72.7±12.9	<0.0001	93.6±32.8	62.9±12.8	<0.0001	−17.4±21.5	−27.9±19.8	0.01
LVEF (%)	42.3±13.9	48.4±13.3	0.01	42.4±14.7	55.3±11.9	<0.0001	32.0±47.3	36.4±35.9	0.72
BNP (pg/ml)	460.7±371.2	195.2±231.7	<0.0001	445.9±460.8	154.5±174.1	<0.0001	−42.3±57.0	−50.3±51.6	0.48
eGFR ($ml \cdot min^{-1} \cdot m^{-2}$)	59.9±23.1	50.0±18.5	0.02	61.1±20.4	56.1±20.1	<0.0001	−4.0±26.5	−8.0±19.8	0.45

Abbreviations see in Table 3.

Table 6. Clinical Outcomes of AF Patients in the Carvedilol Group, Those in the Bisoprolol Group and Changes in Clinical Outcomes After 18 Months of Treatment With Either Carvedilol or Bisoprolol

	Carvedilol (n=40)		P-value	Bisoprolol (n=43)		P-value	Carvedilol (n=40)	Bisoprolol (n=43)	P-value
	Baseline	After 18 months		Baseline	After 18 months		% change	% change	
SBP (mmHg)	136.2±31.0	123.6±15.1	0.03	132.6±20.3	120.7±17.9	0.02	−3.6±18	−6.3±14.5	0.59
DBP (mmHg)	83.7±18.8	73.9±15.9	0.04	82.0±17.2	73.2±13.2	0.02	−5.9±24.6	−12.9±16.7	0.28
HR (beats/min)	96.9±22.0	72.3±11.8	<0.0001	108.2±36.2	61.5±12.8	<0.0001	−27.2±17.5	−38.5±20.2	0.04
LVEF (%)	42.9±13.2	51.8±11.3	0.04	43.2±13.5	60.5±7.5	<0.0001	38.4±49.2	53.6±61.2	0.52
BNP (pg/ml)	431.1±372.4	179.9±238.5	0.004	493.5±417.4	139.4±189	<0.0001	−41.5±52.5	−69.0±23.2	0.04
eGFR ($ml \cdot min^{-1} \cdot m^{-2}$)	53.9±21.4	52.2±21.8	0.63	63.7±24.5	62.0±22	0.83	−2.7±19.1	−0.8±27.4	0.84

Abbreviations see in Table 3.

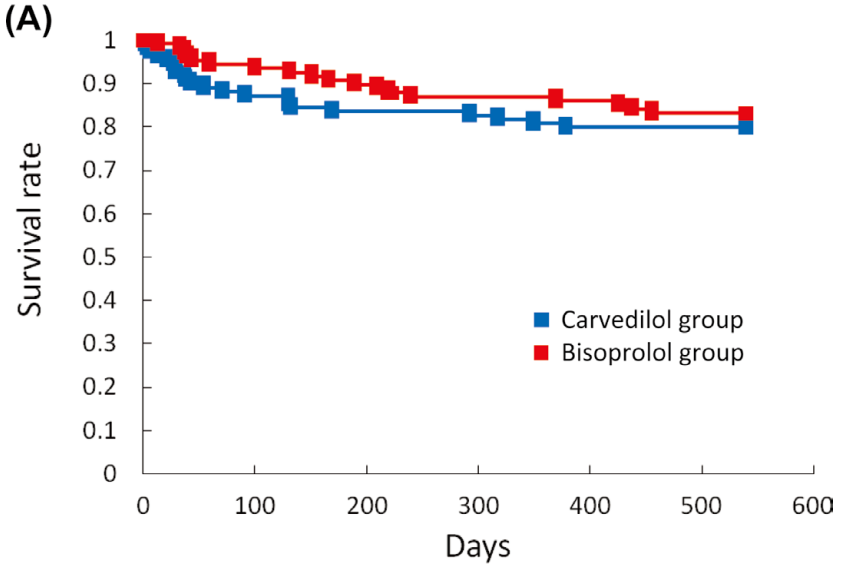
dose of 3.31±1.66 mg per day. After 18 months of treatment, the mean dose of carvedilol was 7.38±4.11 mg per day. In the bisoprolol group, patients were first administered a dose of 2.22±0.67 mg per day and, after 18 months, the mean dose had increased to 3.37±1.41 mg per day. For patients with AF, carvedilol was administered at 3.43±1.97 mg per day, increasing to a mean dose of 7.50±4.24 mg per day after 18 months of treatment. The corresponding dose for AF patients treated with bisoprolol was 2.29±0.81 mg per day, increasing to 2.76±1.26 mg per day after 18 months.

