Beta-blocker Therapy and Cardiovascular Outcomes in Patients Who Have Undergone Percutaneous Coronary Intervention After ST-elevation Myocardial Infarction

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Abstract

The effect of β-blockers in ST-elevation myocardial infarction (STEMI) patients who have undergone primary percutaneous coronary intervention (PCI) has not been adequately evaluated. Using a large multi-center registry in Japan, we identified 3,692 patients who underwent PCI within 24 hours from onset of STEMI and were discharged alive from 2005 to 2007. Three-year cardiovascular outcomes were compared between the 2 groups of patients with (N = 1,614) or without (N = 2,078) β-blocker prescription at discharge. Compared with patients in the no-β group, patients in the β group were younger, more frequently male, more often had hypertension and atrial fibrillation but less often had chronic obstructive pulmonary disease than in the no-β group. Statins and angiotensin-converting enzyme inhibitors /angiotensin receptor blockers were more frequently prescribed in the β group. Crude incidence of cardiac death and/or recurrent myocardial infarction (cardiac death/MI) tended to be higher in the β group (7.6% vs. 6.2%, log-rank p = 0.1). After adjusting for potential confounders, β-blockers were associated with significantly higher risk for cardiac death/MI (hazard ratio 1.43, 95% confidence interval: 1.06-1.94, p = 0.01). Beta-blocker prescription at discharge was not associated with better cardiovascular outcomes in patients who underwent PCI after STEMI. Large-scale randomized controlled trials are needed to evaluate the role of β-blocker therapy in these patients.

Key Words: Beta-blocker, myocardial infarction, percutaneous coronary intervention, prognosis

Introduction

The current clinical guidelines for treatment of ST-segment elevation acute myocardial infarction (STEMI) recommend administration of oral β-blockers indefinitely to patients who have no contraindications. [1,2] The guidelines were established on the basis of results from studies conducted in the pre-fibrinolytic era or from studies including a relatively small proportion of patients with early revascularization by thrombolytic therapy or percutaneous coronary intervention (PCI). [3,4] However, conclusions from observational studies in patients treated with PCI after STEMI were discordant regarding the efficacy of oral β-blocker therapy. [5,6] In the Primary Angioplasty in Acute Myocardial Infarction (PAMI) study, it was reported that β-blockers after PCI were associated with lower 6-month mortality in patients with acute myocardial infarction (AMI). [5] In contrast, in the j-Cypher study, β-blockers were not associated with 3-year mortality in patients who underwent PCI after STEMI and survived the index hospitalization. [6] However, the sample sizes were relatively small and neither the types nor the doses of β-blockers were known in the previous studies. Therefore, the present study was designed to examine whether prescription of β-blockers at discharge was independently associated with improved cardiovascular outcomes in patients who underwent PCI after STEMI using a recent large registry in Japan.

Methods

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI registry is a physician-initiated non-company sponsored multi-center registry that enrolled consecutive AMI patients undergoing coronary revascularization within 7 days of the symptom onset between January 2005 and December 2007 across 26 tertiary hospitals in Japan (Supplemental Appendix A). Among 5,429 patients enrolled in the registry, 4,444 patients

were diagnosed as STEMI. Excluding 494 patients who underwent PCI beyond 24 hours and 258 patients who died during the index hospitalization, the current study population consisted of 3,692 patients who underwent PCI within 24 hours from onset of STEMI and survived the index hospitalization (Figure 1). Demographics, clinical factors, angiographic data, and discharge medications were collected from hospital charts or hospital databases according to pre-specified definitions by experienced clinical research coordinators (Supplemental Appendix B). Follow-up data were obtained from hospital charts or by contacting patients or referring physicians through 3 years. The relevant review boards or ethics committees in all 26 participating centers approved the study protocol.

Definitions

Prior myocardial infarction (MI), heart failure (HF), hypertension, current smoking, atrial fibrillation, chronic obstructive lung disease (COPD), liver cirrhosis, and malignancy were regarded as present when these diagnoses were recorded in the hospital charts. Prior stroke was defined as infarction or intracranial bleeding with neurological symptoms lasting > 24 hours. Peripheral vascular disease was regarded to be present when carotid, aortic, or other peripheral vascular diseases were being treated or scheduled for surgical or endovascular interventions. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or by echocardiography within 3 months after PCI and low LVEF was defined as LVEF ≤ 40%.

During the follow-up, death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. MI was defined according to the definition in the Arterial Revascularization Therapy Study. [7] Events such as cardiac death and MI were adjudicated by a clinical event committee. Hospitalization for HF was defined as hospitalization due to worsening HF requiring intravenous drug therapy. The primary outcome measure for the current analyses was a

composite endpoint of cardiac death and recurrent MI (cardiac death/MI). The secondary outcome measures assessed included all-cause death, cardiac death, recurrent MI, and hospitalization for HF.

Statistical methods

Cumulative incidences of clinical event rates were estimated by the Kaplan-Meier method and differences were assessed with the log-rank test. We used multivariable Cox proportional-hazards model stratified by centers to estimate the hazard ratio (HR) of β-blocker therapy at discharge for primary and secondary outcome measures by incorporating β-blocker therapy together with clinically relevant risk-adjusting variables. Adjusted HR and their 95% confidence interval (CI) were calculated. We computed adjusted cumulative incidence curves of β group and no-β group using the multivariable Cox proportional-hazards model in conjunction with methods described by Ghali et al. [8,9] The associations between β-blocker therapy at discharge and cardiovascular outcomes in the subgroup of patients with preserved and low LVEF were analyzed in the same way. We also performed subgroup analyses of different types and doses of β-blockers among patients in the β group.

Because clinical factors related to treatment selection may be expected to confound the rate of cardiovascular outcomes, we performed a propensity score-matched analysis between the β and no-β groups as a sensitivity analysis. Logistic regression was used to calculate the propensity score of prescription of β-blockers using clinically relevant variables and center. Patients in the β group were randomly matched to patients in the no-β group using a greedy matching strategy. [10] Survival analysis comparing the cases and controls was conducted using the Kaplan-Meier method, and statistical comparisons were drawn using the log-rank test.

All analyses were conducted by physicians (B.B. and N.O.) and a statistician (T.M.) using JMP 8 and SAS 9.2 (SAS

Institute Inc., Cary, NC), and all the reported p values were two-sided. A p value < 0.05 was regarded as statistically significant.

Results

Among the total of 3,692 study patients, oral β-blockers were prescribed in 1,614 patients (β group, 43.7%) at hospital discharge, while 2,078 patients were not (no-β group, 56.3%) (Figure 1). There were significant differences in baseline characteristics between the β and no-β groups (Table 1). Patients in the β group were younger, more frequently male, and more often had hypertension, high body weight, high body mass index (BMI), anterior MI, atrial fibrillation, and target of proximal left anterior descending artery. COPD were less prevalent in the β group. Statins, angiotensin-converting enzyme inhibitors (ACE-I) /angiotensin receptor blockers, and warfarin were more frequently prescribed in the β group (Table 1).

Clinical outcomes

Median follow-up duration was 955 (IQR: 693-1,248) days. Clinical follow-up were completed in 93.6% at 1 year, and 87.2% at 2 years. Three-year incidence of cardiac death/MI was 6.6% for the entire study population. Crude 3-year incidence of cardiac death/MI was not significantly different between patients in the β group and those in the no-β group (7.6% vs. 6.2%, log-rank p = 0.11, Table 2 and Figure 2A). However, after adjusting for 39 potential confounders listed in Table 1, the risk for cardiac death/MI was significantly higher in the β group (adjusted HR 1.43, 95% CI: 1.06-1.94, p = 0.01, Supplemental Table 1 and Figure 2A). The risk for hospitalization for HF was also significantly higher in the β group, however, the risk for all-cause death was not different between the groups (Table 2).

