

# Effects of Bisoprolol Are Comparable with Carvedilol in Secondary Prevention of Acute Myocardial Infarction in Patients Undergoing Percutaneous Coronary Intervention

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Although the benefits of carvedilol have been demonstrated in the era of percutaneous coronary intervention (PCI), very few studies have evaluated the efficacy of bisoprolol in the secondary prevention of acute myocardial infarction (MI) in patients treated with PCI. We hypothesized that the effect of bisoprolol would not be different from carvedilol in post-MI patients. A total of 13,813 patients who underwent PCI were treated either with carvedilol or bisoprolol at the time of discharge. They were enrolled from the Korean Acute MI Registry (KAMIR). After 1:2 propensity score matching, 1,806 patients were enrolled in the bisoprolol group and 3,612 patients in the carvedilol group. The primary end point was the composite of major adverse cardiac events (MACEs), which was defined as cardiac death, nonfatal MI, target vessel revascularization, and coronary artery bypass surgery. The secondary end point was defined as all-cause mortality, cardiac death, nonfatal MI, any revascularization, or target vessel revascularization. After adjustment for differences in baseline characteristics by propensity score matching, the MACE-free survival rate was not different between the groups (HR=0.815, 95% CI: 0.614-1.081, p=0.156). In the subgroup analysis, the cumulative incidence of MACEs was lower in the bisoprolol group in patients having a Killip class of III or IV than in the carvedilol group (HR=0.512, 95% CI: 0.263-0.998, p=0.049). The incidence of secondary end points was similar between the two beta-blocker groups. In conclusion, the benefits of bisoprolol were comparable with those of carvedilol in the secondary prevention of acute MI.

**Key Words:** *Bisoprolol; Carvedilol; Myocardial Infarction; Percutaneous Coronary Intervention; Secondary Prevention*

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## INTRODUCTION

Although beta-blockers are recommended as a standard medical treatment after myocardial infarction (MI), most studies supporting the use of beta-blockers were conducted in the pre-thrombolytic or thrombolytic era.<sup>1-3</sup> Recently, several studies have reported that beta-blockers improve clinical outcomes in acute MI patients treated by percuta-

neous coronary intervention (PCI).<sup>4,5</sup> The current guidelines recommend that beta-blockers should be used in all post-MI patients, unless there are contraindications.<sup>6,7</sup>

In real clinical practice, a nonselective beta-blocker such as carvedilol or a beta-1-selective beta-blocker such as metoprolol, bisoprolol, or nebivolol are frequently used in the secondary prevention of acute MI. Whereas the benefits of carvedilol were demonstrated in a randomized controlled

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trial, there have been very few studies about the impact of bisoprolol on patients with acute MI.<sup>8</sup> Since the pharmacologic action of bisoprolol is somewhat different from that of carvedilol, it is necessary to evaluate the differences in terms of benefits between carvedilol and bisoprolol.<sup>9</sup> The purpose of this study was to compare the clinical benefits of bisoprolol with those of carvedilol in post-MI patients.

## MATERIALS AND METHODS

### 1. Study population and protocol

From November 2005 to January 2012, a total of 36,580 patients with acute MI were registered from the Korea Acute MI Registry (KAMIR). Among the enrolled patients, those who died in the hospital (n=1795) or who were not treated with a beta-blocker at discharge (n=10,396) were excluded. Patients who did not undergo PCI or who were treated with other types of beta-blockers were also excluded. After the exclusion of these patients, 10,281 patients were defined as the carvedilol group and 3,532 patients as the bisoprolol group.

To adjust for selection bias and differences in baseline characteristics, propensity score matching was performed. After the 2:1 propensity score matching, 3612 patients treated with carvedilol and 1806 patients treated with bisoprolol were analyzed. The initial dose of beta-blockers was determined by the individual clinicians, and titration was performed according to each patient's clinical status. The use of a beta-blocker was continued unless the patient presented with side effects such as bradycardia or hypotension during follow-up.

The KAMIR is a multi-center observational trial that was organized to address the demographic and angiographic features and cardiovascular outcomes of acute MI. This registry was supported by a research grant from the Korean Circulation Society and the study protocol was evaluated and recognized by the ethics committee at each hospital.

Acute MI was defined as a typical pattern of increase or decrease of the levels of cardiac biomarkers and at least one of the following: 1) typical angina pain or angina-equivalent symptom, 2) pathologic Q wave in the electrocardiogram, 3) new significant ST segment or T wave deviation or new-onset left bundle branch block, or 4) identification of coronary artery lesion by angiography.<sup>10</sup> Patients over 18 years of age, who had been treated with a beta-blocker before the episode of acute MI, were included in this study. Patients without significant coronary artery stenosis on angiography or those with MI due to coronary artery spasm were excluded.