Clinical Outcome

After 18 months, SBP, DBP, HR, BNP levels and LVEF in the both groups significantly improved (Table 5). These parameters in patients with AF of the both groups also significantly improved after the β-blocker treatment (Table 6). The percentage change in SBP, DBP, LVEF, BNP levels, and eGFR was not significantly different between the 2 groups. However, the decrease in HR was greater in the bisoprolol group than in the carvedilol group (Table 5). The changes in SBP, DBP, LVEF, and eGFR were also similar in patients with AF treated with either drug, although bisoprolol induced greater decrease in HR and BNP levels than carvedilol (Table 6). In addition, we assessed the characteristics and the percentage changes in these parameters by classifying patients depending on their LVEF values : >40% or <40%; there were no significant differences in the 2 groups. Evaluation of the causes of death showed that 1 patient died from ACS, 1 from sudden cardiac death, and 20 from ADHF in the carvedilol group, whereas in the bisoprolol group, 3 patients died from ACS and 15 from ADHF in the bisoprolol group. As shown in Figure 1, the survival and cardiac event-free rates were not significantly different in the 2 treatment groups. There was also no difference in these rates in patients with AF treated with either drug (Figure 2). However, the defibrillation rate was significantly higher in the bisoprolol group (48%) than in the carvedilol group (16%, P=0.03). The number of AF patients who were defibrillated during the β-blocker treatment was as follow: 2 patients with paroxysmal AF and 1 patient with persistent AF in the carvedilol group, and 6 patients with paroxysmal AF and 8 patients with persistent AF in the bisoprolol group.

Discussion

In the present study, the characteristics of the 2 treatment groups before the study were not different; therefore, the effectiveness of carvedilol and bisoprolol is clearly comparable. Despite all the patients in the study having severe HF, defined as NYHA Class 3 or 4, their average LVEF was pre-



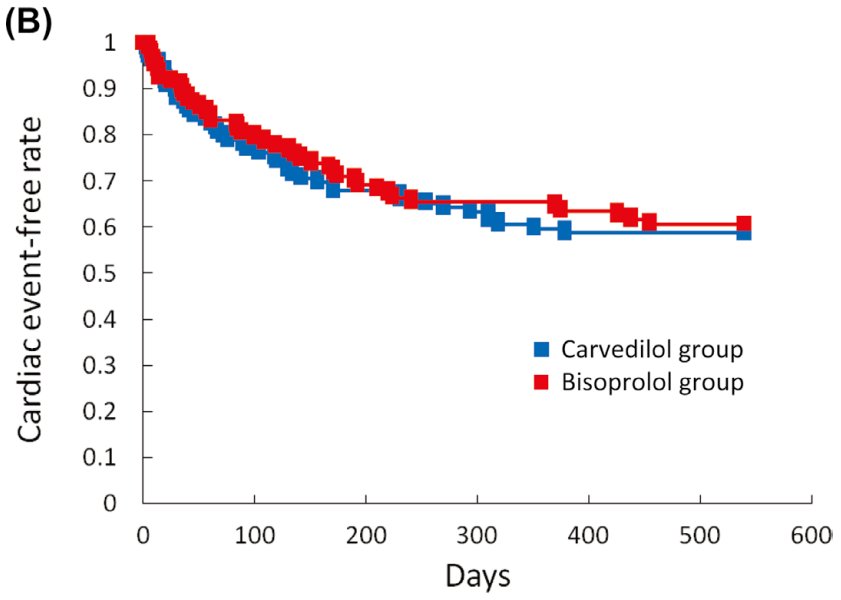


Figure 1. Kaplan–Meier curves of (**A**) survival of patients in the 2 treatment groups (P=0.45) and (**B**) cardiac event-free patients in the 2 treatment groups (P=0.81). Note: Time is expressed in days. P-value refers to the log-rank analysis.

served at above 40%, indicating that many patients had diastolic HF with preserved systolic function. In both groups, blood pressure (BP), HR, LVEF, and BNP levels improved significantly, whereas eGFR deteriorated following treatment. These effects were not only attributable to the β-blockers but also to other drugs such as diuretics, ACE-Is, and ARBs taken by many of the patients prior to the start of the β-blocker therapy. According to the results of previous large-scale clinical trials, the use of agents such as diuretics, ACE-Is and ARBs is beneficial in preventing the progression of HF.[12–20] Because many of the patients in our study were taking diuretics, this might have affected renal function and resulted in prerenal failure and a decrease in eGFR.