Subgroup analyses

In 2,944 patients with LVEF data, 2,494 patients (84.7%) had preserved LVEF at baseline. The differences in baseline characteristics between the β and no-β groups in the preserved- and low- LVEF subgroups were similar to the differences in the entire study population (Supplemental Tables 2 and 3). After adjusting for confounding variables, the incidence of cardiac death/MI was higher in the β group both in the preserved-LVEF subgroup (adjusted HR 1.27, 95% CI: 0.87-1.86, p = 0.21) and in the low-LVEF subgroup (adjusted HR 1.75, 95% CI: 0.69-4.47, p = 0.24), although the differences were not statistically significant (Table 2, Figures 2B and 2C).

Types and doses of β-blockers

Among 1,614 patients in the β group, carvedilol was prescribed in 1,456 patients (90.2%). The median dose of carvedilol in the current study population was 5 (range: 0.25-60.0) mg per day. Among 1,456 patients with carvedilol, 385 (26.5%) received carvedilol ≥ 10 mg per day, while 1,071 (73.6%) received < 10 mg per day (Supplemental Table 4). Crude incidence of 3-year cardiac death/MI was significantly lower in patients who received carvedilol ≥ 10 mg per day than in patients who received carvedilol < 10 mg per day (4.7% vs. 8.9%, log-rank p = 0.02, Supplemental Table 5). However, after adjusting for clinically relevant risk-adjusting variables, the risk for cardiac death/MI was not significantly different (adjusted HR 0.65, 95% CI: 0.38-1.05, p = 0.08, Supplemental Table 5).

Sensitivity Analyses

Propensity score of prescription of β-blockers was calculated using 24 clinically relevant variables (listed in Supplemental Table 6). In the propensity-score matched model, no significant differences in the baseline characteristics were found between the β and no-β groups, except that patients in the β group more frequently had prior HF and shock at presentation (Supplemental Table 6). There was no significant difference in the 3-year incidence of cardiac death/MI

between the β and no-β groups in this model (7.6% vs. 6.1%, log-rank p = 0.2, Supplemental Table 7). However, more hospitalizations for HF were observed in the β-group (7.2% vs. 3.9%, log-rank p < 0.0001) (Supplemental Table 7).

Discussion

The major findings of this recent registry analyses were as follows: (1) the 3-year cardiovascular event rate of patients who underwent PCI after STEMI was relatively low; (2) β-blocker prescription at discharge was not associated with better cardiovascular outcomes in these patients.

Despite the recommendations of the clinical guidelines, β-blocker use in STEMI has been less prevalent in the real-world clinical practice.[11] In the current study population, only 43.7% of patients received oral β-blocker therapy at discharge. That was less than the frequencies of β-blocker prescription reported from the PAMI study conducted in the USA (68.0%), [5] but similar to the rate reported in the Heart Institute of Japan Acute Myocardial Infarction registry (HIJAMI) study (32.2%) and the j-Cypher study (38.4%) conducted in Japan. [6,12]

The main mechanisms of the beneficial effects of β-blockers in patients with STEMI are considered to be the prevention of the cardiotoxic effects of catecholamines and the attenuation of the myocardial oxygen demand. β-blockers are also thought to be effective in reducing tachyarrhythmic events. Previous studies conducted in the pre-PCI era showed markedly lower mortality rate with β-blocker therapy in STEMI patients. [3,4] However, in the present study, relatively low 3-year cardiovascular event rate was observed despite the low prescription rate of β-blockers at discharge. In addition to the preserved LVEF in most STEMI patients who have undergone emergent PCI, the high use of up-to-date medications such as ACE-I /angiotensin receptor blockers and statins may result in the improved clinical outcomes of these patients. On the other hand, the adverse effects of β-blockers such as coronary spasm should be considered in these

patients as they are disadvantageous. In the Japanese β-blocker and Calcium Antagonist Myocardial Infarction (JBCMI) study, the incidence of coronary spasm was significantly higher in patients with β-blocker therapy than those with calcium antagonist therapy (1.2% vs. 0.2%, p = 0.02), but no significant difference was observed in cardiac mortality (1.7% vs. 1.1%, p = 0.37). [13] It's important to note that a majority of STEMI patients have hypertension (85.9% of patients in the β group had hypertension in the present study) and the adverse effects of β-blockers have been a concern in patients with hypertension on the basis of recent clinical trials. [14-16]

Study limitations

Our study has several important limitations. First, 90.2% of the β-blockers prescribed were carvedilol in the present study. The impacts of different types of β-blockers on clinical outcomes were difficult to compare. However, carvedilol, a nonselective β-blocker with alpha 1-adrenergic receptor blocking and antioxidant effects, has been reported to have superior cardioprotective effects compared to other β-blockers on reducing the risk of events after AMI. [17,18] Second, the relatively low dose of β-blockers prescribed could be one of the reasons why β-blockers were not associated with better clinical outcomes in this study. The median dose of carvedilol was 5 mg per day in this study, which was lower than the dose previously reported. In the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial, 12.5-50 mg per day of carvedilol reduced all-cause mortality, cardiovascular-cause mortality, and reinfarction when given to patients with recent AMI and LVEF ≤ 40%. [19] Another study reported that Carvedilol produced dose-related reductions in mortality and hospitalization rate in patients with HF. [20] In the current analysis, use of higher-dose carvedilol (≥ 10 mg per day) was associated with a tendency of better clinical outcomes compared with use of lower-dose carvedilol (< 10 mg per day) in a risk-adjusted model (p = 0.08). However, the relatively low dose of β-blockers

prescribed in the study patients was probably attributed to the physical and racial differences of the study patients. Japanese patients had lower body weight compared to the American patients. The median body weight of the Japanese STEMI patients observed in the β group in this study was 62 (IQR: 54-70) kg, which is obviously lower compared to the American STEMI patients at 80 (IQR: 70-91) kg. [21] In addition, Asian patients are predisposed to hypotension and bradycardia with high-dose β-blockers. [22] According to investigations conducted in Japan, the approved dose of carvedilol for the treatment of hypertension, coronary artery disease, and HF is 2.5 to 20 mg per day for Japanese patients. [23] Thus, the dose of β-blockers used in this study is thought to be reasonable for the study patients and it definitely reflected the real-world clinical practice in Japan. Third, we do not have information on which patients in the β group continued β-blockers during the years after discharge. Prescription of β-blockers at discharge might not be representative of long-term use of β-blockers after STEMI. However, previous studies reported that > 80% of patients continued to receive β-blockers 6 months after AMI. [24] In addition, patients not discharged on β-blockers are unlikely to be started on them as outpatients. [25] Forth, the current study did not have adequate power to assess outcomes in the subgroup with low LVEF. In this study, the use of β-blockers was not associated with better clinical outcomes in patients with low LVEF. The current result in the low-LVEF subgroup was inconsistent with the previous report from the j-Cypher registry that showed β-blockers after primary PCI were associated with reduced 3-year mortality in a subgroup of patients with low LVEF.[6] It was also inconsistent with the PAMI study in which β-blockers were associated with lower 6-month mortality in patients with LVEF ≤ 50%. [5] Although all of these studies are observational and including relatively small number of patients with low LVEF, beneficial effect of β-blocker for STEMI patients with low LVEF has been reported in a large-scale randomized controlled trial in which about a half of the patients underwent reperfusion therapy mainly by

thrombolytic therapy.[19] Finally, selection bias for use of β-blockers is inevitable in this type of observational study. Although we included potential confounders in the multivariable Cox proportional-hazards models and we tried to minimize the difference of baseline characteristics between patients in the β and no-β groups with propensity matching in the sensitivity analyses, we could not exclude influences of unmeasured confounders on clinical outcomes. The effect of β-blockers in patients with STEMI after successful PCI should be evaluated by a randomized controlled study with a large sample size.

