International Medical Society
http://imedicalsociety.org

International Archives of Medicine
Section: Cardiology
ISSN: 1755-7682

2016
Vol. 9 No. 115
doi: 10.3823/1986

Impact of Beta Blockers on Left Ventricular Reverse Remodeling Following Primary Coronary Intervention for ST-elevation Myocardial Infarction

ORIGINAL

Toshiharu Fujii[1], Hirofumi Nagamatsu[1], Manabu Kimura[1], Masataka Nakano[1], Yohei Ohno[1], Gaku Nakazawa[1], Norihiko Shinozaki[1], Fuminobu Yoshimachi[1], Yuji Ikari[1]

1 Division of Cardiology, Tokai University School of Medicine, Isehara, Japan.

Contact information:

Yuji Ikari, M.D. Ph.D.
Professor of Medicine, Department of Cardiology.

Address: Tokai University School of Medicine. 143 Shimokasuya, Isehara, 259-1193, Japan.
Tel: 81-463-93-1121.
Fax: 81-463-93-6679.

ikari@is.icc.u-tokai.ac.jp

Abstract

Background: Benefits of beta-adrenergic receptor blockers (BB) following ST-elevation myocardial infarction (STEMI) are based on data before primary percutaneous coronary intervention (PCI) became the therapeutic first choice. This study examined the relationship between BB dose and magnitude of left ventricular ejection fraction (LVEF) improvement in STEMI following primary PCI.

Methods and Findings: A total of 235 STEMI patients following primary PCI who underwent echocardiography during the acute phase and over 6 months from onset were studied retrospectively. Serial LVEFs were assessed for three groups: no BB (n=33), carvedilol (n=163), and bisoprolol (n=42). Left ventricular reverse remodeling (RR) was defined as LVEF improvement ≥10%. All patients received fixed doses of BB and renin-angiotensin system inhibitor during observation. The median interval between echocardiographs was 526 days. The mean LVEF change was +2.6% (acute: 53.9±9.9%, chronic: 56.4±10.6%). Carvedilol and bisoprolol groups showed LVEF improvement, but none was seen in the no BB group (+3.7±6.5%, +3.8±6.9%, -4.2±5.0%, P<0.0001, respectively). The LVEF improvement effect was BB dose dependent. Therapy with BBs had a high rate of RR (no BB 0%, carvedilol 19.4%, bisoprolol 16.7%, P=0.0225, respectively). Multivariate analysis showed the following predictors of RR: baseline LVEF <50% and regular dose of BB, ≥10 mg of carvedilol or ≥1.25 mg of bisoprolol (Odds ratio 2.35, 95% Confidence Interval [CI] 1.12-5.02, P=0.0242; Odds ratio 4.45, 95% CI 2.06-10.27, P=0.0001).

Conclusions: Immediate BB administration following primary PCI for STEMI provided a dose-dependent LVEF improvement. A LVEF <50% and regular dose of BB are predictors of RR.

Keywords
ST-Elevation Myocardial Infarction; Beta-Adrenergic Blockers; Reverse Remodeling; Left Ventricular Ejection Fraction.

Introduction

Various large clinical trials confirmed that renin-angiotensin system inhibitors or beta-adrenergic blockers (BB) have a preventive effect in left ventricular remodeling and improvement in long-term survival. [1-8] Left ventricular reverse remodeling (RR) produced by these optimal medical therapy was recognized as an important surrogate marker toward improvement of clinical outcomes. Current practice guidelines on the management of ST-elevation myocardial infarction (STEMI) recommends immediate BB introduction during hospitalization. [9, 10] However, these guidelines are mainly based on data before primary percutaneous coronary intervention (PCI) became the first choice for revascularization.

Recent studies, such as the OACIS trial and post-hoc sub-analysis of the J-Cypher registry, proved that BB did not always contribute to the improvement of long-term outcomes in STEMI. [9, 11] The beneficial effects seen in those studies were limited in patients with higher risk or low left ventricular ejection fraction (LVEF). These studies suggested potential room for revision regarding BB dose or indication for STEMI in the current era, when prompt revascularization by primary PCI is a standard therapy.

In this study, serial echocardiographic LVEF data at acute and chronic phase were analyzed to study the relationship between the dosage of BB and the magnitude of LVEF improvement in STEMI following standard primary PCI.