PCI was performed according to a standard protocol, and administration of anticoagulation agents such as unfractionated or lower molecular weight heparin was left to the decision of the individual clinicians. The decision between pre-dilatation and direct stenting was made by the operator. For ST-segment elevation MI (STEMI) patients, primary PCI was done to restore blood flow in the target

vessel as soon as possible. The prescription of other medications such as anti-platelet agents, renin-angiotensin system blocker, statin, or aldosterone antagonist was based on the patient's clinical status.

### 2. End points and follow-up

The primary endpoint was defined as a major adverse cardiac event (MACE). The secondary end point was the incidence of all-cause death, cardiac death, recurrent non-fatal MI, any revascularization, or target-vessel revascularization respectively. The cumulative incidences of primary and secondary endpoints over 2 years were compared between the carvedilol and bisoprolol groups. MACEs were defined as the composite of cardiac death, nonfatal MI, target vessel revascularization, and coronary artery bypass surgery. Cardiac death was defined as all-cause death without a definite noncardiac cause, and recurrent MI was defined as recurrent symptoms or new electrocardiographic change with elevation of cardiac biomarkers at least double the upper limit of the reference range. Any repeated coronary intervention in the previous target vessel was defined as target vessel revascularization.

To adjust for differences in clinical and angiographic characteristics, we used propensity score matching. We compared baseline characteristics and evaluated clinical outcomes before and after propensity score matching. To address other factors that may interfere with the benefit of these two beta-blockers, we performed subgroup analyses for MACEs and all-cause mortality.

### 3. Statistical analysis

All analyses were performed using SPSS version 21. Categorical baseline characteristics were presented as counts and percentages and continuous variables as average values±standard deviations. Continuous baseline characteristics were compared and evaluated by use of the Student's t-test and the categorical baseline variables by Pearson's chi-square test. The cumulative MACE-free survival and all-cause-death-free survival rates were evaluated using the life-table method and were compared by the log-rank method between the carvedilol and bisoprolol groups. The hazard ratio (HR) of treatment with bisoprolol compared with carvedilol was calculated by Cox regression analysis. HRs and 95% confidence intervals (CIs) were calculated and all tests were two-tailed. p values < 0.05 were considered significant.

Comparison of baseline characteristics and survival analyses was also done after propensity matching. The logistic regression model was used in propensity score matching. The covariants matched in this analysis were systolic and diastolic blood pressure, type of MI, left ventricular ejection fraction, Killip classification, cardiac biomarkers, the level of high-sensitivity C-reactive protein, and the use of a renin-angiotensin system blocker, statin, or spironolactone. The predicted accuracy of this propensity score matching model was evaluated with an area under the receiver operating characteristic curve (C statistic),

which was 0.506 (95% CI: 0.489 to 0.522). If this value does not differ significantly from 0.5, then the allocation can be considered random.

## RESULTS

Before propensity score matching, systolic and diastolic blood pressure were lower and heart rate was higher in the bisoprolol group. Also, the left ventricular ejection fraction was lower and the percentage of patients with a Killip class  $\geq$

II was higher in the bisoprolol group. The level of high-sensitivity C-reactive protein on admission and the rate of use of a renin-angiotensin system blocker also differed significantly between the two groups. After propensity score matching however, there were no significant differences in baseline clinical characteristics between the two groups (Table 1).

Several angiographic and procedural characteristics also differed between the two groups before propensity score matching. The angiographic type and location of the culprit

**TABLE 1.** Comparison of clinical baseline characteristics between the carvedilol and bisoprolol groups before and after propensity score matching