Conclusions

In this study, oral β-blocker prescription at discharge was not associated with better cardiovascular outcomes in patients who underwent PCI after STEMI. Most of these patients had preserved LVEF and fair prognosis without β-blocker use. Large-scale randomized controlled trials are needed to evaluate the role of β-blocker therapy in these patients.

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All authors have contributed to the design of the study, interpretation of results, revising the manuscript, and approve the final version of the manuscript. We thank the members of the cardiac catheterization laboratories of the participating centers and the clinical research coordinators (Supplemental Appendix).

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Conflict of interest: none declared.

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Figure Legends

Figure 1. Study Flow Chart.

CABG = coronary artery bypass surgery, PCI = percutaneous coronary intervention, and STEMI = ST-segment elevation myocardial infarction.

Figure 2. Cardiac Death/MI Rates in the Study Population.

Crude and adjusted cumulative incidence curves for cardiac death/MI among patients treated with or without β-blockers in the entire cohort (A), in the preserved LVEF subgroup (B), and in the low LVEF subgroup (C).

LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention.

Table 1. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in All Patients

	β group	**No-β group**	**p**
	N = 1,614	**N = 2,078**	**value**
(A) Clinical characteristics			
Age (years)	65.8 ± 12.2	68.0 ± 12.1	< 0.0001
*Age ≥ 75 years	416 (25.8%)	668 (32.1%)	< 0.0001
*Male	1,255 (77.8%)	1,500 (72.2%)	0.0001
Body weight (kg)	62.4 (54.2-70.0) ‡	60.0 (53.0-68.0) ‡	< 0.0001†
BMI	23.5 (21.5-25.9)	23.3 (21.3-25.3)	0.0008†
*BMI < 25.0	1,103 (68.3%)	1,529 (73.6%)	0.0005
Onset-to-balloon time (hours)	4.1 (2.7-6.7) §	4.3 (2.9-7.6) §	0.002†
Onset-to-balloon time ≤ 6 hours	987 (70.4%) §	1,237 (67.3%) §	0.06
Door-to-balloon time (hours)	1.5 (1.0-2.2) ‖	1.5 (1.0-2.2) ‖	0.24†
*Anterior infarction	850 (52.7%)	955 (46.0%)	< 0.0001
*Hypertension	1,386 (85.9%)	1,521 (73.2%)	< 0.0001
Diabetes mellitus	494 (30.6%)	667 (32.1%)	0.33
*on insulin therapy	58 (3.6%)	92 (4.4%)	0.2

Table 1. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in All Patients (cont)

*Current smoking	686 (42.5%)	850 (40.9%)	0.32
*Heart failure	452 (28.0%)	556 (26.8%)	0.39
*Shock at presentation	234 (14.5%)	268 (12.9%)	0.15
*Multivessel disease	814 (50.4%)	1,048 (50.4%)	0.99
*Mitral regurgitation grade 3/4	38 (2.4%)	53 (2.6%)	0.7
LVEF (%)	52.4 ± 12.6 #	54.3 ± 12.2 #	< 0.0001
LVEF ≤ 40%	228 (16.7%) #	222 (14.1%) #	0.04
*Prior myocardial infarction	140 (8.7%)	177 (8.5%)	0.86
*Prior stroke	121 (7.5%)	194 (9.3%)	0.04
*Peripheral vascular disease	45 (2.8%)	60 (2.9%)	0.85
*eGFR < 30ml/min, not on dialysis	50 (3.1%)	70 (3.4%)	0.64
*Dialysis	24 (1.5%)	21 (1.0%)	0.19
*Atrial fibrillation	163 (10.1%)	171 (8.2%)	0.04
*Anemia (Hb < 11.0g/dl)	133 (8.2%)	172 (8.3%)	0.96
*Platelet < 100*109/L	28 (1.7%)	27 (1.3%)	0.27
*COPD	31 (1.9%)	94 (4.5%)	< 0.0001
*Liver cirrhosis	43 (2.7%)	46 (2.2%)	0.37

Table 1. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in All Patients (cont)

*Malignancy	117 (7.3%)	175 (8.4%)	0.19
(B) Procedural characteristics			
*DES use	480 (29.7%)	614 (29.5%)	0.89
Number of target lesions	1 (1-2)	1 (1-2)	0.17†
*Target of proximal LAD	947 (58.7%)	1,055 (50.8%)	< 0.0001
*Target of unprotected LMCA	42 (2.6%)	48 (2.3%)	0.56
*Target of CTO	51 (3.2%)	58 (2.8%)	0.51
*Target of bifurcation	414 (25.7%)	530 (25.5%)	0.92
*Side-branch stenting	45 (2.8%)	62 (3.0%)	0.72
Total number of stents	1 (1-2) #	1 (1-2) #	0.42†
Total stent length (mm)	25 (18-43) **	24(18-42) **	0.03†
*Total stent > 28mm	663 (44.3%) **	799 (42.0%) **	0.18
Minimum stent size (mm)	3 (2.5-3.5) **	3 (2.5-3.5) **	0.42†
*Minimum stent size < 3.0mm	479 (32.0%) **	589 (31.0%) **	0.51
(C) Discharge Medication			
Antiplatelet therapy			
Thienopyridine	1,565 (97.0%)	1,998 (96.1%)	0.18

Table 1. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in All Patients (cont)

Ticlopidine	1,426 (88.4%)	1,838 (88.5%)	0.92
Clopidogrel	139 (8.6%)	159 (7.7%)	0.28
Aspirin	1,608 (99.6%)	2,064 (99.3%)	0.21
*Cilostazol	541 (33.5%)	770 (37.1%)	0.02
Other medications			
*Statins	1,034 (64.1%)	1,056 (50.8%)	< 0.0001
*ACE-I/ARB	1,342 (83.2%)	1,451 (69.8%)	< 0.0001
*Nitrates	421 (26.1%)	696 (33.4%)	< 0.0001
*Calcium channel blockers	333 (20.6%)	429 (20.6%)	0.99
*Nicorandil	488 (30.2%)	600 (28.9%)	0.36
*Warfarin	238 (14.8%)	192 (9.2%)	< 0.0001
*Proton pump inhibitors	588 (36.4%)	697 (33.5%)	0.06
*H2-blockers	533 (33.0%)	774 (37.2%)	0.007

Variables are mean ± SD, n (%), or median (IQR). *Clinically relevant risk adjusting variables selected for multivariable Cox proportional-hazards model for β-blocker therapy.

† Wilcoxon p value.

‡ Values were missing for body weight (kg) in 107 patients, 30 in β group and 77 in no-β group.

§ Values were missing for onset-to-balloon time (hours) in 453 patients, 212 in β group and 241 in no-β group.

|| Values were missing for door-to-balloon time (hours) in 495 patients, 240 in β group and 255 in no-β group.

Values were missing for LVEF in 748 patients, 249 in β group and 499 in no-β group.

** Exclude 292 patients without stent implantation, 117 in β group and 175 in no-β group.

ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, COPD = chronic obstructive pulmonary disease, DES = drug-eluting stent, CTO = chronic total occlusion, eGFR = estimated glomerular filtration rate, H2-blocker = histamine type2 receptor blocker, LAD = left anterior descending coronary artery, LMCA = left main coronary artery, and LVEF = left ventricular ejection fraction.