In the bisoprolol group, the change in HR was greater than in the carvedilol group. Despite this difference, the survival and cardiac event-free rates were not significantly different between the 2 groups. Schafers et al showed that the stimulation of β1-adrenergic receptors induces the inotropic and chronotropic effects of norepinephrine.[21] Similar results were reported by McDavitt, who emphasized that the ability of β1-adrenergic receptor signaling to initiate arrhythmia is illustrated by exercise-induced tachyarrhythmias caused by norepinephrine release from sympathetic nerve ending.[22] Taken together, these results and our results suggest that bisoprolol has greater ability to suppress HR of patients with HF than carvedilol, as the former is a highly selective β1-adrenergic receptor blocker. Excessive reduction of HR might however exacerbate the clinical course of HF by causing cardiac events and death. In this study, the decrease in the defibrillation rate in AF patients between the 2 treatment groups was unexpected. First, the dose of carvedilol in patients was inadequate compared to that of bisoprolol. Nishiyama et al showed that carvedilol has dose-related effects for cardiac sympathetic nerve activity and mortality.[23] Tsuboi et al suggested that postoperative treatment with carvedilol at 20 mg per day prevents paroxysmal AF after coronary artery bypass

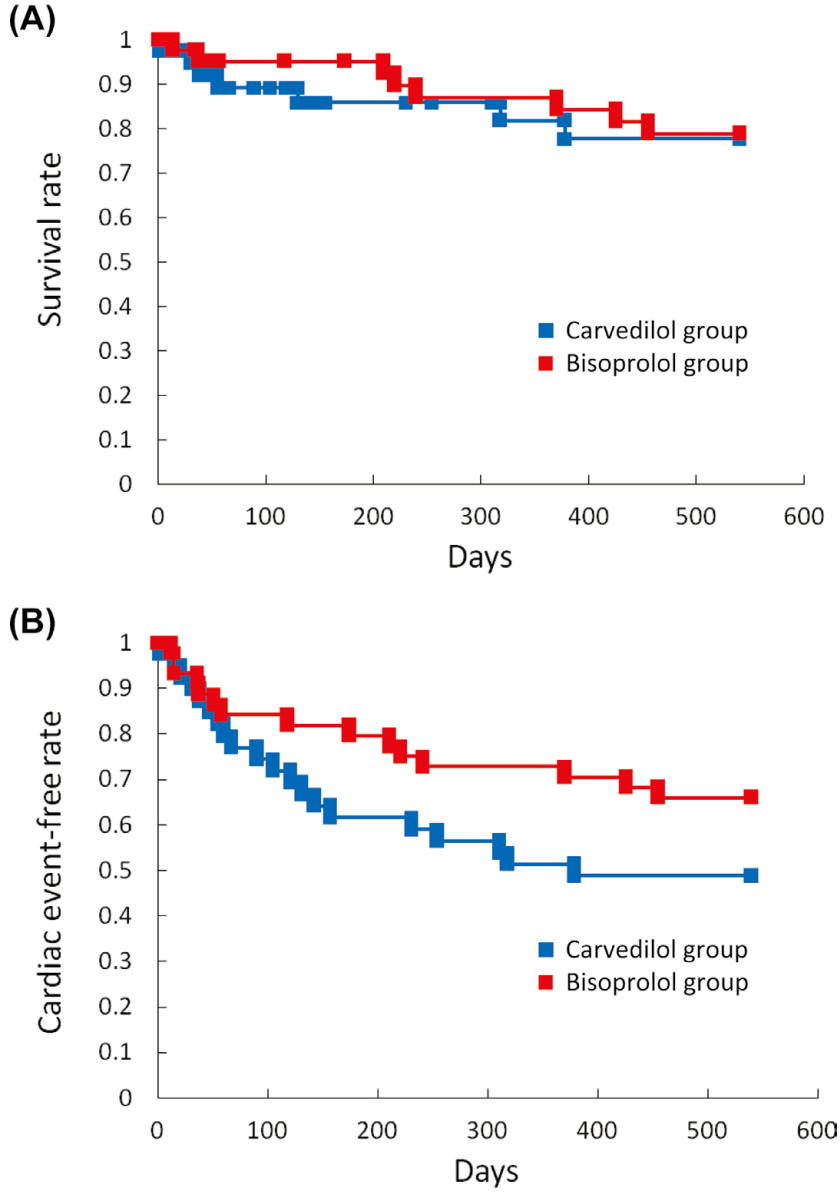


Figure 2. Kaplan–Meier curves of (**A**) survival of patients with AF in the 2 treatment groups (P=0.95) and (**B**) cardiac event-free patients with AF in the 2 treatment groups (P=0.06). Note: Time is expressed in days. P-value refers to the log-rank analysis.

grafting.[24] Bristow et al also reported that carvedilol produces dose-related improvements in HF patients,[4] whereas a study by Dungen et al showed that the potency of carvedilol at a target dose of 50 mg per day and bisoprolol at 10 mg per day is approximately equal.[25] Second, the dosages of the 2 β-blockers in our study were lower than the common dosages found in the many large-scale trials. Asanuma et al reported that carvedilol suppressed the frequency of ventricular fibrillation and death through reducing infarct size after ischemia reperfusion injury.[26] This report supports our results that the number of patients died from ACS was lower in the carvedilol group than that in the bisoprolol group. Thus, the dosages of the 2 β-blockers in our study could be sufficient to improve HF. Several trials performed on Japanese patients with HF have shown that the BP and HR decrease adequately by administering low dosages of carvedilol and bisoprolol.[8,27] Tamura et al also reported that low dosages of cavedilol significantly improve LVEF and BNP levels in HF patients after 6 months of treatment.[28] These differences in the dosages used between Japanese patients and other nationalities can be illustrated by the pharmacological heterogeneity of β-blockers. Further investigation on the racial differences of the effects is required. In this study, although the electrophysiological parameters were not investigated in detail, we found a difference in the HR between the 2 groups. Ishiguro et al reported that bisoprolol has a defibrillation effect that causes AF to convert to sinus rhythm in paroxysmal AF patients because of reduction in HR.