	Before propensity matching			After propensity matching		
	Carvedilol group (n=10281)	Bisoprolol group (n=3532)	p-value	Carvedilol group (n=3612)	Bisoprolol group (n=1806)	p-value
Age, years	65.5±12.6	65.4±12.7	0.902	65.9±12.3	65.2±12.5	0.482
Gender (male %)	7,485 (73.1%)	2,526 (71.8%)	0.148	2,605 (72.4%)	1302 (72.3%)	0.933
Body mass index, kg/m <sup>2</sup>	24.0±3.2	24.0±3.1	0.418	24.1±3.2	24.0±3.0	0.244
SBP (mmHg)	131.6±27.5	129.9±27.5	0.002	131.7±27.1	130.9±26.7	0.689
DBP(mmHg)	80.0±16.2	79.3±16.5	0.042	80.2±16.1	79.5±16.4	0.116
HR (bpm)	77.8±18.4	78.7±19.1	0.020	77.6±18.0	78.0±18.4	0.542
IHD Hx.(%)	1,337 (13.3%)	506 (14.5%)	0.075	468 (13.0%)	219 (12.2%)	0.361
HTN Hx.(%)	5,087 (50.6%)	1,825 (52.3%)	0.079	1,925 (53.5%)	957 (53.0%)	0.753
DM Hx. (%)	2,725 (27.1%)	982 (28.2%)	0.226	1,013 (28.3%)	491 (27.2%)	0.422
HL Hx.(%)	1,328 (13.2%)	425 (12.2%)	0.119	473 (13.2%)	213 (11.8%)	0.151
MI type						
STEMI (%)	5,915 (58.0%)	1784 (50.9%)	< 0.001	1,838 (51.1%)	927 (51.4%)	0.834
NSTEMI (%)	4,292 (42.0%)	1724 (49.1%)		1,762 (48.9%)	878 (48.6%)	
LVEF, %	53.5±26.0	52.3±14.9	0.002	52.5±11.3	52.4±10.5	0.809
Killip class $\geq$ II	2,282 (24.1%)	859 (27.6%)	< 0.001	922 (25.6%)	465 (25.8%)	0.905
Peak CK-MB, ng/mL	120.5±199.9	97.4±173.2	< 0.001	112.9±218.9	104.1±138.2	0.089
Peak troponin-I, ng/mL	41.0±115.1	36.0±142.9	0.050	40.3±140.3	41.6±182.9	0.775
Total cholesterol, mg/mL	185.4±46.5	183.1±45.1	0.013	185.2±44.7	183.7±45.1	0.251
Triglyceride, mg/dL	134.8±106.0	135.6±108.8	0.715	134.0±108.2	138.0±104.9	0.205
HDL cholesterol, mg/dL	43.9±15.6	44.4±20.6	0.162	43.8±16.6	44.2±22.0	0.462
LDL cholesterol, mg/dL	116.3±40.0	116.2±39.1	0.887	115.8±39.2	116.6±39.9	0.521
Hs CRP, mg/L	7.2±35.9	12.0±56.0	< 0.001	8.7±38.0	10.7±46.8	0.156
NT pro BNP, pg/mL	2,126±5,362	2,377±5,894	0.077	2,199±5,601	1,901±46,420	0.081
HbA1c, %	6.6±2.6	6.7±2.5	0.578	6.6±2.6	6.7±3.1	0.384
Glucose, mg/dL	168.0±77.7	170.2±81.3	0.181	167.5±78.1	169.0±78.6	0.499
Creatinine	1.1±1.3	1.1±1.9	0.791	1.1±1.3	1.0±0.8	0.279
Unfractionated heparin (%)	6,472 (64.5%)	2,167 (62.4%)	0.026	2,592 (72.7%)	1,300 (72.4%)	0.814
LMWH (%)	2,217 (22.1%)	616 (17.7%)	< 0.001	607 (17.0%)	277 (15.4%)	0.136
Glycoprotein IIb/IIIa inhibitor (%)	1,548 (17.2%)	476 (16.4%)	0.344	614 (17.9%)	297 (17.3%)	0.644
Aspirin (%)	10,137 (98.9%)	3,483 (98.8%)	0.914	3,564 (99.3%)	1,791 (99.5%)	0.390
Clopidogrel (%)	9,904 (96.3%)	3,390 (96.0%)	0.341	3,513 (97.6%)	1,791 (97.6%)	0.962
Calcium channel blocker (%)	577 (6.0%)	214 (6.3%)	0.547	186 (5.4%)	112 (6.3%)	0.190
RAS blocker (%)	8,716 (84.8%)	3,086 (87.4%)	< 0.001	3,225 (89.6%)	1,610 (89.2%)	0.662
Statin (%)	8,185 (79.6%)	2,749 (77.8%)	0.025	2,960 (82.2%)	1,478 (81.9%)	0.759
Spirolactone (%)	744 (7.8%)	227 (6.7%)	0.035	278 (8.1%)	138 (7.7%)	0.666

Data are presented as mean±SD or No.(%). SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, IHD: ischemic heart disease, HTN: hypertension, DM: diabetes mellitus, HL: hyperlipidemia, MI: myocardial infarction, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, LVEF: left ventricular ejection fraction, HDL: high-density lipoprotein, LDL: low-density lipoprotein, Hs-CRP: high sensitivity C-reactive protein, NT pro-BNP: N-terminal brain natriuretic peptide, HbA1c: glycosylated hemoglobin, LMWH: low molecular weight heparin, RAS: renin-angiotensin system.

