Beta-blocker therapy in the era of primary percutaneous intervention for ST elevation myocardial infarction

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A Dissertation Submitted to The Graduate School of Ajou University in Partial fulfillment of The Requirements for The Degree of Master of Medicine

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February, 2014

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- ABSTRACT -

Beta-blocker therapy in the era of primary percutaneous intervention for ST elevation myocardial infarction

Background: The potential benefit of beta-blocker for ST-elevation myocardial infarction (STEMI) was believed as therapeutic effects of left ventricular (LV) dysfunction. With present therapeutic advance, numbers of STEMI patients with LV dysfunction have been decreased. We studied the long term clinical outcomes of beta-blocker therapy after successful primary percutaneous coronary intervention (PCI) on STEMI.

Methods: We analyzed the data and clinical outcomes of 901 STEMI patients who underwent primary PCI . We classified patients into beta-blocker (N=598) and non beta-blocker groups (N=303) according to its use at discharge. Mean follow up month was 54±30 months. Primary end point was all-cause death and secondary end point was major adverse cardiac event (MACE; all-cause death, recurrent MI, target vessel revascularization).

Results: The beta-blocker group had lower Killip class, higher ejection fraction, younger ages, more male gender, statin use, hypertension, obesity, use of drug eluting stent and left anterior descending artery infarct. Cumulative incidence of all-cause death was 10.0% (60 patients) in beta-blocker group during mean follow up months of 56±28 and 25.4% (77 patients) in non beta-blocker group during mean follow up months of 49±32 ($p<0.001$) (Table 3). Incidence of MACE was 22.1% (132 patients) in beta-blocker group and 34.3% (104 patients) in non beta-blocker group ($p<0.001$). The relative hazard ratios (HR) for all-cause death and MACE, in beta-blocker group with abnormal LVEF (left ventricle ejection fraction, EF<50%), were 0.54 (95% confidence interval (CI) 0.34-0.85, P=0.008) and 0.72 (95% CI 0.50-1.04, P=0.082). In beta-blocker

group with normal LVEF (EF≥50%), the relative HR for death and MACE were 0.50 (95% CI 0.29-0.86, P=0.012) and 0.80 (95% CI 0.54-1.19, P=0.275). After propensity score matching to adjust difference of baseline characteristics, Kaplan-Meier survival curve of beta-blocker group in abnormal LVEF and normal LVEF demonstrated significant lower mortality (P=0.02, P=0.001, respectively).

Conclusions: Beta-blocker has benefit on clinical outcomes in patients with STEMI after primary PCI regardless of LVEF.

Keyword: beta-blocker, ST-elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI), left ventricular ejection fraction (LVEF)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATION

STEMI : ST-elevation myocardial infarction

PCI : Percutaneous coronary intervention

LV : Left ventricle

LVEF : Left ventricular ejection fraction

MACE : Major adverse cardiac events

MI : Myocardial infarction

CCB : Calcium channel blocker

I. INTRODUCTION

Beta-blocker had been well known for its beneficial effect on ST elevation myocardial infarction (STEMI) as primary medical treatment and for secondary prevention. Many randomized controlled studies and meta analysis have showed the benefits of beta-blockers on clinical outcomes in STEMI patients (1981; Hjalmarson et al., 1981; Hawkins et al., 1983; Olsson et al., 1985; Gottlieb et al., 1998; Freemantle et al., 1999). But firm confidence about the benefit of beta-blocker has gotten weak in low risk patients of STEMI, as the clinical outcomes of STEMI have been improved due to generalized primary percutaneous coronary intervention (PCI) and advance of medical treatment such as anti-platelet agent, angiotensin converting enzyme inhibitor and statin (Kezerashvili et al., 2012). In Asian people especially, there have been concerns of beta blocker about more frequent coronary artery vasospasm and more sensitive response of heart rate and blood pressure with lower dose of beta-blocker (Pristipino et al., 2000; Hori et al., 2004; Konishi et al., 2010). While some retrospective studies which were published recently demonstrated that there were no clinical benefits of beta-blocker in patients of normal or near normal left ventricular function, last updated ACC/AHA guideline still recommended beta blocker use in all patients with STEMI regardless of presence of left ventricular (LV) dysfunction (class I, level of evidence B) (Kernis et al., 2004; Ozasa et al., 2010; Bao et al., 2013; O'Gara et al., 2013).

To provide additive evidence to this controversy, we designed present study about the long term clinical benefits of beta-blocker in patients of STEMI with normal and abnormal LVEF (left ventricle ejection fraction).

II. Material and Method

A. Study deign and population

We analyzed data collected from single center (Department of cardiology, Ajou University school of Medicine, Suwon, Korea) retrospectively which included STEMI patients who underwent successful primary PCI without mortality after 30 days from 2003 to 2009. All clinical data sources of in hospital or follow-up information was based on hospital charts and the information about death of follow-up loss patients was collected from national health insurance service. In our data, 901 patients (716 males, 58±13 year-old) who were diagnosed as STEMI and underwent successful primary PCI without mortality after 30 days were recruited. These 901 patients were classified into beta-blocker (N=598, 491 males, 56±12 year-old) and non beta-blocker groups (N=303, 225 males, 61±13 year-old) according to beta-blocker use at discharge. After subdivided of each group into normal LVEF (left ventricular ejection fraction) group and abnormal LVEF group, long-term clinical outcomes were evaluated and compared as use of beta-blocker or not. Normal LVEF was defined as ≥50%

B. Study end points

Primary end point was all cause death and secondary end point was major adverse cardiac event (MACE) composed of death, recurrent myocardial infarction (MI), target vessel revascularization. MI was defined according to the universal definition of myocardial infarction (Thygesen et al., 2007).