Table 2. **Crude Event Rates and Adjusted Hazard Ratio Through 3 Years**

	β group	**No-β group**	**Log-rank p value**	**Adjusted HR [95%CI]**	**p value**
(A) All patients	**N = 1,614**	**N = 2,078**			
Cardiac death/MI	110 (7.6%)	118 (6.2%)	0.11	1.43 [1.06-1.94]	0.01
All-cause death	99 (7.5%)	150 (8.2%)	0.18	0.99 [0.73-1.34]	0.96
Cardiac death	50 (3.7%)	62 (3.3%)	0.86	1.44 [0.91-2.28]	0.11
MI	73 (4.9%)	63 (3.3%)	0.01	1.55 [1.07-2.27]	0.02
Hospitalization for HF	104 (7.2%)	105 (5.6%)	0.06	1.68 [1.21-2.33]	0.001
(B) Preserved LVEF	**N = 1,137**	**N = 1,357**			
Cardiac death/MI	66 (6.3%)	73 (5.9%)	0.57	1.27 [0.87-1.86]	0.2

Table 2. Crude Event Rates and Adjusted Hazard Ratio Through 3 Years (cont)

				0.87	
All-cause death	46 (4.9%)	71 (6.0%)	0.17	[0.56-1.37]	0.57
				1.40	
Cardiac death	21 (2.1%)	27 (2.3%)	0.76	[0.67-2.92]	0.36
				1.19	
MI	49 (4.6%)	49 (3.8%)	0.32	[0.77-1.85]	0.42
				1.82	
Hospitalization for HF	54 (5.4%)	48 (3.9%)	0.09	[1.12-2.96]	0.01
(C) Low LVEF	**N = 222**	**N = 228**			
				1.75	
Cardiac death/MI	25 (12.5%)	20 (9.8%)	0.44	[0.69-4.47]	0.24
				1.81	
All-cause death	29 (15.5%)	33 (17.0%)	0.35	[0.76-4.34]	0.17
				2.20	
Cardiac death	19 (10.3%)	18 (8.9%)	0.86	[0.65-7.41]	0.20
MI	11 (5·2%)	4 (2.0%)	0.04	—	—*
				1.26	
Hospitalization for HF	34 (16.0%)	34 (17.1%)	0.63	[0.62-2.53]	0.51

Incidences at 3 years were estimated by the Kaplan-Meier method.

* Adjusted HR of MI in low LVEF group could not be evaluated.

CI = confidence interval, HF = heart failure, HR = hazard ratio, LVEF = left ventricular ejection fraction, and MI = myocardial infarction.

Figure1.

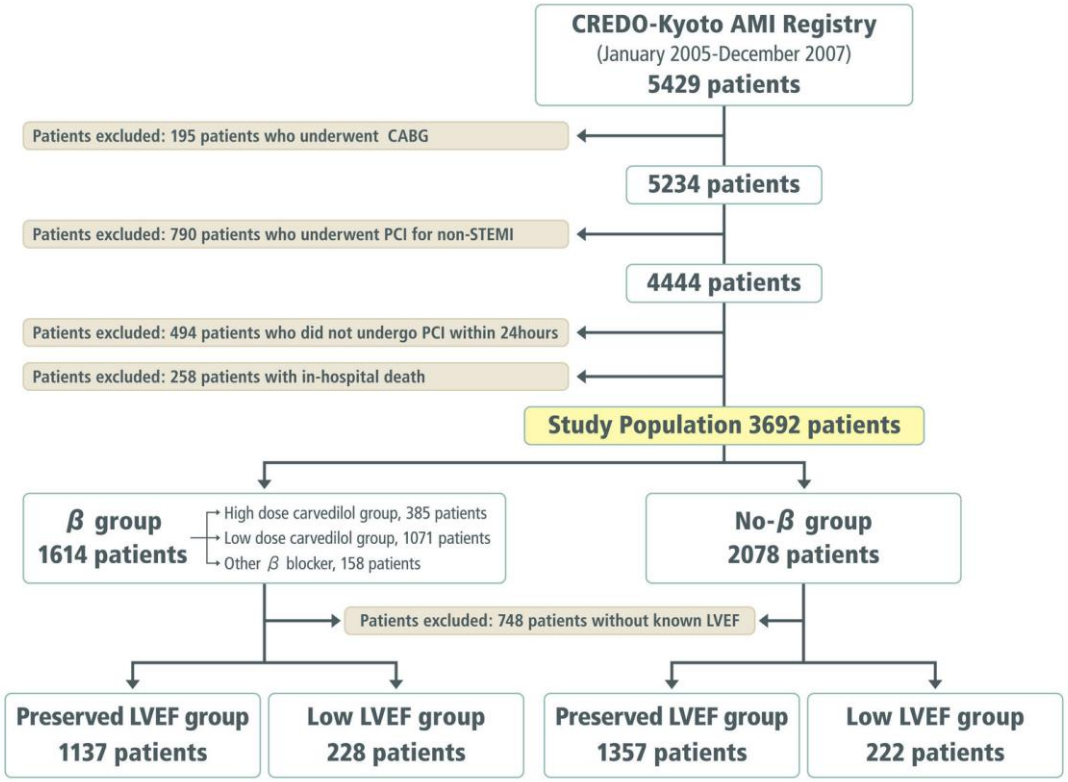
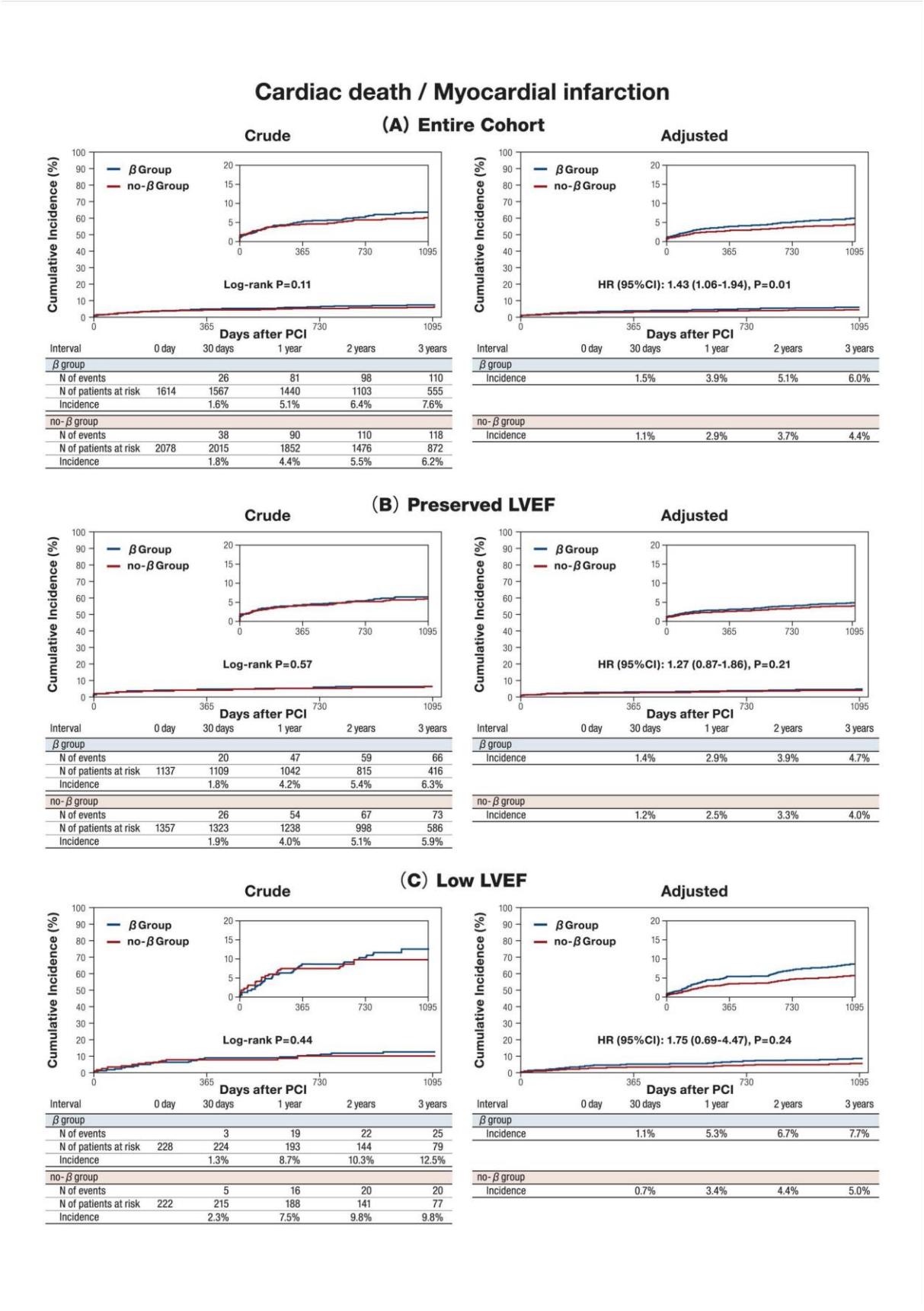