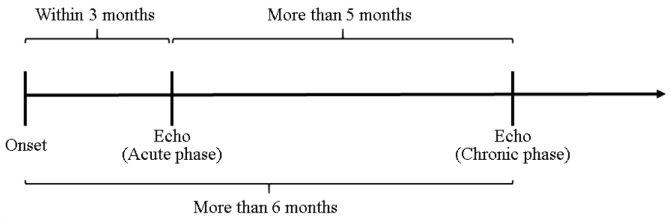
Methods

Study design and population.

To study the relationship between the dosage of BB and the magnitude of LVEF improvement in STEMI following primary PCI, this study surveyed STEMI patients who underwent primary PCI during January 2006 and March 2015 retrospectively at Tokai University School of Medicine. The BB dose at hospital discharge was assessed for discussion regarding the dosing-improvement relationship.

Inclusion criteria included those patients who were administrated BB during hospitalization and continued on a fixed dose of BB their echocardiographic LVEF evaluation at the acute phase to the chronic phase. A total of 235 patients were included in the study population and divided into three groups by type of BB administered: no BB (n=33), carvedilol (n=163), or bisoprolol (n=42). To determine the change in LVEF from acute phase to chronic phase, LVEF was evaluated by echocardiography within 3 months from STEMI onset (defined as the acute phase) and at more than 6 months from STEMI onset with more than a 5-month interval from acute phase echocardiography (defined as the chronic phase) **(Figure 1)**.

Figure 1: Time line of echocardiographic evaluations.



Exclusion criteria were as follows: STEMI patients who did not undergo primary PCI, those whose BB dose changed during the observation period, those who did not receive renin-angiotensin system inhibitor during observation period, those who had been administrated BB before STEMI onset, those without acute phase echocardiographic evaluation within 3 months from STEMI onset, those without chronic phase echocardiographic evaluation performed more than 5 months from the acute phase echocardiographic evaluation and more than 6 months from STEMI onset, those with new onset of myocardial infarction or any cardiac surgery (including coronary artery bypass grafting) after STEMI and during the observation period, and those patients who were treated with a BB other than carvedilol or bisoprolol.

All patients gave written informed consent; this study was designed in accordance with the ethical standards of the General Clinical Research Center of Tokai University School of Medicine. This study obtained all required approvals by the Tokai University institutional review board.

Medications.

The timing of introduction, dose, or selection of proper medications including BB during hospitalization was determined by an experienced cardiologist team with consideration of patients' general status. All study patients received fixed doses of BB and renin-angiotensin system inhibitor, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blockers during the observation period.

Serial echocardiographic evaluations.

All echocardiographic studies were performed by an experienced investigator with the patient in the supine position, using the Xario XG with a 1.8-4.2-MHz PST-25AT transducer (Toshiba Medical Systems Corporation; Tochigi, Japan). The recorded echocardiographic data were evaluated and assessed based on the recommendations of the American Society of Echocardiography. [12] To assess the improvement of LVEF and RR effect by BB, serial LVEFs were evaluated by 2-dimensional echocardiography at the acute and chronic phases with a more than 5-month interval between evaluations. Acute phase evaluation was performed under stable hemodynamic status within 3 months after STEMI onset. Chronic phase evaluation was performed at least 6 months from STEMI onset **(Figure 1)**. For 2-dimensional measurements, the LVEF was calculated in apical 4-chamber and apical 2-chamber views at end-diastole and at end-systole by modified Simpson's rule. [12, 13] Serial LVEFs at acute and chronic phases were evaluated using the same clearest angle. Papillary muscles were excluded from the cavity in the tracking. End-diastole was defined at the onset of the QRS wave on electrocardiographic (ECG) monitoring, and end-systole was defined as the time of the frame preceding mitral valve opening.

In M-mode recording, the septal wall thickness, posterior wall thickness, and left ventricular internal dimensions were measured over several cardiac cycles in the parasternal short-axis acoustic window to optimize medial-lateral beam orientation. These parameters were measured at the level of the mitral valve leaflet tips at the left ventricular minor axis. The thickness of the ventricular wall and chamber size were measured as the distance between the leading edge echoes.

Definitions

STEMI was defined as acute when the patient presented within 24 hours of symptom onset and ECG

findings on arrival showed persistent ST-segment elevation >1 mm in two contiguous leads, with new or presumed new left bundle branch block. The final diagnosis was made by emergency coronary angiography, and all patients were underwent primary PCI.