C. Statistical analysis

PASW statistics (version 18) was used for statistical analysis. Continuous variables were expressed as mean ± standard deviation and were compared by independent t test or Mann-Whitney U test. A 2-sided p value of <0.05 was regarded as statistical significance. Categorical variables were expressed as number and percentages and were compared with chi-square test or Fisher's exact test. Cumulative incidences of primary and secondary end

point in each group were estimated by the Kaplan-Meier curves and differences were evaluated with log-rank test. To assess adjusted relative hazard ratio of beta-blocker to the study end point, we used Cox proportional hazard model with potential variables associated with clinical outcomes. Adjusted covariates for Cox proportional hazard model were old age (>65 year-old), Diabetes mellitus, hypertension, smoking, family history of cardiovascular disease, history of cerebrovascular disease, use of statin, use of angiotensin blockade agent (angiotensin converting enzyme inhibitor or angiotensin receptor blocker), multi-vessel disease, Killip stage >1 and end-stage renal disease. Results of multivariable analysis are expressed as adjusted hazard ratios and their 95% confidence intervals of PCI for clinical outcomes. To adjust difference of baseline characteristics, we used propensity score matching about two groups (beta blocker group and non beta blocker group) in normal LVEF and abnormal LVEF patients. Covariate used for matching were age, sex, LVEF, Killip stage, hypertension, infarct related vessel of left anterior descending artery and use of drug eluting stent which showed significant difference of two groups. After propensity score matching, cumulative incidences of primary and secondary end point were also estimated by the Kaplan-Meier curves with log-rank test.

III. Results

A. Beta-blocker use

Among enrolled 901 patients, 598 (66.4%) patients discharged with beta-blocker after successful primary PCI and in-hospital management. Carvedilol was used most frequently in 277 patients (46.3% in beta blocker group) and metoprolol in 268 patients (44.8%). These two beta-blockers were majority (91.1%) in beta-blocker group. The other beta-blockers (8.9%) used in this study were bisoprolol, bevantolol, atenolol and propranolol.

B. Baseline characteristics

The beta-blocker group had more Killip class I, less Killip class IV, younger ages, more male, higher LVEF, shorter LV end systolic diameter, more statin use, less calcium channel blocker (CCB) use, more hypertension, more obesity, more use of drug eluting stent and more left anterior descending artery infarct (Table 1, Table 2). The other baseline characteristics were not different between two groups in statistical significance.

Table 1. Baseline characteristics of clinical findings

	Beta-blocker group (N=598)	Non beta-blocker group (N=303)	p
Male	491 (82.1%)	225 (74.3%)	0.006*
Age	56±12	61±13	<0.001*
Killip class			
1	480 (80.3%)	207 (68.3%)	<0.001*
2	63 (10.5%)	42 (13.9%)	0.142
3	40 (6.7%)	30 (9.9%)	0.089
4	15 (2.5%)	24 (7.9%)	<0.001*
Diabetes mellitus	136 (22.7%)	61 (20.1%)	0.370
Hypertensin	257 (43.0%)	104 (34.3%)	0.012*
Smoking	387 (64.7%)	197 (65%)	0.929

Dyslipidemia	48 (8%)	19 (6.3%)	0.343
Family history of CAD	34 (5.7%)	12 (4.0%)	0.266
Old cerebrovascular attack	16 (2.7%)	13 (4.3%)	0.194
End stage renal disease	3 (0.3%)	0 (0%)	0.218
Obecity (BMI>25, kg/m^2)	218 (45.1%)	68 (33.8%)	0.006*
Prior MI	19 (3.2%)	10 (3.3%)	0.921
Prior CABG	1 (0.2%)	1 (0.3%)	0.624
Prior PCI	40 (6.7%)	25 (8.3%)	0.392
Discharge medication			
Aspirin	593 (99.2%)	301 (99.3%)	0.564
clopidogrel	552 (92.3%)	268 (88.4%)	0.056
Other antiplatelet agent	146 (24.4%)	75 (24.8%)	0.911
ACE inhibitor or ARB	567 (94.8%)	273 (90.1%)	0.008
Calcium channel blocker	72 (12%)	87 (28.7%)	<0.001*
Statin	421 (70.4%)	176 (58.1%)	<0.001*
Nitrate & other anti-anginal drugs	475 (79.4%)	234 (77.2%)	0.445

Values are mean ± SD or n (%), $p<0.05$ were expressed as '*'

CAD, coronary artery disease; BMI, body mass index; MI, myocardial infarction; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

Table 2. Baseline characteristics of angiographic & echocardiographic findings

	Beta-blocker group (N=598)	Non beta-blocker group (N=303)	
Number of diseased vessel			
1 vessel disease	260 (43.5%)	131 (43.2%)	0.944
2 vessel disease	197 (32.9%)	94 (31.0%)	0.560
3 vessel disease	141 (23.6%)	78 (25.7%)	0.474
Multivessel disease	338 (56.5%)	172 (56.8%)	0.944
Infarct-related vessels			
LAD	339 (56.7%)	147 (48.5%)	0.020*
LCX	42 (7.0%)	36 (11.9%)	0.014*
RCA	213 (35.6%)	119 (39.3%)	0.283
Left main	3 (0.5%)	1 (0.3%)	0.714
Graft vessel	1 (0.2%)	0 (0%)	0.476
Kind of stent			
Drug eluting stent	458 (76.6%)	196 (64.7%)	<0.001*
Bear metal stent	143 (27.7%)	107 (35.3%)	<0.001*
Findings of echocardiogram			
LVEF, %	53±10	49±12	<0.001*
LVEDD, mm	50±5	50±6	0.241
LVESD, mm	34±6	35±7	0.006*
Ischemic MR	9 (1.5%)	10 (3.3%)	0.076

Values are mean ± SD or n (%), $p<0.05$ were expressed as '*', Ischemic MR was defined as moderate to severe MR without primary valvular heart disease.

LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-sistolic dimension; MR, mitral regurgitation

C. Clinical outcomes

Cumulative incidence of all-cause death was 10.0% (60 patients) in beta-blocker group during mean follow up months of 56±28 and 25.4% (77 patients) in non beta-blocker group during mean follow up months of 49±32 (p<0.001) (Table 3). Incidence of MACE was 22.1% (132 patients) in beta-blocker group and 34.3% (104 patients) in non beta-blocker group (p<0.001) (Table 3). Kaplan-Mayer survival curve of beta-blocker group in all patients showed significant lower all-cause death and MACE (Figure 1, p<0.001, p<0.001, respectively). Adjusted hazard ratio of beta blocker for all-cause death and MACE were 0.52 (95% confidence interval (CI) 0.37 to 0.74, P<0.001) and 0.75 (95% CI 0.57 to 0.97, P=0.031) (Figure 2).