CREDO-Kyoto AMI Registry
(January 2005-December 2007)
5429 patients
Patients excluded: 195 patients who underwent CABG
5234 patients
Patients excluded: 790 patients who underwent PCI for non-STEMI
4444 patients
Patients excluded: 494 patients who did not undergo PCI within 24hours
Patients excluded: 258 patients with in-hospital death
Study Population 3692 patients
β group
1614 patients
High dose carvedilol group, 385 patients
Low dose carvedilol group, 1071 patients
Other β blocker, 158 patients
No-β group
2078 patients
Patients excluded: 748 patients without known LVEF
Preserved LVEF group
1137 patients
Low LVEF group
228 patients
Preserved LVEF group
1357 patients
Low LVEF group
222 patients

Figure 2.



Interval	0 day	30 days	1 year	2 years	3 years
β group					
N of events		26	81	98	110
N of patients at risk	1614	1567	1440	1103	555
Incidence		1.6%	5.1%	6.4%	7.6%
no-β group					
N of events		38	90	110	118
N of patients at risk	2078	2015	1852	1476	872
Incidence		1.8%	4.4%	5.5%	6.2%

Interval	0 day	30 days	1 year	2 years	3 years
β group					
Incidence		1.5%	3.9%	5.1%	6.0%
no-β group					
Incidence		1.1%	2.9%	3.7%	4.4%

Interval	0 day	30 days	1 year	2 years	3 years
β group					
N of events		20	47	59	66
N of patients at risk	1137	1109	1042	815	416
Incidence		1.8%	4.2%	5.4%	6.3%
no-β group					
N of events		26	54	67	73
N of patients at risk	1357	1323	1238	998	586
Incidence		1.9%	4.0%	5.1%	5.9%

Interval	0 day	30 days	1 year	2 years	3 years
β group					
Incidence		1.4%	2.9%	3.9%	4.7%
no-β group					
Incidence		1.2%	2.5%	3.3%	4.0%

Interval	0 day	30 days	1 year	2 years	3 years
β group					
N of events		3	19	22	25
N of patients at risk	228	224	193	144	79
Incidence		1.3%	8.7%	10.3%	12.5%
no-β group					
N of events		5	16	20	20
N of patients at risk	222	215	188	141	77
Incidence		2.3%	7.5%	9.8%	9.8%

Interval	0 day	30 days	1 year	2 years	3 years
β group					
Incidence		1.1%	5.3%	6.7%	7.7%
no-β group					
Incidence		0.7%	3.4%	4.4%	5.0%

SUPPLEMENTAL MATERIAL.

Supplemental Appendix A: List of Participating Centers and Investigators for the CREDO-Kyoto AMI Registry Cohort-2

Cardiology

Kyoto University Hospital: Takeshi Kimura

Kishiwada City Hospital: Mitsuo Matsuda, Hirokazu Mitsuoka

Tenri Hospital: Yoshihisa Nakagawa

Hyogo Prefectural Amagasaki Hospital: Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi

Kitano Hospital: Ryuji Nohara

Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda

Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi

Maizuru Kyosai Hospital: Ryozo Tatami

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani

Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Natsuhiko Ehara

Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa

Kansai Denryoku Hospital: Katsuhisa Ishii

Osaka Red Cross Hospital: Masaru Tanaka

University of Fukui Hospital: Jong-Dae Lee, Akira Nakano

Shizuoka City Shizuoka Hospital: Akinori Takizawa

Hamamatsu Rosai Hospital: Masaaki Takahashi

Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima

Japanese Red Cross Wakayama Medical Center: Takashi Tamura

Shimabara Hospital: Mamoru Takahashi

Kagoshima University Medica and Dental Hospital: Chuwa Tei, Shuichi Hamasaki

Shizuoka General Hospital: Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi

Kurashiki Central Hospital: Kazuaki Mitsudo, Kazushige Kadota

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi

Kumamoto University Hospital: Hisao Ogawa, Seigo Sugiyama

Shimada Municipal Hospital: Ryuichi Hattori, Takeshi Aoyama, Makoto Araki

Juntendo University Shizuoka Hospital: Satoru Suwa

Cardiovascular Surgery

Kyoto University Hospital: Ryuzo Sakata, Tadashi Ikeda, Akira Marui

Kishiwada City Hospital: Masahiko Onoe

Tenri Hospital: Kazuo Yamanaka

Hyogo Prefectural Amagasaki Hospital: Keiichi Fujiwara, Nobuhisa Ohno

Kokura Memorial Hospital: Michiya Hanyu

Maizuru Kyosai Hospital: Tsutomu Matsushita

Nara Hospital, Kinki University Faculty of Medicine: Noboru Nishiwaki, Yuichi Yoshida

Kobe City Medical Center General Hospital: Yukikatsu Okada, Michihiro Nasu

Osaka Red Cross Hospital: Shogo Nakayama

University of Fukui Hospital: Kuniyoshi Tanaka, Takaaki Koshiji, Koichi Morioka

Shizuoka City Shizuoka Hospital: Mitsuomi Shimamoto, Fumio Yamazaki

Hamamatsu Rosai Hospital: Junichiro Nishizawa

Japanese Red Cross Wakayama Medical Center: Masaki Aota

Shimabara Hospital: Takafumi Tabata

Kagoshima University Medica and Dental Hospital: Yutaka Imoto, Hiroyuki Yamamoto

Shizuoka General Hospital: Katsuhiko Matsuda, Masafumi Nara

Kurashiki Central Hospital: Tatsuhiko Komiya

Mitsubishi Kyoto Hospital: Hiroyuki Nakajima

Kumamoto University Hospital: Michio Kawasuji, Syuji Moriyama

Juntendo University Shizuoka Hospital: Keiichi Tanbara

Supplemental Appendix B: List of Clinical Research Coordinators

Research Institute for Production Development: Kumiko Kitagawa, Misato Yamauchi, Naoko Okamoto, Yumika Fujino, Saori Tezuka, Asuka Saeki, Miya Hanazawa, Yuki Sato, Chikako Hibi, Hitomi Sasae, Emi

Takinami, Yuriko Uchida, Yuko Yamamoto, Satoko Nishida, Mai Yoshimoto, Sachiko Maeda, Izumi Miki, Saeko Minematsu.