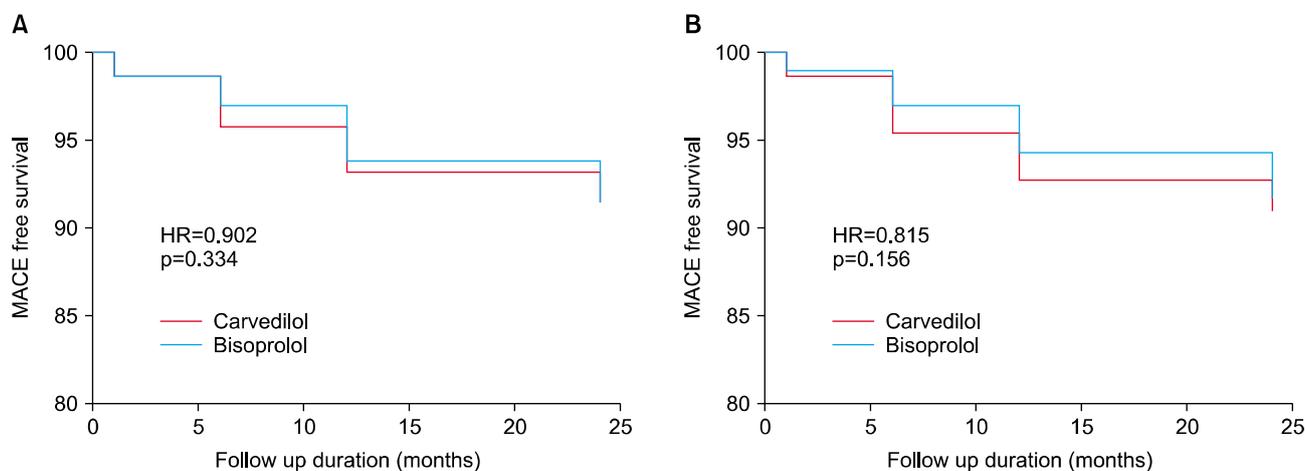
lesion differed, as did the rate of use of bare-metal stents or drug-eluting stents. However, these differences were also adjusted appropriately with propensity score matching (Table 2). In the primary end point, there was no significant difference in the cumulative incidence of MACEs between the groups (HR=0.902, 95% CI: 0.732-1.112, p=0.334; Fig. 1A). In the propensity-score-matched population also, the

cumulative incidence of MACEs was not significantly different between the two groups (HR=0.815, 95% CI:0.614-1.081, p=0.156; Fig. 1B). In the overall population, all-cause-death-free survival was similar between the groups (HR=0.900, 95% CI:0.686-1.181, p=0.446; Fig. 2A). The results were also not significantly different after propensity matching (HR=0.937, 95% CI:0.646-1.357, p=0.729; Fig.

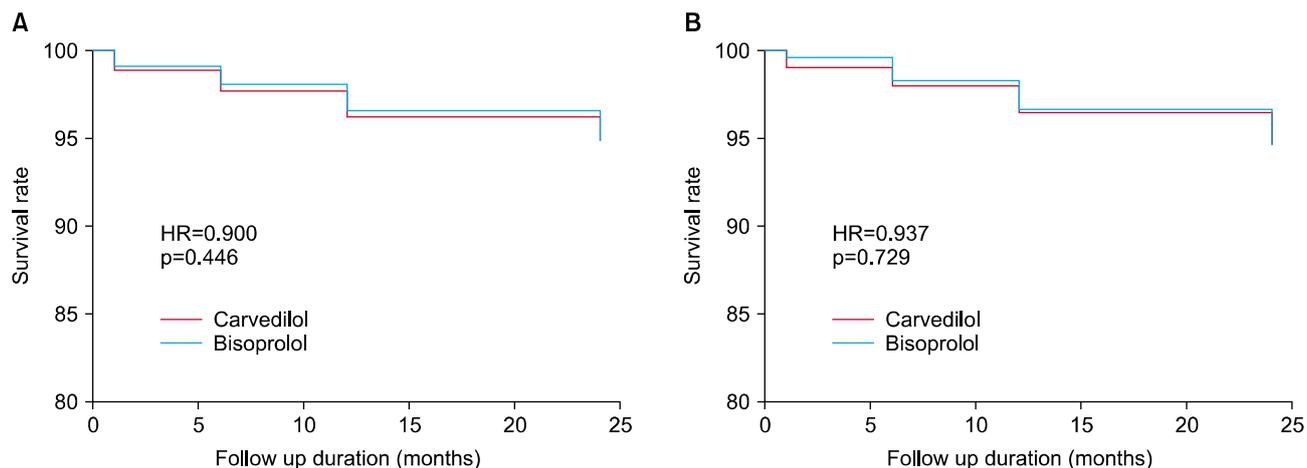
**TABLE 2.** Comparison of coronary angiographic and procedural characteristics between the carvedilol and bisoprolol groups before and after propensity score matching