Table 3. Study endpoints in all patients

	Beta-blocker	Non beta-blocker	P value	relative HR of beta-blocker (95% Confidence interval, p value)
All patient (N=901)	N=598	N=303		
All cause death	60 (10.0%)	77(25.4%)	<0.001 *	0.52 (0.37~0.74, p<0.001*)
Myocardial infarction	26 (4.3%)	15 (5.0%)	0.682	
TVR	65 (10.9%)	28 (9.2%)	0.448	
MACE	132 (22.1%)	104 (34.3%)	<0.001 *	0.75 (0.57~0.97, p=0.031*)
Follow-up duration (months)	56±28	49±32	0.003	

Values are mean ± SD or n (%), p value was analyzed by Chi-Square test and p<0.05 were expressed as '*', relative HR of beta-blocker was derived from Cox-proportional hazard model with multivariate analysis before propensity score matching

TVR, target vessel revascularization; MACE, major adverse cardiac events; HR, hazard ratio

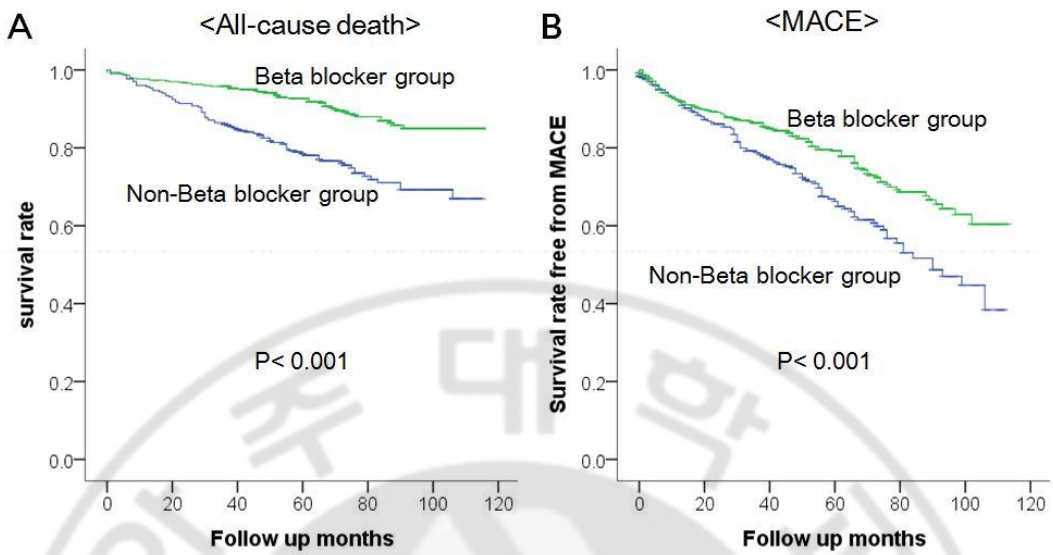

Fig. 1. Kaplan-Meier event-free survival curve in all patients

A. Beta-blocker group in all patients showed significant higher survival rate free from all-cause death. B. Beta-blocker group also showed significant higher survival rate free from MACE.

P value was derived from the Log-rank test; MACE, major adverse cardiac events

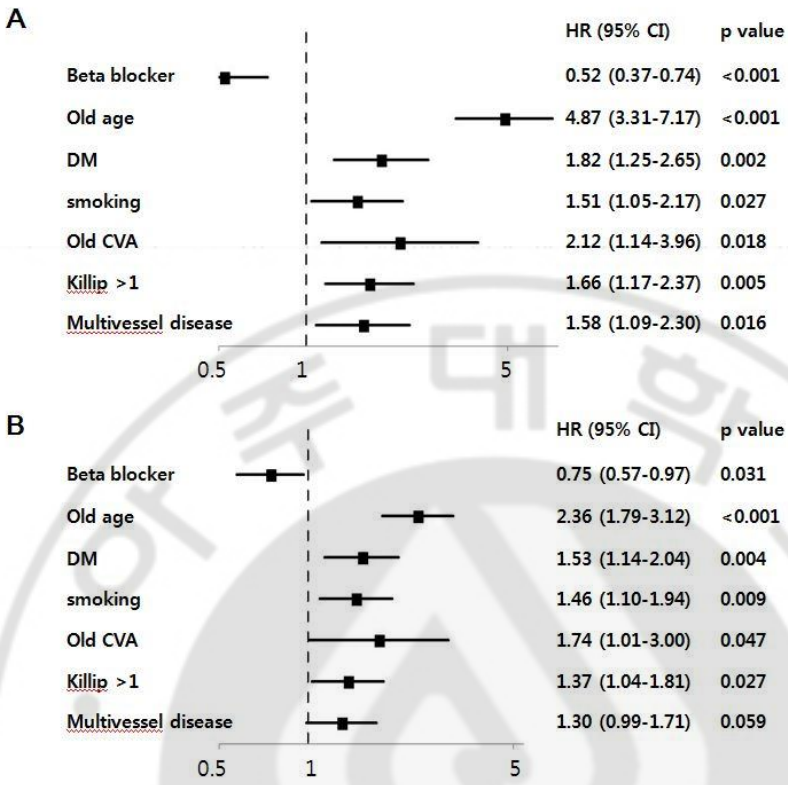

Fig. 2. Multivariate predictors of study end points using Cox-proportional hazard model.

A. All-cause death. B. Major adverse cardiac events.

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular attack

Table 4 showed study end points in patients with normal and abnormal LVEF. In patients with normal LVEF (N=506), the cumulative incidence of all-cause death was 7.6% (28 patients) in beta-blocker group during mean follow up months of 57±29 and 18.7% (26 patients) in non beta-blocker group during mean follow up months of 52±33 ($p<0.001$). And with abnormal LVEF, the cumulative incidence of all-cause death was 13.9% (32 patients) in beta-blocker group during mean follow up months of 53±28 and 31.1% (51 patients) in non beta-blocker group during mean follow up months of 47±31 ($p<0.001$). The cumulative incidence of MACE was 20.2% (74 patients) in beta-blocker group and 29.5% (41 patients) in non beta-blocker group with normal LVEF ($p=0.025$). And the incidence of MACE was 25.1% (58 patients) in beta-blocker group and 38.4% (63 patients) in non beta-blocker group with abnormal LVEF ($p=0.005$). Kaplan-Mayer survival curve of beta-blocker group in patients with both of normal and abnormal LVEF demonstrated significant higher survival rate of all-cause death ($p=0.001$, $p<0.001$, respectively) (Figure 3 A,B). And beta-blocker group also showed significant higher survival rate free from MACE in normal LVEF and abnormal LVEF patients ($p=0.036$, $p=0.008$, respectively) (Figure 3 C,D).