Supplemental Table 1. Multivariable Cox Proportional-hazards Model for 3-year Risk of Cardiac Death/MI

	Hazard Ratio	95% CI	p value
β-blockers	1.43	1.06-1.94	0.01
Age ≥ 75 years	2.07	1.51-2.86	< 0.0001
Male	0.97	0.69-1.37	0.87
BMI < 25.0	1.17	0.84-1.65	0.35
Anterior infarction	1.25	0.83-1.88	0.28
Hypertension	1.18	0.81-1.71	0.38
DM on insulin therapy	1.45	0.84-2.50	0.18
Current smoking	1.37	1.00-1.86	0.04
Heart failure	1.17	0.80-1.73	0.42
Shock at presentation	1.25	0.80-1.96	0.33
Multivessel disease	1.26	0.92-1.73	0.15
Mitral regurgitation grade 3/4	0.84	0.38-1.87	0.66
Prior myocardial infarction	1.64	1.09-2.48	0.01
Prior stroke	1.27	0.82-1.97	0.28

Supplemental Table 1. Multivariable Cox Proportional-hazards Model for 3-year Risk of Cardiac Death/MI (cont)

Peripheral vascular disease	1.48	0.80-2.73	0.2
eGFR < 30ml/min, not on dialysis	1.83	1.07-3.15	0.02
Dialysis	1.97	0.75-5.20	0.16
Atrial fibrillation	1.14	0.73-1.79	0.56
Anemia (Hb < 11.0g/dl)	1.10	0.71-1.70	0.66
Platelet < 100*109/L	2.23	1.13-4.41	0.02
COPD	2.39	1.35-4.23	0.002
Liver cirrhosis	0.99	0.47-2.06	0.97
Malignancy	1.37	0.91-2.05	0.13
DES use	0.62	0.40-0.96	0.03
Target of proximal LAD	1.09	0.71-1.67	0.69
Target of unprotected LMCA	1.42	0.70-2.88	0.33
Target of CTO	1.68	0.90-3.11	0.1
Target of bifurcation	0.92	0.64-1.31	0.63
Side-branch stenting	1.38	0.71-2.68	0.33
Total stent > 28mm	1.40	1.01-1.93	0.04

Supplemental Table 1. Multivariable Cox Proportional-hazards Model for 3-year Risk of Cardiac Death/MI (cont)

Minimum stent size < 3.0mm	1.16	0.83-1.61	0.39
Cilostazol	1.00	0.64-1.56	0.99
Statins	0.81	0.60-1.09	0.15
ACE-I/ARB	0.60	0.43-0.83	0.001
Nitrates	0.86	0.60-1.23	0.4
Calcium channel blockers	0.88	0.62-1.25	0.47
Nicorandil	0.97	0.68-1.38	0.85
Warfarin	1.18	0.76-1.84	0.45
Proton pump inhibitors	1.50	1.06-2.12	0.02
H2-blockers	1.16	0.80-1.68	0.43

ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CTO = chronic total occlusion, DES = drug-eluting stent, eGFR = estimated glomerular filtration rate, H2-blocker = histamine type2 receptor blocker, LAD = left anterior descending coronary artery, LMCA = left main coronary artery, and MI = myocardial infarction.

Supplemental Table 2. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Preserved LVEF

	β group N = 1137	No-β group N = 1357	p value
(A) Clinical characteristics			
Age (years)	65.3 ± 11.9	67.4 ± 12.1	< 0.0001
Age ≥ 75 years	266 (23.4%)	398 (29.3%)	0.0008
Male	885 (77.8%)	972 (71.6%)	0.0004
Body weight (kg)	63 (55-70) ‡	60 (53-68) ‡	< 0.0001
BMI	23.6 (21.8-25.9)	23.4 (21.3-25.4)	0.0008*
BMI < 25.0	765 (67.3%)	986 (72.7%)	0.003
Onset-to-balloon time (hours)	4 (2.7-6.6) §	4.2 (2.9-7.5) §	0.06*
Onset-to-balloon time ≤ 6 hours	687 (70.8%) §	803 (67.8%) §	0.13
Door-to-balloon time (hours)	1.5 (1.0-2.2) ‖	1.5 (1.0-2.2) ‖	0.95*
Anterior infarction	568 (50.0%)	584 (43.0%)	0.0006
Hypertension	983 (86.5%)	1000 (73.7%)	< 0.0001
Diabetes mellitus	335 (29.5%)	431 (31.8%)	0.21

Supplemental Table 2. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Preserved LVEF (cont)

on insulin therapy	35 (3.1%)	59 (4.4%)	0.09
Current smoking	491(43.2%)	554 (40.8%)	0.23
Heart failure	248 (21.8%)	296 (21.8%)	0.99
Shock at presentation	120 (10.6%)	153 (11.3%)	0.56
Multivessel disease	565 (49.7%)	673 (49.6%)	0.96
Mitral regurgitation grade 3/4	20 (1.8%)	37 (2.7%)	0.1
LVEF (%)	55 (49-63)	57 (50-65)	0.0002*
Prior myocardial infarction	78 (6.9%)	108 (8.0%)	0.29
Prior stroke	77 (6.8%)	106 (7.8%)	0.32
Peripheral vascular disease	30 (2.6%)	40 (3.0%)	0.64
eGFR < 30 ml/min, not on dialysis	26 (2.3%)	35 (2.6%)	0.63
Dialysis	13 (1.1%)	11 (0.8%)	0.39
Atrial fibrillation	109 (9.6%)	104 (7.7%)	0.08
Anemia (Hb < 11.0g/dl)	87 (7.7%)	98 (7.2%)	0.68
Platelet < $100*10^9$/L	21 (1.9%)	14 (1.0%)	0.08
COPD	25 (2.2%)	66 (4.9%)	< 0.0001

Supplemental Table 2. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Preserved LVEF (cont)

Liver cirrhosis	30 (2.6%)	32 (2.4%)	0.65
Malignancy	74 (6.5%)	112 (8.3%)	0.09
(B) Procedural characteristics			
DES use	341 (30.0%)	410 (30.2%)	0.9
Number of target lesions	1 (1-2)	1 (1-2)	0.21*
Target of proximal LAD	647 (56.9%)	659 (48.6%)	< 0.0001
Target of unprotected LMCA	26 (2.3%)	27 (2.0%)	0.6
Target of CTO	31 (2.7%)	37 (2.7%)	0.99
Target of bifurcation	292 (25.7%)	323 (23.8%)	0.27
Side-branch stenting	31 (2.7%)	37 (2.7%)	0.99
Total number of stents	1 (1-2) ||	1 (1-2) ||	0.65*
Total stent length (mm)	25 (18-43) #	24 (18-43) #	0.17*
Total stent > 28mm	465 (43.7%) #	526 (42.0%) #	0.39
Minimum stent size (mm)	3 (2.5-3.5) #	3 (2.5-3.5) #	0.61*
Minimum stent size < 3.0mm	332 (31.2%) #	407 (32.5%) #	0.52

Supplemental Table 2. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Preserved LVEF (cont)

(C) Discharge Medication			
Antiplatelet therapy			
Thienopyridine	1110 (97.6%)	1312 (96.7%)	0.15
Ticlopidine	1013 (89.1%)	1207 (88.9%)	0.47
Clopidogrel	97 (8.5%)	104 (7.7%)	0.47
Aspirin	1133 (99.6%)	1351 (99.5%)	0.76†
Cilostazol	343 (30.2%)	434 (32.0%)	0.32
Other medications			
Statins	753 (66.2%)	720 (53.1%)	< 0.0001
ACE-I/ARB	981 (86.3%)	997 (73.5%)	< 0.0001
Nitrates	306 (26.9%)	448 (33.0%)	0.0009
Calcium channel blockers	247 (21.7%)	294 (21.7%)	0.97
Nicorandil	329 (28.9%)	366 (27.0%)	0.27
Warfarin	151 (13.3%)	108 (8.0%)	< 0.0001
Proton pump inhibitors	422 (37.1%)	444 (32.7%)	0.02
H2-blockers	381 (33.5%)	496 (36.6%)	0.11

Supplemental Table 2. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Preserved LVEF (cont)

Variables are mean ± SD, n (%), or median (IQR).