		Before propensity matching			After propensity matching		
		Carvedilol group (n=10281)	Bisoprolol group (n=3532)	p-value	Carvedilol group (n=3612)	Bisoprolol group (n=1806)	p-value
Type of culprit lesion	A	375 (4.4%)	47 (1.7%)	< 0.001	154 (4.3%)	39 (2.1%)	0.078
	B1	1,425 (16.9%)	491 (17.9%)		546 (15.2%)	316 (17.5%)	
	B2	2,730 (32.3%)	2,730 (32.3%)		1,329 (36.9%)	675 (37.3%)	
	C	3,910 (46.3%)	3,910 (46.3%)		1,571 (43.6%)	775 (42.9%)	
Location of culprit lesion	LM	182 (1.9%)	34 (1.1%)	0.003	79 (2.2%)	23 (1.3%)	0.039
	LAD	4,667 (49.2%)	1,462 (47.4%)		1,696 (47.2%)	854 (47.4%)	
	LCX	1,579 (16.6%)	543 (17.6%)		669 (18.6%)	310 (17.2%)	
	RCA	3,060 (32.3%)	1,044 (33.9%)		1,148 (32.0%)	614 (34.1%)	
PreTIMI flow	0	4,279 (49.1%)	1,452 (50.7%)	0.108	1,764 (50.2%)	905 (51.1%)	0.356
	I	1,082 (12.4%)	357 (12.5%)		413 (11.8%)	196 (11.1%)	
	II	1,158 (13.3%)	395 (13.8%)		429 (12.2%)	226 (12.8%)	
	III	2,201 (25.2%)	658 (23.0%)		902 (25.7%)	444 (25.1%)	
PostTIMI flow	0	126 (1.5%)	37 (1.3%)	0.197	46 (1.3%)	24 (1.4%)	0.473
	I	98 (1.2%)	21 (0.8%)		31 (0.9%)	9 (0.5%)	
	II	392 (4.6%)	117 (4.2%)		153 (4.5%)	72 (4.2%)	
	III	7,873 (92.7%)	2,618 (93.7%)		3,202 (93.3%)	1,629 (93.9%)	
Type of stent	BMS	600 (7.4%)	141 (6.9%)	0.001	217 (7.0%)	93 (6.1%)	0.192
	DES	7,531 (92.6%)	2,442 (94.5%)		2,882 (93.0%)	1,430 (93.9%)	
Stent size, mm		23.5±7.4	23.3±8.1	0.281	23.5±7.7	23.3±8.3	0.326
Stent diameter, mm		3.1±0.4	3.1±0.4	0.036	3.1±0.4	3.1±0.4	0.593
Reference diameter, mm		3.0±0.6	3.0±0.6	0.071	3.0±0.6	3.0±0.6	0.125
Lesion length, mm		23.8±11.7	23.4±11.4	0.327	24.3±12.4	23.9±8.3	0.486