Adjusted hazard ratio of beta-blocker for all-cause death in patients with normal and abnormal LVEF were 0.50 (95% CI 0.29 to 0.88, P=0.016) and 0.55 (95% CI 0.35 to 0.86, P=0.009) (Figure 4). Adjusted hazard ratio of beta-blocker for MACE in patients with normal and abnormal LVEF were 0.075(95% CI 0.51 to 1.12, P=0.162) and 0.75 (95% CI 0.51 to 1.09, P=0.125) (Figure 5).

Table 4. Study endpoints in patients with normal LVEF and abnormal LVEF before propensity score matching

	Beta-blocker	Non beta-blocker	P value	relative HR of beta-blocker (95% Confidence interval, p value)
Normal LVEF group (N=506)	N=367	N=139		
All cause death	28 (7.6%)	26 (18.7%)	<0.001 *	0.50 (0.29~0.88, p=0.016*)
Myocardial infarction	18 (4.9%)	5 (3.6%)	0.529	
TVR	41 (11.2%)	13 (9.4%)	0.554	
MACE	74 (20.2%)	41 (29.5%)	0.025 *	0.75 (0.51~1.12, p=0.162)
Follow-up duration (months)	57±29	52±33	0.07	
abnormal LVEF group (N=395)	N=231	N=164		
All cause death	32 (13.9%)	51 (31.1%)	<0.001 *	0.55 (0.35~0.86, p=0.009*)
Myocardial infarction	8 (3.5%)	10 (6.1%)	0.216	
TVR	24 (10.4%)	15 (9.1%)	0.683	
MACE	58 (25.1%)	63 (38.4%)	0.005*	0.75 (0.51~1.10, p=0.125)
Follow-up duration (months)	53±28	47±31	0.053	

Values are mean ± SD or n (%), p value was analyzed by Chi-Square test and p<0.05 were expressed as '*', relative HR of beta-blocker was derived from Cox-proportional hazard model with multivariate analysis before propensity score matching

TVR, target vessel revascularization; MACE, major adverse cardiac events; HR, hazard ratio

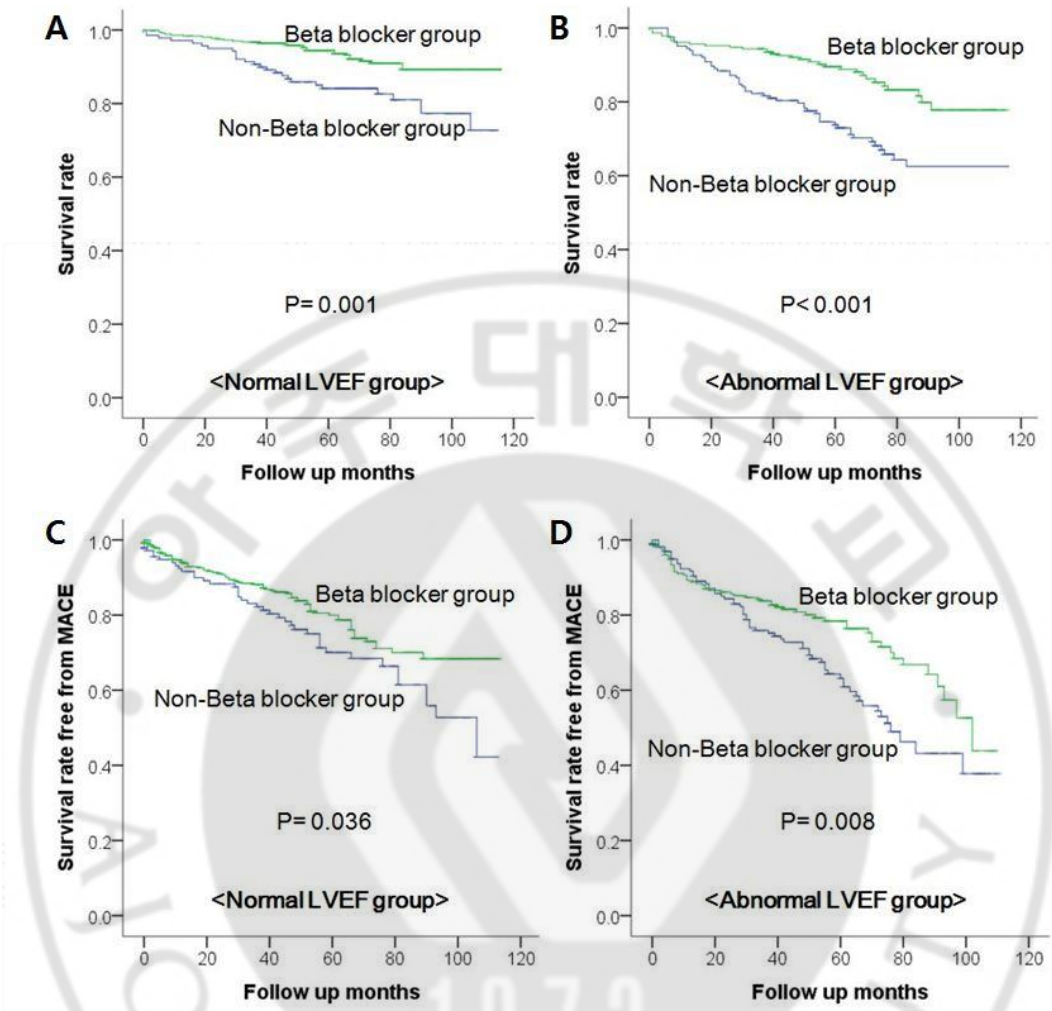

Fig. 3. Kaplan-Meier event-free survival curve in patients with normal and abnormal LVEF.

A. Survival rate free from all-cause death in patients with normal LVEF. B. Survival rate free from all-cause death in patients with abnormal LVEF. C. Survival rate free from MACE in patients with normal LVEF. D. Survival rate free from MACE in patients with abnormal LVEF.