*Wilcoxon p value. † Fisher p value.

‡ Values were missing for body weight (kg) in 48 patients, 15 in beta group and 33 in no-beta group.

§ Values were missing for onset-to-balloon time (hours) in 338 patients, 166 in beta group and 172 in no-beta group.

|| Values were missing for door-to-balloon time (hours) in 364 patients, 184 in beta group and 180 in no-beta group.

Exclude 176 patients without stent implantation, 73 in beta group and 103 in no-beta group.

ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CTO = chronic total occlusion, DES = drug-eluting stent, eGFR = estimated glomerular filtration rate, H2-blocker = histamine type2 receptor blocker, LAD = left anterior descending coronary artery, LMCA = left main coronary artery, and LVEF = left ventricular ejection fraction.

Supplemental Table 3. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Low LVEF

	β group N = 228	No-β group N = 222	p value
(A) Clinical characteristics			
Age (years)	67.0 ± 12.4	70.5 ± 11.9	0.002
Age ≥ 75 years	71 (31.1%)	90 (40.5%)	0.03
Male	179 (78.5%)	160 (72.1%)	0.11
Body weight (kg)	60 (52-69) ‡	59 (50-66) ‡	0.07
BMI	22.9 (20.7-25.1)	22.9 (20.5-24.5)	0.38*
BMI < 25.0	170 (74.6%)	181 (81.5%)	0.07
Onset-to-balloon time (hours)	4.2 (2.7-7.0) §	5.1 (1.3-10.1) §	0.002*
Onset-to-balloon time ≤6 hours	136 (68.0%) §	115 (58.1%) §	0.04
Door-to-balloon time (hours)§	1.6 (1.0-2.4) ‖	1.6 (1.0-2.3) ‖	0.59*
Anterior infarction	152 (66.7%)	159 (71.6%)	0.25
Hypertension	192 (84.2%)	167 (75.2%)	0.01
Diabetes mellitus	83 (36.4%)	69 (31.1%)	0.23

Supplemental Table 3. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Low LVEF (cont)

on insulin therapy	12 (5.3%)	11 (5.0%)	0.88
Current smoking	94 (41.3%)	84 (37.8%)	0.46
Heart failure	122 (53.5%)	113 (50.9%)	0.57
Shock at presentation	65 (28.5%)	42 (18.9%)	0.01
Multivessel disease	119 (52.2%)	117 (52.7%)	0.91
Mitral regurgitation grade 3/4	14 (6.1%)	10 (4.5%)	0.43
LVEF (%)|	35 (30-38)	36 (30.8-39)	0.07*
Prior myocardial infarction	33 (14.5%)	34 (15.3%)	0.8
Prior stroke	22 (9.7%)	32 (14.4%)	0.11
Peripheral vascular disease	9 (4.0%)	10 (4.5%)	0.76
eGFR < 30 ml/min, not on dialysis	16 (7.0%)	12 (5.4%)	0.47
Dialysis	6 (2.6%)	6 (2.7%)	0.96
Atrial fibrillation	31 (13.6%)	24 (10.8%)	0.36
Anemia (Hb < 11.0g/dl)	24 (10.5%)	28 (12.6%)	0.48
Platelet < $100*10^9$/L	5 (2.2%)	8 (3.6%)	0.36
COPD	3 (1.3%)	15 (6.8%)	0.003

Supplemental Table 3. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Low LVEF (cont)

Liver cirrhosis	7 (3.1%)	4 (1.8%)	0.38
Malignancy	19 (8.3%)	22 (9.9%)	0.56
(B) Procedural characteristics			
DES use	80 (35.1%)	81 (36.5%)	0.75
Number of target lesions	1 (1-2)	1 (1-2)	0.14*
Target of proximal LAD	159 (69.7%)	159 (71.6%)	0.66
Target of unprotected LMCA	11 (4.8%)	8 (3.6%)	0.51
Target of CTO	8 (3.5%)	10 (4.5%)	0.58
Target of bifurcation	63 (27.6%)	76 (34.2%)	0.12
Side-branch stenting	4 (1.8%)	8 (3.6%)	0.21
Total number of stents	1 (1-2) #	1 (1-2) #	0.09*
Total stent length (mm)	28 (20-44) #	24 (18-40.3) #	0.07*
Total stent > 28mm	98 (45.6%) #	80 (38.8%) #	0.16
Minimum stent size (mm)	3 (2.5-3.5) #	3 (2.8-3.5) #	0.37*
Minimum stent size < 3.0mm	79 (36.7%) #	55 (26.7%) #	0.02

Supplemental Table 3. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Low LVEF (cont)

(C) Discharge Medication			
Antiplatelet therapy			
Thienopyridine	221 (96.9%)	214 (96.4%)	0.75
Ticlopidine	200 (87.7%)	204 (91.9%)	0.04
Clopidogrel	21 (9.2%)	10 (4.5%)	0.04
Aspirin	226 (99.1%)	221 (99.6%)	1†
Cilostazol	72 (31.6%)	98 (44.1%)	0.005
Other medications			
Statins	133 (58.3%)	97 (43.7%)	0.001
ACE-I/ARB	185 (81.1%)	163 (73.4%)	0.05
Nitrates	59 (25.9%)	75 (33.8%)	0.06
Calcium channel blockers	44 (19.3%)	44 (19.8%)	0.88
Nicorandil	57 (25.0%)	54 (24.3%)	0.86
Warfarin	63 (27.6%)	43 (19.4%)	0.03
Proton pump inhibitors	98 (43.0%)	80 (36.0%)	0.13
H2-blockers	65 (28.5%)	80 (36.0%)	0.08

Supplemental Table 3. Baseline Clinical Characteristics, Procedural Characteristics and Baseline Medications in Patients with Low LVEF (cont)

Variables are mean ± SD, n (%), or median (IQR).

*Wilcoxon p value. † Fisher p value.

‡ Values were missing for body weight (kg) in 21 patients, 5 in beta group and 16 in no-beta group.

§ Values were missing for onset-to-balloon time (hours) in 52 patients, 28 in beta group and 24 in no-beta group.

|| Values were missing for door-to-balloon time (hours) in 64 patients, 37 in beta group and 27 in no-beta group.

Exclude 29 patients without stent implantation, 13 in beta group and 16 in no-beta group.

ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CTO = chronic total occlusion, DES = drug-eluting stent, eGFR = estimated glomerular filtration rate, H2-blocker = histamine type2 receptor blocker, LAD = left anterior descending coronary artery, LMCA = left main coronary artery, and LVEF = left ventricular ejection fraction.