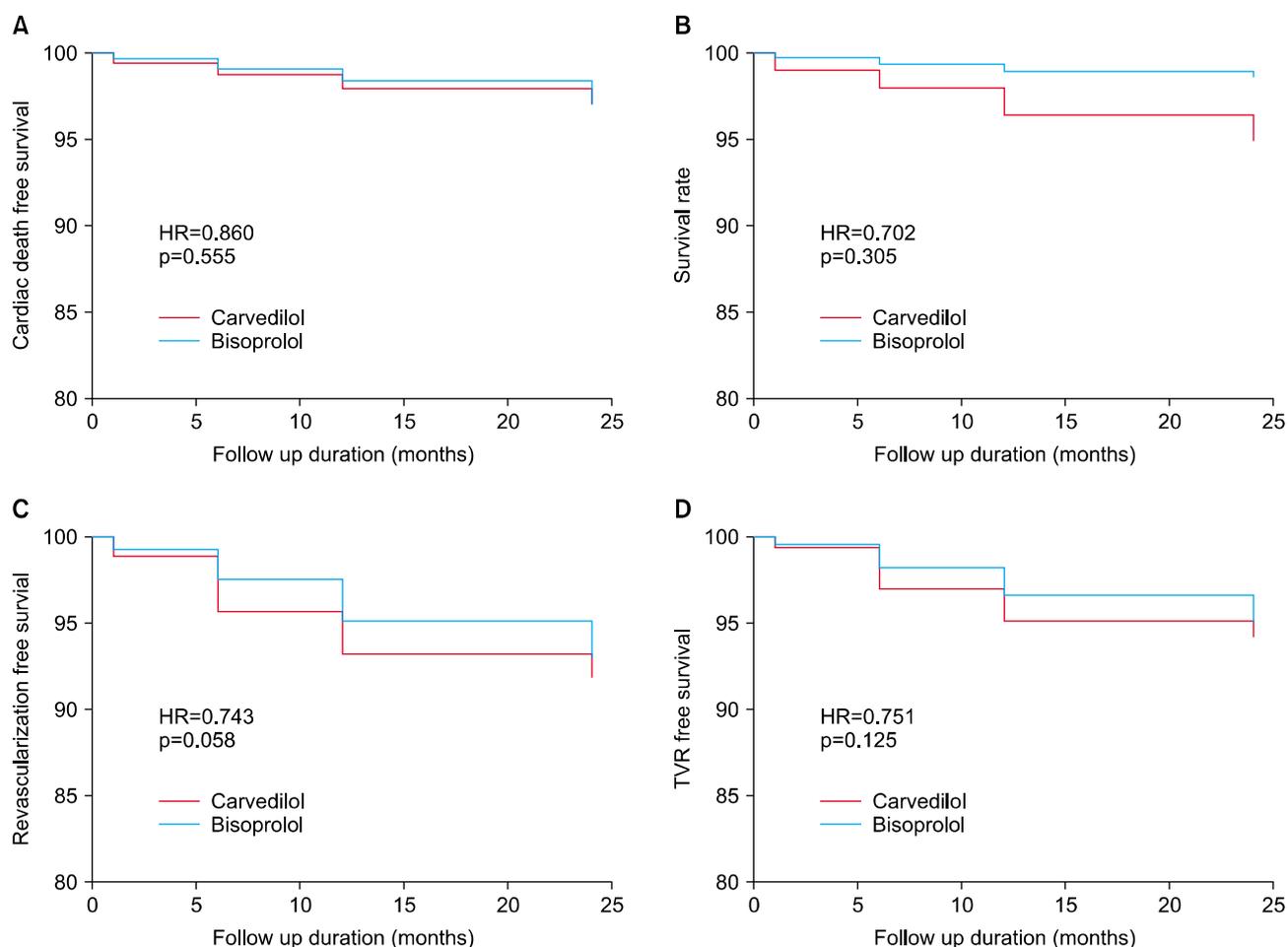
Data are presented as mean±SD or No.(%). LM: left main, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, BMS: bare metal stent, DES: drug eluting stent, TIMI: thrombolysis in myocardial infarction.



**FIG. 1.** Comparison of the major adverse cardiac event (MACE)-free survival rate between the carvedilol and bisoprolol groups in post-myocardial infarction patients before (A) and after (B) propensity score matching. HR: hazard ratio.



**FIG. 2.** Comparison of the cumulative survival rate between the carvedilol and bisoprolol groups in post-myocardial infarction patients before (A) and after (B) propensity score matching. HR: hazard ratio.



**FIG. 3.** Comparison of secondary end points between the carvedilol and bisoprolol groups in post-myocardial infarction patients after propensity score matching: (A) cardiac death, (B) nonfatal myocardial infarction (MI), (C) repetition of revascularization, and (D) target vessel revascularization (TVR).

2B). Treatment with bisoprolol did not reduce the risk of cardiac death, recurrence of MI, any revascularization, or target-vessel revascularization compared with carvedilol

(Fig. 3). To clarify the factors that intervene in the impact of bisoprolol or carvedilol, subgroup analyses were performed for MACEs or all-cause mortality. The analysis in

the propensity-matched population showed that the cumulative incidence of MACEs was lower in the bisoprolol group in patients having a Killip class of III or IV (HR= 0.512, 95% CI: 0.263-0.998, p=0.049). However, the benefit of bisoprolol was not significantly different from that of carvedilol in MI patients with a Killip class of I or II. The interaction between type of beta-blocker and Killip classification was not significant (p=0.157). Other factors such as age, type of MI, hypertension, diabetes mellitus, hyperlipidemia, and the left ventricular ejection fraction did not significantly affect the benefits of bisoprolol or carvedilol (Fig. 4). The subgroup analysis for all-cause death revealed that the benefit of bisoprolol was similar to that of carvedilol in all subgroups (Fig. 5).