P value was derived from the Log-rank test; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events

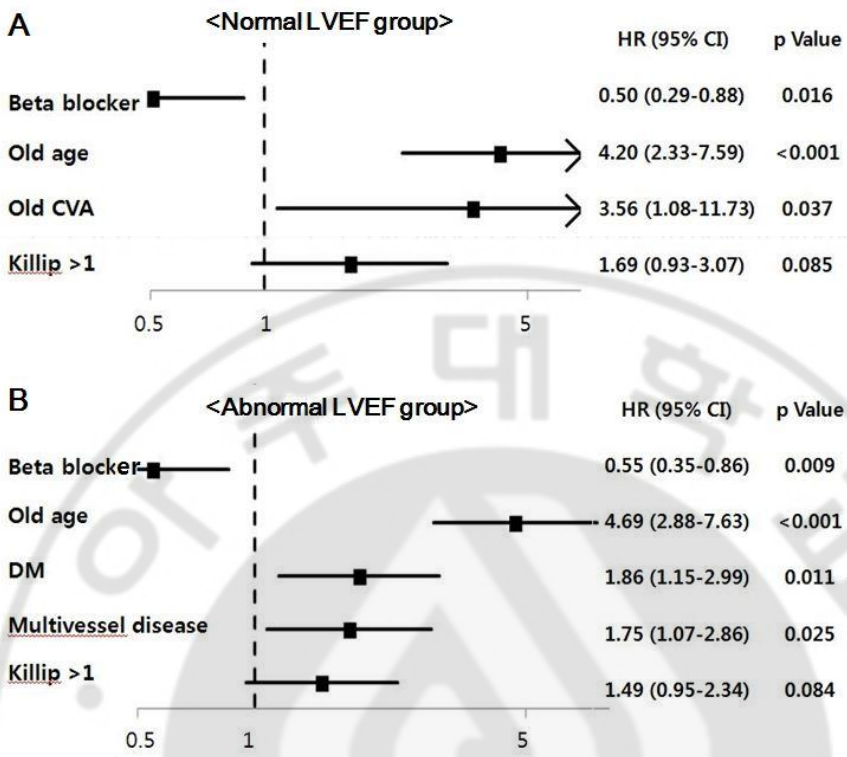

Fig. 4. Multivariate predictors of all-cause death using Cox-proportional hazard model in patients with normal and abnormal LVEF.

A. Predictors of all-cause death in patients with normal LVEF. B. In patients with abnormal LVEF

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular attack

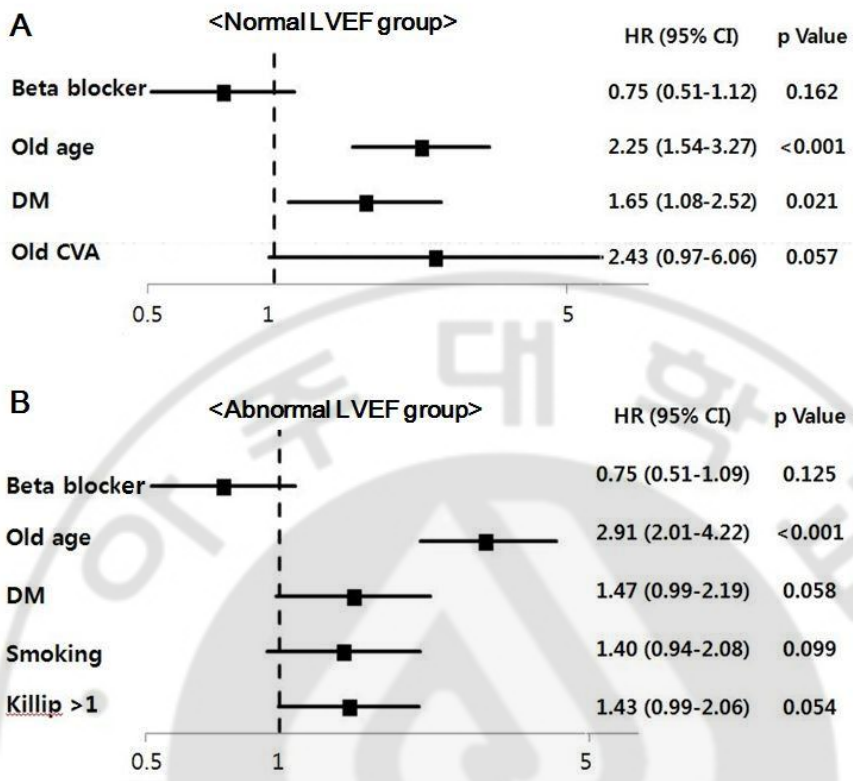

Fig. 5. Multivariate predictors of MACE using Cox-proportional hazard model in patients with normal and abnormal LVEF.

A. Predictors of MACE in patients with normal LVEF. B. In patients with abnormal LVEF

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; CVA, cerebrovascular attack

After propensity score matching (1:1) to adjust difference of baseline characteristics, 140 patients of each group (beta-blocker versus non beta-blocker) in patients with abnormal LVEF were selected and 137 patients of each group in patients with normal LVEF were selected. Baseline characteristics of two groups in normal LVEF and abnormal LVEF patients showed no significant difference in all variables except the use of CCB (Table 5, Table 6). We allowed the difference in the use of CCB intentionally through not including it in matching variables because it was reasonable to give more CCB as anti-anginal drug to patients who did not take beta-blocker and CCB had little effect to clinical outcomes in STEMI patients.

Table 5. Baseline characteristics after propensity score matching in normal LV function patients

	Beta-blocker group (N=137)	Non beta-blocker group (N=137)	p
Male	97 (70.8%)	100 (73.0%)	0.687
Age	58±13	59±13	0.496
Killip class			0.98
1	114 (83.2%)	112 (81.8%)	0.751
2	15 (10.9%)	15 (10.9%)	1
3	5 (3.6%)	6 (4.4%)	0.758
4	3 (2.2%)	4 (2.9%)	0.702
Diabetes mellitus	28 (20.4%)	28 (20.4%)	1
Hypertensin	55 (40.1%)	52 (38.0%)	0.71
Smoking	78 (56.9%)	88 (64.2%)	0.216
Dyslipidemia	13 (9.5%)	8 (5.8%)	0.256
Family history	8 (5.8%)	6 (4.4%)	0.583
Creatine level	0.97±0.69	1.02±0.43	0.363
Obecity (BMI>25)	45 (42.9%)	32 (35.6%)	0.298
Discharge medication			
Aspirin	137 (100%)	136 (99.3%)	1
Plavix	122 (89.1%)	117 (85.4%)	0.366
Cilostazole	20 (14.6%)	25 (18.2%)	0.415
ACEi	90 (65.7%)	90 (65.7%)	1
ARB	37 (27.0%)	36 (26.3%)	0.891
Calcium channel blocker	21 (15.%)	50 (36.5%)	<0.001*
Statin	91 (66.4%)	87 (63.5%)	0.612
Nitrate	103 (75.2%)	99 (72.3%)	0.583
Multivessel disease	83 (60.6%)	74 (54.0)	0.272
Culprit vessel			
LAD	43 (31.4%)	36 (26.3%)	0.351
LCX	16 (11.7%)	19 (13.9%)	0.587
RCA	78 (56.9%)	82 (59.9%)	0.624
Kind of stent			