Improvement in LVEF was assessed from the difference calculated by subtracting LVEF at chronic phase from the value determined in the acute phase. RR was defined as LVEF improvement >10%. [14, 15]

Statistical analysis

Numerical factors with normal distribution are shown as mean ± standard deviation. Numerical factors with skewed distribution are shown as medians (interquartile range). Student's t-test was used to determine statistically significant differences in clinical parameters between two groups with normal distribution. The Wilcoxon rank-sum test was used to determine statistically significant differences in clinical values between two different groups with skewed distribution. Analysis of variance test was performed to compare numerical parameters among the three groups. Fisher's exact test was applied to determine the difference between three categorical variables. The Steel-Dwass test was used to test for between-group differences in numerical factors with skewed distribution. The multiple logistic regression model for examine the parameters to achieve RR included variables with p <0.10 in the univariate analysis. The goodness of fit for multivariable analysis was tested by the Hosmer-Lemeshow test. P-values in the tables show the statistical comparison among the three groups. The results of multivariate analysis were summarized by odds ratios (OR) and 95% confidence intervals (CI). A value of P <0.05 was considered statistically significant. All statistical calculations were performed using JMP version 11 (SAS Institute, Inc.; Cary, NC, USA).

Results

To study the relationship between dosage of BB and the magnitude of LVEF improvement in STEMI following primary PCI, our study examined the serial echocardiographic evaluations at acute and chronic phase. Baseline characteristics are shown in **Table 1**. Among the total of 235 patients, the mean age

Table 1. Distribution of the domains and facets of QoL. João Pessoa, PB, 2015.

	Overall (n=235)	No BB (n=33)	Carvedilol (n=160)	Bisoprolol (n=42)	P value
Age, years	63.3 ± 12.1	66.9 ± 13.7	62.4 ± 12.1	64.0 ± 10.8	0.1362
Male	192 (83.8%)	23 (69.7%)	137 (85.6%)	32 (76.2%)	0.0584
Height, cm	162.5 ± 8.3	160.0 ± 8.6	163.5 ± 7.9	161.0 ± 9.1	0.0292
Weight, kg	64.1 ± 13.0	58.5 ± 12.6	65.7 ± 12.8	62.3 ± 12.8	0.0084
Current smoking	90 (38.3%)	8 (24.2%)	70 (43.8%)	12 (28.6%)	0.0834
Diabetes mellitus	79 (33.6%)	14 (42.4%)	55 (34.4%)	10 (23.8%)	0.2233
Insulin	7 (3.0%)	2 (6.1%)	5 (3.1%)	0	0.3033
Dyslipidemia	173 (73.6%)	19 (57.6%)	126 (78.8%)	28 (66.7%)	0.0270
Hypertension	173 (73.6%)	25 (75.8%)	121 (75.6%)	27 (64.3%)	0.3178
Family history	31 (13.2%)	4 (12.1%)	22 (13.8%)	5 (11.9%)	0.9336
Prior PCI	22 (9.4%)	3 (9.1%)	13 (8.1%)	6 (14.3%)	0.4744
Prior CABG	1 (0.4%)	0	1 (0.6%)	0	0.7903