### DISCUSSION

Although beta-blockers as the optimal medical therapy are recommended in post-MI patients, the superiority or inferiority of carvedilol relative to bisoprolol is not known and the pharmacological actions of these two beta-blockers differ.<sup>9</sup> However, very few trials have evaluated the differences in clinical benefits between carvedilol and bisoprolol in post-MI patients treated by PCI. The results of the present study demonstrated that bisoprolol had comparable benefits with carvedilol in the secondary prevention of acute MI.

Treatment with beta-blockers reduces major coronary events and improves survival in patients with acute MI.<sup>3,11,12</sup> However, most trials that support the use of be-

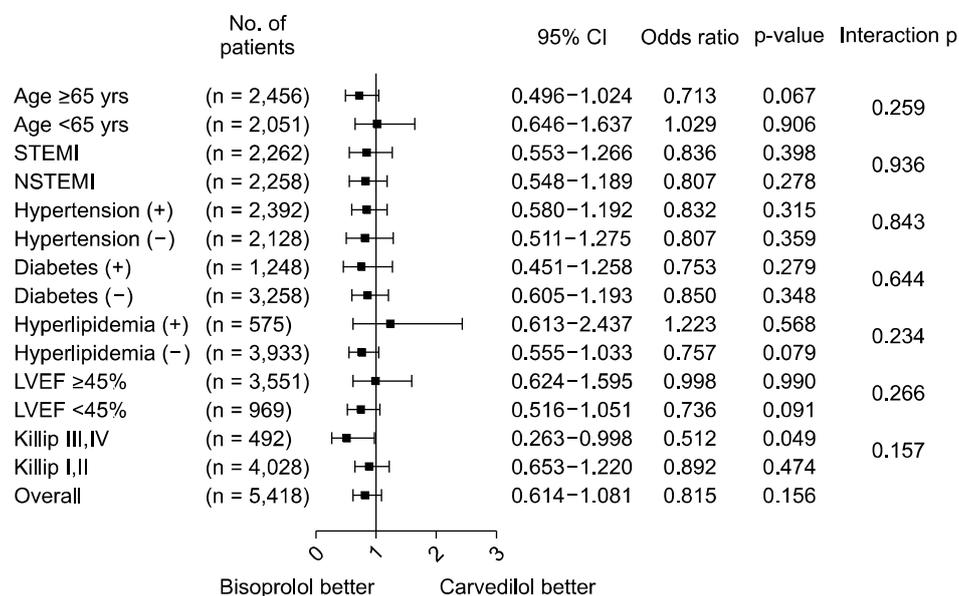


FIG. 4. Subgroup analysis for the cumulative incidence of major adverse cardiac events. STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, LVEF: left ventricular ejection fraction.

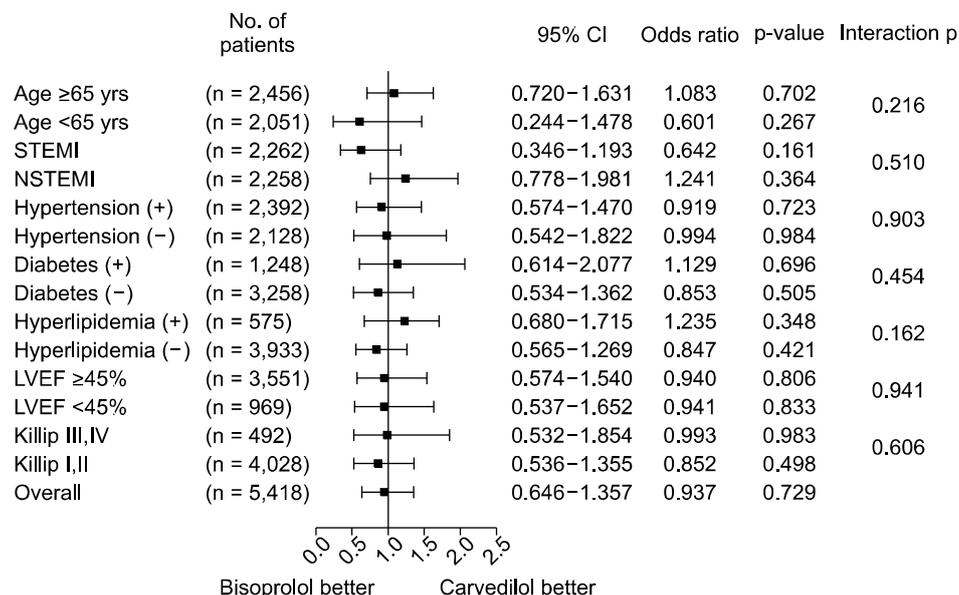


FIG. 5. Subgroup analysis for the cumulative incidence of all-cause death. STEMI: ST-segment elevation myocardial infarction, NSTEMI: non ST-segment elevation myocardial infarction, LVEF: left ventricular ejection fraction.