Drug eluting stent	94 (68.6%)	84 (61.3%)	0.205
Bear metal stent	46 (33.6%)	50 (36.5%)	0.612
Findings of echocardiogram			
LVEF, %	59±7	59±8	0.744
LVEDD, mm	48±5	49±5	0.179
LVESD, mm	31±5	31±5	0.541
Ischemic MR	3 (2.2%)	2 (1.5%)	1

Values are mean ± SD or n (%), $p<0.05$ were expressed as '*'. Ischemic MR was defined as moderate to severe MR without primary valvular heart disease.

BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-sistolic dimension; MR, mitral regurgitation

Table 6. Baseline characteristics after propensity score matching in abnormal LV function patients

	Beta-blocker group (N=140)	Non beta-blocker group (N=140)	p
Male	112 (80.0%)	108 (77.1%)	0.560
Age	58±13	60±12	0.147
Killip class			0.557
1	92 (65.7%)	88 (62.9%)	0.618
2	20 (14.3%)	26 (18.6%)	0.333
3	21 (15%)	16 (11.4%)	0.378
4	7 (5%)	10 (7.1%)	0.453
Diabetes mellitus	31 (22.1%)	29 (20.7%)	0.771
Hypertensin	50 (35.7%)	46 (32.9%)	0.615
Smoking	95 (67.9%)	96 (68.6%)	0.898
Dyslipidemia	8 (5.7%)	11 (7.9%)	0.476
Family history	10 (7.1%)	5 (3.6%)	0.184
Creatine level	1.02±0.32	1.01±0.44	0.829
Obecity (BMI>25, kg/m^2)	45 (40.5%)	32 (34.0%)	0.338
Discharge medication			

Aspirin	137 (97.9%)	139 (99.3%)	0.622
Plavix	128 (91.4%)	128 (91.4%)	1
Cilostazole	25 (17.9%)	20 (14.3%)	0.416
ACEi	83 (59.3%)	79 (56.4%)	0.628
ARB	54 (38.6%)	47 (33.6%)	0.384
Calcium channel blocker	14 (10%)	35 (25%)	0.001*
Statin	90 (64.3%)	81 (57.9%)	0.27
Nitrate	103 (73.6%)	101 (72.1%)	0.788
Multivessel disease	76 (54.3%)	81 (57.9%)	0.547
Culprit vessel			
LAD	101 (72.1%)	99 (70.7%)	0.791
LCX	5 (3.6%)	12 (8.6%)	0.08
RCA	31 (22.1%)	29 (20.7%)	0.771
Left main	3 (2.1%)	0 (0%)	0.247
Kind of stent			
Drug eluting stent	101 (72.1%)	96 (68.6%)	0.513
Bear metal stent	40 (28.6%)	46 (32.9%)	0.437
Findings of echocardiogram			
LVEF, %	42±6	41±6	0.41
LVEDD, mm	51±6	52±6	0.326
LVESD, mm	37±7	38±7	0.424
Ischemic MR	2 (1.4%)	5 (3.6%)	0.447

Values are mean ± SD or n (%), $p<0.05$ were expressed as '*'. Ischemic MR was defined as moderate to severe MR without primary valvular heart disease.

BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-sistolic dimension; MR, mitral regurgitation

In matched group, cumulative incidence of death was 5.8% (8 patients) in beta-blocker group during mean follow up months of 58±32 and 19% (26 patients) in non beta-blocker group during mean follow up months of 51±33 with normal LVEF (p=0.001). And in patients with abnormal LVEF, cumulative incidence of death was 15.7% (22 patients) in beta-blocker group during mean follow up months of 53±29 and 27.9% (39 patients) in non beta-blocker group during mean follow up months of 49±31 (p=0.014) (Table 7). Incidence of MACE defined as a composite of all-cause death, recurrent MI, TVR was 19% (26 patients) in beta-blocker group and 29.2% (40 patients) in non beta-blocker group with normal LVEF (p=0.048). With abnormal LVEF, the incidence of MACE was 27.9% (39 patients) in beta-blocker group and 36.4% (51 patients) in non beta-blocker group (p=0.125) (Table 7).

Kaplan-Mayer survival curve of beta-blocker group also showed significantly higher survival rate free from all-cause death in patients with normal LVEF and abnormal LVEF after propensity score matching (p=0.001, p=0.020, respectively) (Figure 6 A,B). The survival rate free from MACE was significantly higher in beta-blocker group with normal LVEF, but not significantly different in both group with abnormal LVEF (p=0.046, p=0.184, respectively) (Figure 6 C,D).

Table 7. Study endpoints after propensity score matching

	Beta-blocker	Non beta-blocker	P value
normal LVEF group	N=137	N=137	274
Death	8 (5.8%)	26 (19%)	0.001*
Myocardial infarction	6 (4.4%)	5 (3.6%)	0.758
TVR	18 (13.1%)	12 (8.8%)	0.246
MACE	26 (19%)	40 (29.2%)	0.048*
Follow-up duration (months)	58±32	51±33	0.068
abnormal LVEF group	N=140	N=140	280
Death	22 (15.7%)	39 (27.9%)	0.014*
MI	6 (4.3%)	9 (6.4%)	0.426
TVR	15 (10.7%)	14 (10.0%)	0.845
MACE	39 (27.9%)	51 (36.4%)	0.125
Follow-up duration (months)	53±29	49±31	0.242

Values are mean ± SD or n (%), p value was analyzed by Chi-Square test and $p<0.05$ were expressed as '*', relative HR of beta-blocker was derived from Cox-proportional hazard model with multivariate analysis before propensity score matching