	Overall (n=235)	No BB (n=33)	Carvedilol (n=160)	Bisoprolol (n=42)	P value
Prior stroke	24 (10.2%)	3 (9.1%)	18 (11.3%)	3 (7.1%)	0.7172
Hemodialysis	2 (0.9%)	0	1 (0.6%)	1 (2.4%)	0.4618
Hemoglobin, mg/dL	14.4 ± 2.1	14.0 ± 2.0	14.7 ± 1.9	13.5 ± 2.4	0.0014
LDL cholesterol, mg/dL	125.4 ± 39.3	125.0 ± 43.8	125.3 ± 39.4	126.1 ± 36.0	0.9903
HDL cholesterol, mg/dL	50 (40-59)	50 (43-59)	49 (39-59)	53 (40.5-62.5)	0.1920
Triglyceride, mg/dL	100.5 (56-156)	126 (53.5-178)	100 (56-154)	93 (60-140.5)	0.4406
Serum creatinine, mg/dL	0.8 (0.7-1)	0.89 (0.755-1.17)	0.8 (0.7-0.99)	0.835 (0.6675-1)	0.4492
Estimated GFR, ml/min/1.73 m^2	71.5 ± 22.4	65.9 ± 27.5	73.0 ± 20.8	70.0 ± 23.5	0.2298
BNP, pg/dL	45.4 (19.2-154.4)	43.2 (21.1-244.8)	54.1 (18.825-154.025)	40.85 (18.75-118)	0.6579
GRACE risk score	149.4 ± 36.2	155.4 ± 38.8	145.9 ± 34.6	157.7 ± 38.9	0.1000
Systolic BP on arrival, mmHg	135.4 ± 32.3	136.1± 30.2	137.5 ± 34.2	126.8 ± 24.7	0.1621
Diastolic BP in arrival, mmHg	77.0 ± 23.8	71.6 ± 23.9	79.2 ± 24.1	73.2 ± 21.7	0.1292
Shock on arrival	17 (7.2%)	4 (12.1%)	11 (6.9%)	2 (4.8%)	0.4521
Killip I	145 (61.7%)	19 (57.6%)	101 (63.1%)	25 (59.5%)	0.1547
De novo lesion	229 (97.5%)	32 (97.0%)	157 (98.1%)	40 (95.2%)	0.3535
Three vessel disease	11 (4.7%)	1 (3.0%)	8 (5.0%)	2 (4.8%)	0.9027
Peak CPK, IU/L	2497 (1348-4638)	2181 (874-3565.5)	2888 (1398.75-4688.5)	2136 (1242.75-4731.5)	0.8679
Length of hospitalization, day	10 (8-14)	8 (7-16)	10 (8-14)	11 (9-14)	0.0645
Medication at discharge					
ACEI/ ARB	184 (78.3%)/51 (21.7%)	28 (84.9%)/5 (15.2%)	121 (75.6%)/39 (24.4%)	35 (83.3%)/7 (16.7%)	0.3443
Statin	210 (89.3%)	27 (81.8%)	144 (90.0%)	39 (92.9%)	0.2748
DAPT	220 (93.6%)	30 (90.9%)	152 (95.0%)	38 (90.5%)	0.4756

PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; GFR = glomerular filtration rate; BNP = brain natriuretic peptide; BP = blood pressure; CPK = creatine phosphokinase; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; DAPT = dual antiplatelet therapy; BB = beta adrenergic receptor blocker

was 63.3 ± 12.1 years, and 83.8% of patients were male. Blood pressure, shock vitals, decompensated heat failure, GRACE risk score on onset and peak creatine phosphokinase after primary PCI were not significantly different across the three groups. Medications at hospital discharge (including renin-angiotensin system inhibitor, statins, and antiplatelet therapy) were not significantly different across the three groups.

Serial echocardiographic evaluations

Table 2 shows the result of serial echocardiographic evaluations. The median interval of serial echocardiographic evaluations from acute to chronic phase was 526 days (range: 300 to 1041 days), and from STEMI onset to chronic phase echocardiographic evaluation was 537 days (range: 303 to 1042 days). The mean LVEFs at the acute and chronic

Table 2. Serial echocardiographic evaluations.

	Overall (n=235)	No BB (n=33)	Carvedilol (n=160)	Bisoprolol (n=42)	P value
Acute phase					
Days from onset, day	2 (1-11)	1 (1-9.5)	2 (1-13)	2 (1-5.25)	0.3901
LVEF, %	53.9 ± 9.9	58.5 ± 12.5	53.0 ± 9.4	53.6 ± 8.9	0.0134
LA, mm	34.1 ± 7.1	34.5 ± 9.3	33.9 ± 6.6	34.5 ± 7.5	0.8308
LVDd, mm	49.7 ± 6.8	49.3 ± 8.5	49.8 ± 6.6	49.3 ± 5.9	0.8866
LVDs, mm	32.2 ± 6.9	32.3 ± 8.0	32.7 ± 6.9	31.6 ± 6.0	0.5880
IVS, mm	11.0 ± 2.3	10.7 ± 2.2	11.2 ± 2.3	10.5 ± 2.2	0.2505
PW, mm	10.4 ± 1.8	10.4 ± 2.0	10.5 ± 1.7	10.4 ± 1.7	0.9247
EDV, mL	122.5 ± 34.6	115.8 ± 42.2	123.7 ± 33.8	123.3 ± 31.4	0.5211
ESV, mL	45.0 ± 23.0	43.2 ± 25.7	46.2 ± 23.9	42.9 ± 18.1	0.6555
E/A	0.9 ± 0.5	0.9 ± 0.5	0.9 ± 0.5	0.9 ± 0.4	0.8440
DcT, msec	0.21 ± 0.10	0.21 ± 0.05	0.20 ± 0.08	0.23 ± 0.19	0.3123
Late phase					
Days from onset, day	537 (303-1042)	414 (212-816)	560 (338.75-1312.5)	456 (282.25-838.5)	0.0031
Interval from 1st echocardiography	526 (300-1041)	413 (210.5-813)	541 (334-1282.75)	453 (277.5-814)	0.0034
LVEF, %	56.4 ± 10.6	54.1 ± 12.7	56.6 ± 10.0	57.4 ± 11.3	0.3783
LA, mm	36.4 ± 7.6	37.6 ± 9.7	35.8 ± 6.4	37.7 ± 9.7	0.2120
LVDd, mm	51.2 ± 7.0	50.7 ± 7.2	51.3 ±7.2	51.0 ± 6.3	0.9076
LVDs, mm	33.2 ± 7.8	34.2 ± 8.7	33.0 ± 7.6	33.0 ± 8.0	0.7588
IVS, mm	10.3 ± 2.1	10.3 ± 1.7	10.3 ± 2.1	10.0 ± 2.3	0.5695
PW, mm	9.8 ± 1.5	9.8 ± 1.5	9.8 ± 1.5	9.7 ± 1.3	0.8965
EDV, mL	123.5 ± 39.0	128.1 ± 49.7	122.9 ± 38.0	122.0 ± 33.9	0.7764
ESV, mL	46.7 ± 25.4	46.8 ± 24.2	46.2 ± 25.6	48.2 ± 26.4	0.9130
E/A	0.9 ± 0.5	0.8 ± 0.3	0.8 ± 0.3	1.1 ± 1.0	0.0299
DcT, msec	0.23 ± 0.06	0.21 ± 0.04	0.23 ± 0.07	0.21 ± 0.04	0.1017