[27] In our study, reduction of HR was more prominent in the bisoprolol group than that in the carvedilol group at 18 months. Higher percentage of normal sinus rhythm in the bisoprolol group at 18 months could attribute to the lower HR in this group, because HR in AF patients reduces after defibrillation.[29] In our study, the onsets of AF in HF patients before admission were similar in the 2 β-blocker groups, but patients with paroxysmal AF or persistent AF could easily be converted to sinus rhythm

using bisoprolol. This suggested that bisoprolol could be useful for recovering sinus rhythm in HF patients with AF. We also found that reductions in BNP levels of HF patients with AF were greater in the bisoprolol group than in the carvedilol group. BNP is the major hormone for assessing HF status and is known to reduce when HF improves. This result supports the usefulness of bisoprolol in the treatment of HF as compared to carvedilol. Nishio et al suggested that bisoprolol could improve survival in a rat model of HF by attenuating inflammatory changes and oxidative stress.[30] Bisoprolol is a highly selective β1-adrenergic receptor blocker, and appears to have superior effects in HF patients with AF as compared to carvedilol. Further studies are required to investigate the molecular and electrophysiological mechanisms of these beneficial actions. In our study, no patient with AF suffered from thrombo-embolism after defibrillation. Because the defibrillation rate was significantly higher in the bisoprolol group, more careful management of thrombo-embolism might be necessary in these patients.

Study Limitations

This study was performed retrospectively, and patients were selected for the 2 groups on the discretion of the physician. In this study, although no significant differences were observed in blood biochemical parameters between the 2 groups, other indicators should be evaluated to assess the severity and etiology of HF. For example, assessment of atrial natriuretic peptide, N-terminal pro-BNP, and other cytokines associated with HF should be performed. Furthermore, the contribution of these β-blockers on the improvement of cardiac function in the HF patients is not certain, because other cardioprotective drugs, such as ACE-Is and ARBs, were also given in these patients.

Conclusion

Our study demonstrates that therapy with either carvedilol or bisoprolol for 18 months caused similar reductions in BP and HR. The 2 agents were also shown to improve HF as assessed by BNP levels and LVEF. We also found bisoprolol had favorable effects in HF patients with AF. However, further studies of longer duration and a large number of HF patients are needed to determine whether there are any differences between the effects of the 2 β-blockers on improvement of HF.

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