TVR, target vessel revascularization; MACE, major adverse cardiac events; HR, hazard ratio

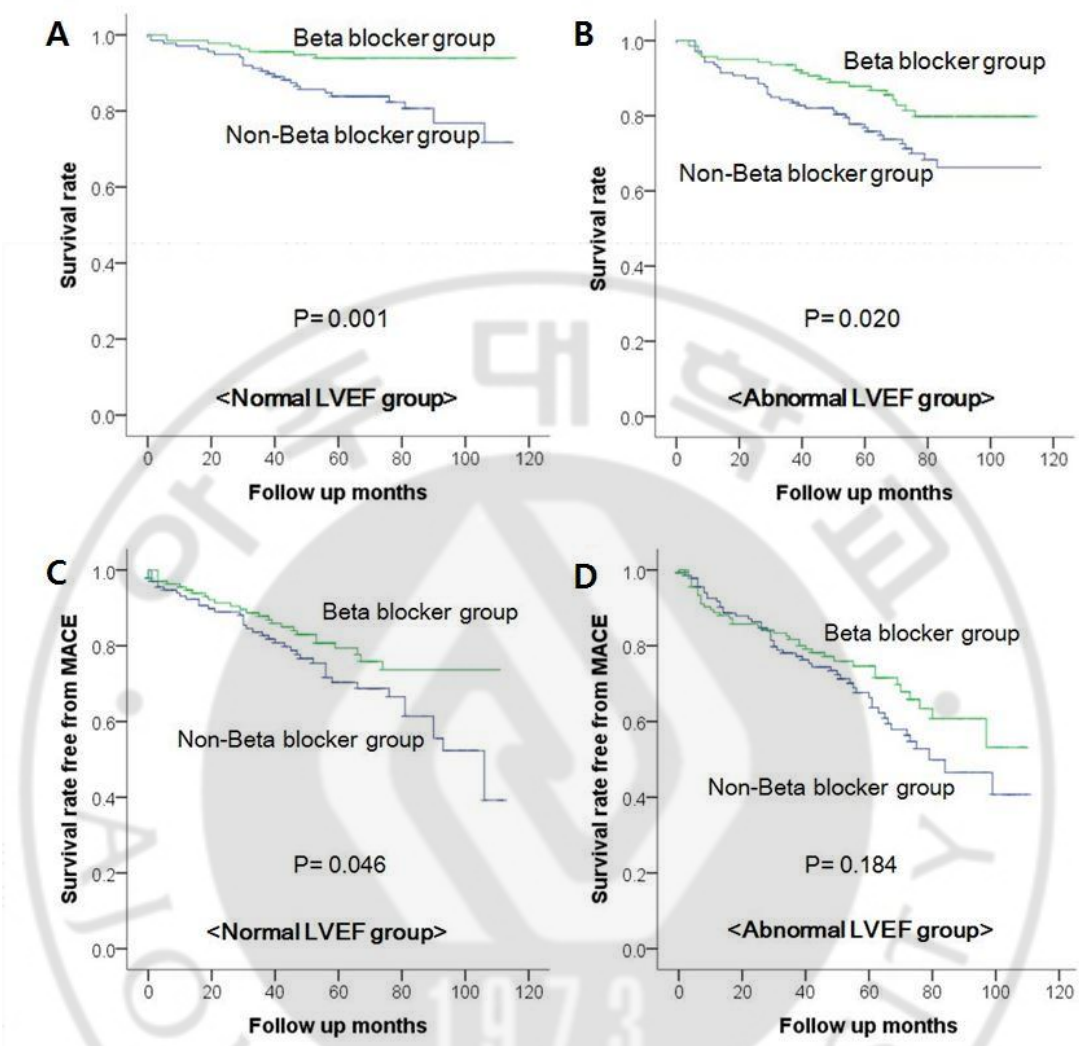

Fig. 6. Kaplan-Meier event-free survival curve in patients with normal and abnormal LVEF after propensity score matching.

A. Survival rate free from all-cause death in patients with normal LVEF. B. Survival rate free from all-cause death in patients with abnormal LVEF. C. Survival rate free from MACE in patients with normal LVEF. D. Survival rate free from MACE in patients with abnormal LVEF.

P value was derived from the Log-rank test; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events

IV. Discussion

In the present study, oral beta-blocker use at discharge in STEMI survivor who underwent primary PCI and had normal LVEF demonstrated better long term clinical outcomes in point of all cause mortality. In patients of abnormal LV function, beta-blocker group also showed higher survival rate. And Kaplan-Meier curve of MACE in beta-blocker group with normal LV function showed better outcomes too, although it was not consistent with Cox-proportional multivariate analysis.

There has been no controversy about the clinical benefit of beta-blocker in patients with LV dysfunction after acute myocardial infarction (AMI) on revascularization era as well as pre-revascularization era (Dargie, 2001; Kernis et al., 2004). But in low risk patients with preserved LV function, the beneficial role of beta-blocker after primary PCI has been in doubt due to lack of evidence in these revascularization era despite ongoing recommendation of current guideline (Task Force on the management of et al., 2012; O'Gara et al., 2013). After Kernis et al. mentioned that there were little beneficial effects of beta-blocker to patients with normal LV function and single vessel disease, several retrospective studies reported that beta-blocker was not associated better clinical outcomes in patients with preserved LV function after primary PCI and even demonstrated poor clinical outcomes in one study (Kernis et al., 2004; Ozasa et al., 2010; Bao et al., 2013). These studies explained that beneficial effects of beta-blocker could be offset by not only general adverse effect of beta-blocker such as hypotension, bradycardia, dizziness, depression, bronchospasm, metabololic disorder, drug allergy but also additive negative effect such as coronary vasospasm, decreased compliance due to additional cost and burden of pills.

But beta-blockers have many important beneficial effects in patients with AMI. Beta-blockers reduce cardiotoxic effect of catecholamine via its anti-adrenergic effect and also reduce myocardial work load through decreasing of heart rate, blood pressure and myocardial contractility (Mueller and Ayres, 1980; Lange et al., 1983; Kjekshus, 1986). Moreover, they have anti-arrhythmic effect, which reduce tachy-arrhythmic events and use of other anti-arrhythmic agents (Ryden et al., 1983; Olsson and Rehnqvist, 1986). These

beneficial effects of beta-blockers limit infarct-size, and reduce recurrent ischemia and mortality including cardiac sudden death (1981; Hjalmarson et al., 1981; Kopecky, 2006).