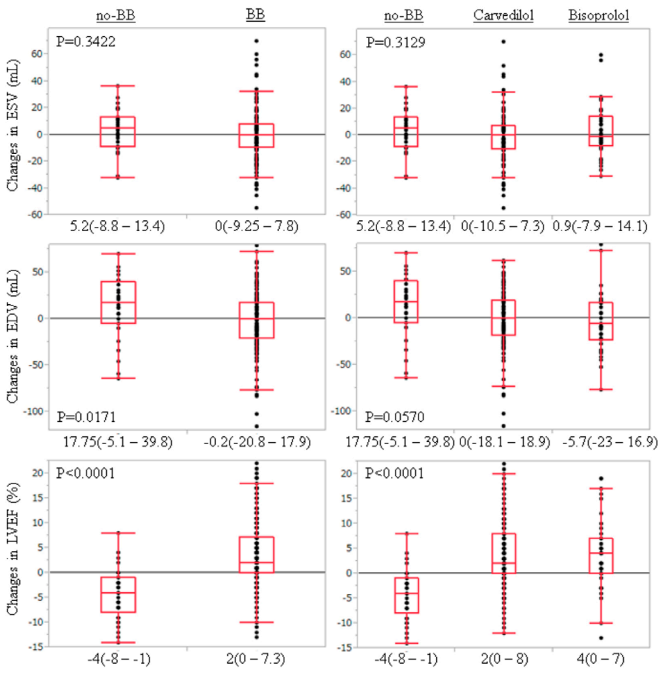
LVEF = left ventricular ejection fraction; LA = left atrium; LVDd = left ventricular diastolic diameter; LVDs = left ventricular systolic diameter; IVS = interventriclr septum; PW = posterior wall; EDV = end-diastolic volume; ESV = end-systolic volume; E/A = early diastolic filling velocity/ atrial filling velocity; DcT = decelaration time; BB = beta adrenergic receptor blocker

phases in the overall population were 53.9 ± 9.9% and 56.4 ± 10.6%, respectively. In the evaluation during the acute phase, the no BB group had a significantly lower LVEF than the BB group (carvedilol and bisoprolol groups combined) (P=0.0134). The changes in end-systolic volume (ESV), end-diastolic volume (EDV), and LVEF are shown in **Figure 2**. The ESV showed no significant differences regardless of BB therapy or no BB therapy (P=0.3422), and EDV in no BB group showed a significant increase at the chronic phase evaluation than seen in the BB therapy group (P=0.0171). The LVEF decreased at chronic phase evaluation point in the no BB group; on the other hand, the BB therapy groups showed LVEF improvement (-4% [range: -8 to -1%] vs. +2% [range: 0 to 7.3%], P<0.0001). In comparison across the three groups, no BB vs. carvedilol vs. bisoprolol, both the carvedilol and bisoprolol groups showed LVEF improvement (-4% [range: -8 to -1%] vs. +2% [range: 0 to 8%] vs. +4% [range: 0 to 7%], respectively; P<0.0001).