ta-blockers were carried out in the era before antiplatelet therapy, angiotensin-converting enzyme inhibitors, statins, or PCI. To resolve this absence of contemporary data, several studies have evaluated the benefit of beta-blockers in the contemporary era of management of post-MI patients. The results of these studies revealed that the use of beta-blockers was associated with lower mortality in high-risk MI patients.<sup>8,13-15</sup>

Several other trials compared the efficacy of metoprolol with carvedilol in post-MI patients.<sup>16-18</sup> Mrdovic et al.<sup>18</sup> reported that treatment with carvedilol versus metoprolol in patients with acute MI and left ventricular systolic dysfunction did not reduce composite cardiac adverse events. However, that study had two major limitations: the study was very small in scale and most of the population was revascularized with thrombolysis. Therefore, these trials did not evaluate the clinical benefit of beta-blockers in the era of PCI.

A meta-analysis compared the efficacy of a beta-1-selective beta-blockers with that of carvedilol in patients with congestive heart failure.<sup>19</sup> That study reported that carvedilol had a more beneficial impact than did other beta-1-selective beta-blockers in congestive heart failure. The potential mechanism of this benefit was postulated to be a pleiotropic effect of carvedilol, such as an antioxidant or vasodilating effect. However, patients with nonischemic heart failure were also included in that analysis, and the beta-1-selective beta-blocker used in the trial was either atenolol or metoprolol.

The benefit of bisoprolol in chronic heart failure was demonstrated by a large-scale randomized controlled trial.<sup>20</sup> In the subgroup analysis of this study, bisoprolol reduced the risk of all-cause mortality in patients with heart failure caused by ischemia. However, the study did not include MI patients without heart failure. Our study enrolled all acute MI patients treated by PCI and evaluated the efficacy of bisoprolol by comparing the benefits with carvedilol. The subgroup analysis of our study revealed that the benefit of bisoprolol on survival was not different from that of carvedilol according to the hemodynamic state of the patients. In patients without heart failure, the benefit of bisoprolol was comparable with carvedilol. The benefit of bisoprolol was also addressed by another trial. That trial reported that treatment with bisoprolol significantly reduced long-term cardiac death and MI in high-risk patients after major cardiac vascular surgery.<sup>21</sup>

The pharmacological effects of bisoprolol are somewhat different from those of carvedilol. A study that analyzed and compared the pharmacological effects of bisoprolol and carvedilol reported that the effects of carvedilol on a heart rate at rest appeared to be weak or nonexistent, whereas bisoprolol was a potent beta-blocker both at rest and during exercise.<sup>22</sup> Furthermore, the blood pressure-effect was more prominent in carvedilol users than in bisoprolol users. The effect of carvedilol on blood pressure was mediated by not only beta-blocking but also alpha-blocking activity. However, this phenomenon may cause a compen-

satory increase in sympathetic tone, and this increase in sympathetic tone might diminish the beta-blocking effect of carvedilol, especially under conditions with physiologically low sympathetic tone. This finding may explain the better beta-blocking effect of bisoprolol in older MI patients or those with decreased systolic function.

Seo et al.<sup>23</sup> reported an impact of carvedilol versus beta-1-selective beta-blocker (bisoprolol, metoprolol, and nebivolol) in patients with acute myocardial infarction undergoing percutaneous coronary intervention from KAMIR data. It is clear that bisoprolol and nebivolol are the same kind of beta-1-selective beta-blocker, but they are different in pharmacodynamics.

Our study had several limitations. First, we did not have data on the dosages and titrations of each beta-blocker. Therefore, we could not evaluate the impact of specific doses of bisoprolol or carvedilol. Second, because of its retrospective nature, differences in baseline characteristics could influence the outcome. To overcome these limitations, we adopted propensity-score matching. However, a large-scale randomized controlled trial may be needed to demonstrate the clinical benefits of bisoprolol compared with carvedilol in post-MI patients treated by PCI. Third, because of the relatively short duration of follow-up (mean duration: 10.2 months), long-term impacts on survival or MACEs were not addressed appropriately.

In conclusion, our study demonstrated the benefit of bisoprolol in the secondary prevention of acute MI regardless of the presence of heart failure. The clinical effects of bisoprolol were comparable with carvedilol in the secondary prevention of acute MI in patients who underwent PCI.

## CONFLICT OF INTEREST STATEMENT

None declared.

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