It is true that clinical outcomes of low risk patients with normal LV function after STEMI was improved (Bramlage et al., 2010), but recurrent myocardial ischemia, tachyarrhythmia and adrenergic activation are still important problems in those patients, and there is no other optimal substitute of beta-blocker to control these important problems effectively. Moreover, the incidence of significant and life-threatening adverse effects of beta-blocker such as hypotension and bradycardia was not higher enough to offset the positive effects of beta-blocker (Ko et al., 2004). Consequently, It is reasonable to assume that beta blocker have positive effects more than negative effects in patients of STEMI with normal LV function.

Although some recent studies in the revascularization era reported negative results about beneficial effects of beta-blockers, they had many limitations including property of retrospective studies (Ozasa et al., 2010; Bao et al., 2013). But many reports which showed beneficial effects of beta-blocker in AMI patients were based on very strong evidence derived from numerous randomized controlled trial and meta-analysis though they were old studies in pre-revascularization era, and those studies also had considerable number of preserved LV function (1981; Hjalmarson et al., 1981; Hawkins et al., 1983; Olsson et al., 1985; Gottlieb et al., 1998; Freemantle et al., 1999). So some limited retrospective studies could not overwhelm strong old studies, and this was why current guidelines still keep to their recommendation of beta-blocker as primary management and secondary prevention of STEMI (Task Force on the management of et al., 2012; O'Gara et al., 2013). The result of our study provided additive evidence to these current guidelines in the era of primary PCI.

There were several important limitations in this study. First, because this study is retrospective observational study, selection bias in use of beta-blockers is inevitable. Although we adjusted the difference of baseline characteristics in two groups through Cox proportional multivariate analysis and propensity score matching, our study could not be free from the influence of unmeasured confounding factors. Second, our data had no information of beta-blocker dose so that beta-blocker was likely to be used insufficiently resulting in reducing its clinical effects. Third, the duration of beta-blocker use after discharge was not

included in our data. So we could not know about the effect of long-term use of beta-blocker and optimal duration of its use in STEMI patients with normal LV function after primary PCI.

V. Conclusion

In our study, use of oral beta-blocker at discharge showed beneficial effects on clinical outcomes in patients with STEMI after primary PCI regardless of LVEF. The potential role of beta-blocker might be beyond the therapeutic effects of LV dysfunction. Now, it's time to evaluate the role of beta-blocker in STEMI patients with normal LV function after primary PCI through large randomized controlled trial.

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– 국문요약 –

ST 분절 상승 급성 심근경색 환자에서 일차적 관상동맥 중재 시술 후 경구 베타 차단제 사용이 장기 예후에 미치는 영향

목적: ST 분절 상승 심근경색 환자들의 치료가 발전함에 따라 좌심실 기능 저하를 보이는 환자들의 수는 줄어 들었고 따라서 이들의 예후도 많이 향상 되었다. 성공적인 일차적 관동맥 중재시술로 정상 좌심실 수축기능을 보이는 ST 분절 상승 심근경색 환자에서 베타 차단제의 역할에 대해서는 지금까지 충분히 연구되지 않았고 최근의 몇몇 연구들은 베타 차단제의 역할에 의문을 제기하고 있다. 본 연구는 ST 분절 상승 심근경색 환자에서 성공적인 일차적 관동맥 중재시술 후 베타 차단제의 사용이 환자의 장기 예후에 미치는 영향에 대해 조사하였다.

방법: 일차적 관동맥 중재시술을 성공적으로 시행한 901 명의 ST 분절 상승 심근경색 환자를 598 명의 베타 차단제 사용 군과 303 명의 베타 차단제 비 사용 군으로 나누었고 각 군을 좌심실 기능 저하의 유무에 따라 비교하였다. 환자의 사망과 사망, 재발성 심근경색, 표적 혈관의 재 개통으로 구성된 주요 심장 사건을 연구하였다.

결과: 베타 차단제 사용 군에서 Killip 분류 1 이 더 많았고, 좌심실 수축기능이 더 높았으며 젊은 연령, 남성, statin 제제의 사용, 고혈압 환자, 비만, 약물 용출 스텐트의 사용 빈도, 좌전하행지 영역의 심근경색의 빈도 등이 더 많게 나타났다. 베타 차단제 사용 군에서 모든 사망의 누적 발생율은 10% (60 명, 평균 관찰 기간:56±28 개월) 이었고 베타 차단제 비사용 군에서는 25.4% (77 명, 평균 관찰 기간: 49±32 개월)이었다 ($p<0.001$). 주요 심장 사건의 누적 발생율의 경우 베타 차단제 사용 군에서 22.1% (132 명) 이었고 베타

차단제 비 사용 군에서는 34.3% (104 명) 이었다 (p<0.001). 좌심실 구혈률이 저하된 (좌심실 구혈률 <50%) 환자에서 베타 차단제 사용의 사망과 주요 심장 사건에 대한 비교 위험도는 0.54 (P=0.008, 95% 신뢰구간(CI) 0.34−0.85)와 0.72 (P=0.082, CI 0.50−1.04)였고 정상 좌심실 구혈률을 가진 (좌심실 구혈률 ≥50) 환자에서는 베타 차단제 사용의 비교 위험도가 각각 0.50 (P=0.012, CI 0.29−0.86)와 0.80 (P=0.275, CI 0.54−1.19) 이었다. 양군간의 임상 양상의 차이를 보정하기 위해 Propensity score matching 을 시행한 후 분석한 Kaplan−Meier 생존 곡선에서 베타 차단제 사용 군은 좌심실 구혈률 저하가 있는 환자와 좌심실 구혈률이 정상인 환자 모두에서 통계적으로 의미 있는 높은 생존율을 보여 주었다 (P=0.02, P=0.001, respectively).

결론: 베타 차단제는 일차적 관동맥 중재 시술을 시행한 ST 분절 상승 심근경색 환자에서 좌심실 기능 저하의 유무와 상관 없이 예후에 긍정적인 영향을 준다.

핵심어: 베타 차단제, ST 분절 상승 심근경색, 일차적 관동맥 중재 시술, 좌심실 기능