Dose-dependence of BB efficacy for LVEF improvement

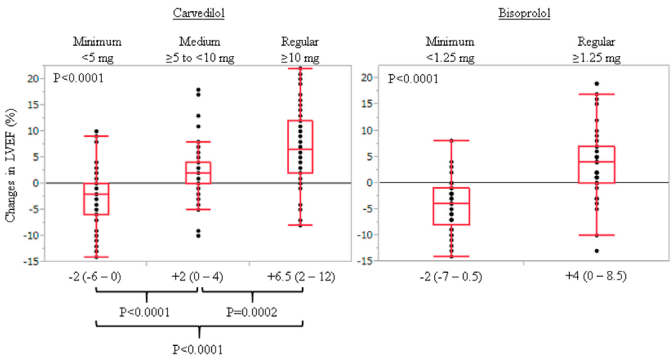
To study the relationship between dosage of BB and the magnitude of LVEF improvement, LVEF improvement was analyzed by dividing into subgroup according to BB dose **(Figure 3)**. The no BB and carvedilol groups were divided into three subgroups: minimum dose: <5 mg (n=65), medium dose: ≥5 mg and <10 mg (n=64), and regular dose: ≥10 mg (n=64). The minimum dose of carvedilol did not have sufficient effect to improve LVEF, however the magnitude of LVEF improvement with carvedilol increased dose-

Figure 2: Comparisons of ESV, EDV, and LVEF transitions between no BB and BB treatment.



Changes in ESV, EDV, and LVEF from acute to chronic phase are demonstrated by BB therapy. The EDV with no BB therapy was significantly greater than seen with BB therapy; however, there was no significant difference in ESV. The LVEF decreased in the no BB group, but improvement was shown in the BB group, carvedilol, and bisoprolol group.

Figure 3: Dose-dependence of BB to LVEF improvement.



The changes in LVEF were demonstrated in the carvedilol (left panel) and bisoprolol (right panel) groups, which was classified according to BB dosage at hospital discharge. The carvedilol group was divided three subgroups: minimum dose (<5 mg), medium dose (≥5 mg and <10 mg), and regular dose (≥10 mg). The LVEF decreased -2% from that of baseline with the minimum dose. In contrast, the medium dose demonstrated +2% improvement with a significant difference compared to the minimum dose. Moreover, the regular dose demonstrated a significantly better +6.5% improvement than seen with the medium dose. The RR achievement rate was 1.5% (1/65), 14.1% (9/64), and 32.8% (21/64), respectively (P<0.0001). The bisoprolol group was divided into two subgroups: minimum dose (<1.25 mg) and regular dose (≥1.25 mg). The minimum dose didn't produce LVEF improvement, but the regular dose did (-2% vs. +4%, P<0.0001). In these patients, the RR achievement rate was 0% (0/42) and 21.2% (7/44), respectively (P=0.0022).

dependently (-2% with minimum dose [range: -6 to 0%] vs. +2% with medium dose [range: 0 to 4%] vs. +6.5% with regular dose [range: 2 to 12%], P<0.0001; left panel, **Figure 3**). The RR achievement rate among these subgroups also showed dose-dependent increases of 1.5% (1/65), 14.1% (9/64), and 32.8% (21/64), respectively (P<0.0001).

The no BB and bisoprolol groups were divided into two subgroups: minimum dose: <1.25 mg (n=42) and regular dose: ≥1.25 mg (n=33). As seen with carvedilol, minimum dose bisoprolol didn't demonstrated LVEF improvement, and the regular dose did lead to LVEF improvement (-2% [range: -7 to 0.5%] vs. +4% [range: 0 to 8.5%], P<0.0001; right panel, Figure 3). The RR achievement rate was 0% (0/42) and 21.2% (7/44), respectively (P=0.0022).

Multivariate analysis for predictors of left ventricular reverse remodeling

RR was shown in 16.2% of the overall population. BB therapy with carvedilol and bisoprolol showed a significantly higher RR achievement rate than did the no BB group (no BB group 0%, carvedilol group 19.4%, bisoprolol group 16.7%, P=0.0225).