Supplemental Table 4. Baseline Clinical Characteristics According to Doses of Carvedilol

	Carvedilol ≥ 10 mg per day N = 385	Carvedilol < 10 mg per day N = 1,071	p value
Clinical characteristics			
Age (years)	63.8 ± 11.8	66.5 ± 12.4	< 0.0001
*Age ≥ 75 years	82 (21.3%)	297 (27.7%)	0.01
*Male	320 (83.1%)	814 (76.0%)	0.003
Body weight (kg)	64 (57-72)	62 (53-70)	< 0.0001
BMI	24.2 (22.0-26.6)	23.4 (21.3-25.5)	< 0.0001†
*BMI < 25.0	242 (62.9%)	760 (71.0%)	0.003
Onset-to-balloon time (hours)	4.1 (2.8-6.5)	4.1 (2.7-6.7)	0.66†
Onset-to-balloon time ≤ 6 hours	244 (72.0%) ‡	649 (70.5%) ‡	0.06
Door-to-balloon time (hours)	1.1 (0.8-1.6) §	1 (0.8-1.5) §	0.06†
*Anterior infarction	196 (50.9%)	583 (54.4%)	0.23
*Hypertension	347 (90.1%)	899 (83.9%)	0.003
Diabetes mellitus	136 (35.3%)	311 (29.0%)	0.02

Supplemental Table 4. Baseline Clinical Characteristics According to Doses of Carvedilol (cont)

*on insulin therapy	14 (3.6%)	36 (3.4%)	0.8
*Current smoking	169 (43.9%)	464 (43.3%)	0.84
*Heart failure	92 (23.9%)	322 (30.1%)	0.02
*Shock at presentation	40 (10.4%)	174 (16.2%)	0.005
*Multivessel disease	205 (53.2%)	525 (49.0%)	0.15
*Mitral regurgitation grade 3/4	8 (2.1%)	25 (2.3%)	0.77
LVEF (%)	54 (47-62) ‖	52 (43-62) ‖	0.001†
LVEF ≤ 40%	37 (11.4%) ‖	169 (18.3%) ‖	0.003
*Prior myocardial infarction	32 (8.3%)	92 (8.6%)	0.86
*Prior stroke	37 (9.6%)	73 (6.8%)	0.07
*Peripheral vascular disease	12 (3.1%)	32 (3.0%)	0.89
*eGFR < 30 ml/min, not on dialysis	17 (4.4%)	27 (2.5%)	0.06
*Dialysis	4 (1.0%)	18 (1.7%)	0.37
*Atrial fibrillation	36 (9.4%)	107 (10.0%)	0.71
*Anemia (Hb < 11.0g/dl)	25 (6.5%)	98 (9.2%)	0.1
*Platelet < $100*10^9$/L	4 (1.0%)	18 (1.7%)	0.37

Supplemental Table 4. Baseline Clinical Characteristics According to Doses of Carvedilol (cont)

*COPD	2 (0.5%)	26 (2.4%)	0.01
*Liver cirrhosis	6 (1.6%)	34 (3.2%)	0.09
*Malignancy	22 (5.7%)	84 (7.8%)	0.16

Variables are mean ± SD, n (%), or median (IQR). *Clinically relevant risk variables selected for multivariable Cox proportional-hazards model for doses of carvedilol.

† Wilcoxon p value.

‡ Values were missing for onset-to-balloon time (hours) in 196 patients, 46 in high dose group and 150 in low dose group.

§ Values were missing for door-to-balloon time (hours) in 220 patients, 51 in high dose group and 169 in low dose group.

|| Values were missing for LVEF in 207 patients, 59 in high dose group and 148 in low dose group.

BMI = body mass index, COPD = chronic obstructive pulmonary disease, and eGFR = estimated glomerular filtration rate, and LVEF = left ventricular ejection fraction.

Supplemental Table 5. Crude Event Rates and Adjusted Hazard Ratio Through 3 Years According to Doses of Carvedilol

	Carvedilol ≥ 10 mg per day N = 385	Carvedilol < 10 mg per day N = 1,071	Log-rank p value	Adjusted HR [95%CI]	p value
Cardiac death/MI	17 (4.7%)	85 (8.9%)	0.02	0.65 [0.38-1.05]	0.08
All-cause death	15 (4.6%)	74 (8.5%)	0.05	0.82 [0.48-1.38]	0.48
Cardiac death	6 (1.8%)	40 (4.6%)	0.02	0.57 [0.23-1.24]	0.16
MI	12 (3.3%)	55 (5.6%)	0.13	0.65 [0.34-1.14]	0.13
Hospitalization for HF	21 (5.9%)	71 (7.5%)	0.68	1.10 [0.56-2.04]	0.76

Variables are n (%). Incidences at 3 years were estimated by the Kaplan-Meier method.

CI = confidence interval, HF = heart failure, HR = hazard ratio, LVEF = left ventricular ejection fraction, and MI = myocardial infarction.

Supplemental Table 6. Baseline Clinical Characteristics in Propensity Score Matched Population

	β group	**No-β group**	**p**
	N = 1,614	**N = 1,614**	**value**
Age ≥ 75 years	416 (25.8%)	392 (24.3%)	0.32
Male	1,255 (77.8%)	1,243 (77.0%)	0.61
BMI < 25.0	1,103 (68.3%)	1,093 (67.7%)	0.7
Anterior infarction	850 (52.7%)	847 (52.5%)	0.91
Hypertension	1,386 (85.9%)	1,388 (86.0%)	0.91
DM on insulin therapy	58 (3.6%)	60 (3.7%)	0.2
Heart failure	452 (28.0%)	398 (24.7%)	0.03
Shock at presentation	234 (14.5%)	187 (11.6%)	0.01
Multivessel disease	814 (50.4%)	856 (53.0%)	0.13
Prior myocardial infarction	140 (8.7%)	141 (8.7%)	0.95
Prior stroke	121 (7.5%)	135 (8.4%)	0.36
Peripheral vascular disease	45 (2.8%)	33 (2.0%)	0.16
Dialysis	24 (1.5%)	28 (1.7%)	0.57

Supplemental Table 6. Baseline Clinical Characteristics in Propensity Score Matched Population (cont)

Atrial fibrillation	163 (10.1%)	183 (11.3%)	0.25
COPD	31 (1.9%)	21 (1.3%)	0.16
Liver cirrhosis	43 (2.7%)	41 (2.5%)	0.82
Malignancy	117 (7.3%)	119 (7.4%)	0.89
Target of proximal LAD	947 (58.7%)	966 (59.9%)	0.49
Target of unprotected LMCA	42 (2.6%)	30 (1.9%)	0.15
Statins	1,034 (64.1%)	1,006 (62.3%)	0.3
ACE-I/ARB	1,342 (83.2%)	1,243 (83.2%)	0.96
Nitrates	421 (26.1%)	405 (25.1%)	0.51
Calcium channel blockers	333 (20.6%)	335 (20.8%)	0.93
Nicorandil	488 (30.2%)	513 (31.8%)	0.34

Variables are n (%). ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, LAD = left anterior descending coronary artery, and LMCA = left main coronary artery.

Supplemental Table 7. Event Rates Through 3 Years in Propensity Score Matched Population

	β group	**No-β group**	**p**
	N = 1,614	**N = 1,614**	**value**
Cardiac death/MI	110 (7.6%)	92 (6.1%)	0.2
All-cause death	99 (7.5%)	117 (8.1%)	0.23
Cardiac death	50 (3.7%)	43 (2.9%)	0.46
MI	73 (4.9%)	59 (3.9%)	0.22
Hospitalization for HF	104 (7.2%)	53 (3.9%)	< 0.0001

Incidences at 3 years were estimated by the Kaplan-Meier method.

HF = heart failure and MI = myocardial infarction.