To identify the clinical predictors of RR, the following variables were examined by multivariate logistic analysis: age, male gender, diabetes mellitus, estimated GFR, LVEF <50% at acute phase, angiotensin-converting enzyme inhibitor use (compared to angiotensin II receptor blockers), statin use, and regular dose of BB (≥10 mg of carvedilol or ≥1.25 mg of bisoprolol) **(Table 3)**. Both LVEF <50% at acute phase and regular dose of BB were found to be independent predictors of RR (LVEF <50% at acute phase: Odds ratio 2.35, 95% CI 1.12-5.02, P=0.0242; regular dose of BB: Odds ratio 4.45, 95% CI 2.06- 10.27, P=0.0001).

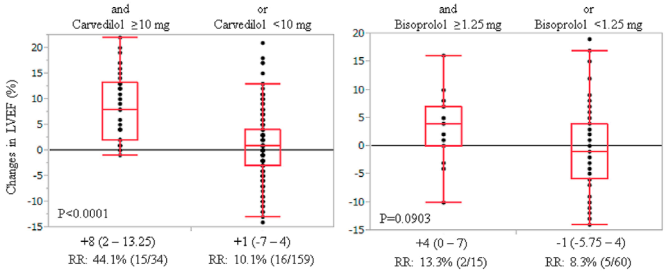
To confirm the above results of multivariate analysis, the three groups were further divided into subgroups according to LVEF <50% and regular dose of BB: baseline LVEF <50% and receiving ≥10 mg of carvedilol (n=34) or not (n=159), or ≥1.25 mg of bisoprolol (n=15) or not (n=60) **(Figure 4)**. In

Table 3. Multivariable analysis for predictors of left ventricular reverse remodeling.

Variables	Univariate	Multivariate	
	P value (95% CI)	Odds ratio (95% CI)	P value
Age	0.5213 (0.98 - 1.03)		
Male	0.1526 (0.13 - 1.28)		
Diabetes mellitus	0.1193 (0.28 - 1.16)		
Estimated GFR	0.2975 (0.99 - 1.02)		
Baseline LVEF <50%	0.0020 (1.50 - 6.33)	2.35 (1.12 - 5.02)	0.0242
Favor ACEI over ARB	0.2498 (0.71 - 3.43)		
Statin	0.1121 (0.82 - 5.63)		
Regular dose of BB‡	<0.0001 (2.45 - 11.83)	4.45 (2.06 - 10.27)	0.0001

GFR = Glomerular filtration rate; LVEF = left ventricular ejection fraction; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta-adrenergic blockers.
‡: ≥10 mg of carvedilol or ≥1.25 mg of bisoprolol IVS = interventriclr septum; PW = posterior wall;
EDV = end - diastolic volume; ESV = end - systolic volume;
E/A = early diastolic filling velocity/ atrial filling velocity;
DcT = decelaration time; BB = beta adrenergic receptor blocker

Figure 4: Impact of regular dose of BB in LVEF <50%.



The impact of the regular dose of BB, which is ≥10 mg of carvedilol or ≥1.25 mg of bisoprolol, on the magnitude of LVEF improvement in patients where the LVEF <50% was assessed.

In the carvedilol group, patients with an LVEF <50% treated with regular dose (n=34) had +8% (range: 2 to 13.25%), and another (n=159) had +1% (range: -7 to 4%) change in LVEF (P<0.0001). The RR achievement rates for these patients were 44.1% and 10.1% (P=0.0006), respectively.

In the bisoprolol group, the change in LVEF was +4% (range: 0 to 7%) and -1% (range: -5.75 to 4%), respectively (P=0.0903). The RR achievement rates were 13.3% (2/15) and 8.3% (5/60), respectively (P=0.6217).

the carvedilol group, the change in LVEF in the "EF <50% and >10 mg group" compared with the "EF ≥50% or <10 mg group" was +8% (range: 2 to 13.25%), and another was +1% (range: -7 to 4%) (P<0.0001). The RR achievement rates were 44.1% (15/34) and 10.1% (16/159), respectively (P=0.0006). In the bisoprolol group, the same tendency was demonstrated, although there was no significant difference: +4% (range: 0 to 7%) vs. -1% (range: -5.75 to 4%), P=0.0903. The RR achievement rate was 13.3% (2/15; the EF <50% and > 1.25 mg group) and 8.3% (5/60; the EF >50% or <1.25 mg group), respectively (P=0.6217).

Discussion

This study revealed the relationship between BB dose and the magnitude of LVEF improvement in STEMI following primary PCI using serial echocardiography assessment. Early BB introduction was related to improvement of LVEF and dose-dependent RR achievement. Baseline LVEF <50% and regular dose of BB administration were suggested as independent predictors of RR achievement.

It is well-established that BB has efficacy in improving LVEF and long-term outcomes in chronic heart failure. [16-22] On the other hand, the impact of BB therapy on STEMI immediately after successful primary PCI may be discussed separately from that of chronic heart failure. In the 2013 American College of Cardiology Foundation/American Heart Association guidelines for treatment of patients with STEMI, BB therapy is recommended for all STEMI patients who do not have signs of heart failure, low output state, increased risk for cardiogenic shock, or other contraindications defined as Class I. [10] In the 2012 European Society of Cardiology guidelines for treatment of patients with STEMI, BB therapy is recommended for STEMI patients with heart failure or left ventricular dysfunction defined as Class IA, and for all STEMI patients without contraindications defined as Class IIa. [23] However, most of these recommendations were based on data obtained before the primary PCI era. [24-32] Recently, some trials have raised an important question regarding BB therapy for STEMI patients. The OACIS trial demonstrated that BB was not always beneficial for all STEMI patients, since low-risk patients defined according to the GRACE risk score did not have clinical benefits. [11] Post-hoc sub-analysis of the J-Cypher registry showed BB therapy produced no significant difference in 3-year mortality or in incidence of major adverse cardiac events in STEMI patients with primary PCI, and only patients with LVEF ≤40% showed improvement in these outcomes. [9] Moreover, sub-analysis of the VALIANT trial demonstrated the additional benefit of BB on renin-angiotensin system inhibitors was unclear in acute myocardial infarction. [33] In the REACH registry, which analyzed over 44,000 patients with prior myocardial infarction, BB therapy did not show superiority in primary outcome of cardiovascular death, nonfatal MI, or nonfatal stroke, even after propensity score-matched adjustment. [34] A meta-analysis published in 2015 showed that depressed LVEF, non-STEMI, and undertreated therapies were suggested as a beneficial subgroup with BB in acute myocardial infarction. [35]

The present study demonstrated that ESV did not change between acute and chronic phases, but EDV decreased significantly. This finding suggests that the effect of BB was prevention of left ventricular dilation, rather than improvement of systolic function. The CAPRICORN Echo Substudy demonstrated +5% improvement of LVEF with carvedilol at 6 months after acute myocardial infarction. [36] Although CAPRICORN did not analyze the dosage of carvedilol, the efficacy is considered as equivalent to our results. As with the above suggestions from the OACIS trial and J-Cypher registry, decreased LVEF patients were evaluated as a subgroup sensitive for BB efficacy. [9, 11]

The necessary BB dosage to improve LVEF or achieve RR has not been discussed enough,

because the major focus in prior studies was whether administration of BBs was better than no administration. Since it is quite unlikely that a minimum dose of BB could improve enough LVEF or RR significantly, the next problem in clinical implications is how much we should increase the dosage when the patients are discharged from the hospital. [37-39] Our study suggests that a minimum dose of BB was not sufficient to achieve RR. Thus, it may be necessary to increase up to regular dose at hospital discharge in STEMI patients following primary PCI. [40-46] Prospective investigation is required to confirm our suggestion, BB administration during 6 months improve LVEF dose-dependently among <5mg, ≥5 to <10mg, and ≥10mg of carvedilol, and between <1.25mg and ≥1.25mg of bisoprolol.

There are several limitations in our study. First, this was a retrospective study. Second, the study may have been underpowered to draw a conclusion on efficacy of BB therapy on LVEF improvement. Third, the duration of BB therapy did not include the present discussion, since the duration of BB therapy and interval of echocardiographic evaluation differed between individuals studied. Fourth, other medications, excluding BB and renin-angiotensin system inhibitor, were not included the present discussion. Fifth, patient compliance with medication is less clear. Present study did not assess the impact of BB initiation timing on LVEF improvement although Bugiardini et al reported earlier administration of oral BB therapy with a greater probability of improving LV function and in-hospital survival rate. [47]

In conclusion, immediate BB administration after STEMI onset following primary PCI provides a dose-dependent LVEF improvement. For patients with decreased LVEF <50%, administration of the regular dose of BB might be reasonable to achieve RR.

Abbreviations

BB: beta-adrenergic blockers
RR: Left ventricular reverse remodeling
STEMI: ST-elevation myocardial infarction
PCI: percutaneous coronary intervention
LVEF: left ventricular ejection fraction
ECG: electrocardiographic
OR: odds ratios
CI: confidence intervals
ESV: end-systolic volume
EDV: end-diastolic volume

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

No other persons have made substantial contributions to this manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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