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Sustained beneficial effect of β-blockers on clinical outcomes after discontinuation in patients with ST elevation myocardial infarction

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Abstract

Our previous study demonstrated that beneficial effect of β-blockers on clinical outcomes in patients with ST elevation myocardial infarction (STEMI). In clinical practice, β-blocker treatment is occasionally discontinued due to their side effect. The purpose of this study is to assess the impact of discontinuation of β-blockers on long-term clinical outcomes in patients with STEMI. We analyzed the data and clinical outcomes of 901 patients (716 males, 58 ± 13-year-old) STEMI patients who underwent successful primary percutaneous coronary intervention. At discharge of index STEMI, 598 patients were treated with β-blockers (491 males, 56 ± 12-year-old). After more than 1-month β-blocker treatment, β-blockers were stopped in 188 patients for any reason. We classified patients into continuation of β-blockers (410 patients, 56 ± 12-year-old) and discontinuation of β-blockers groups (188 patients, 57 ± 11-year-old) according to discontinuation of β-blockers. Occurrence of major adverse cardiovascular events (MACEs; death, recurrent MI and target vessel revascularization) during up to 10 years of follow-up was evaluated. Mean follow-up month was 56 ± 28 month. In 132 patients (22%), MACEs were occurred. The MACE-free survival rates in the 2 groups were not statistically different (log-rank P = .461). Adjusted hazard ratio (HR) of discontinuation of β-blockers for MACEs was 1.006 (95% confidence interval (CI) 0.701–1.445, P = .973; all cause of death, HR = 0.942, 95% CI = 0.547–1.622, P = .828; recurrent MI, HR = 0.476, 95% CI = 0.179–1.262, P = .136; target vessel revascularization, HR = 1.417, 95% CI = 0.865–2.321, P = .166). The MACE-free survival and survival rates of the non β-blockers treatment group was significantly worse than the discontinuation of β-blockers group (log-rank P = .003 and < 0.001, respectively). This study demonstrated that discontinuation of β-blockers was not associated with adverse cardiovascular outcomes after STEMI. The beneficial effect of β-blockers on clinical outcomes may persist in patients with initial β-blockers treatment at index STEMI.

Abbreviations: CI = confidence interval, CRP = C-reactive protein, HR = hazard ratio, IL = interleukin, LVEF = left ventricular ejection fraction, MACEs = major adverse cardiovascular events, PCI = percutaneous coronary intervention, STEMI = ST elevation myocardial infarction, TVR = target vessel revascularization.

Keywords: β-blockers, myocardial infarction, prognosis

1. Introduction

Current guidelines for the management of ST elevation myocardial infarction (STEMI) recommended treatment of β-blockers following MI.[1,2] In the pre-reperfusion era, many data supported concretely that β-blockers reduced mortality in patients with STEMI.[3–5] In the reperfusion era, increased use of percutaneous coronary intervention (PCI) has been shown to reduce mortality rates after STEMI.[6] As the reperfusion therapy improves clinical outcomes, the absolute benefit of β-blockers has been getting smaller. Although some data demonstrated no clinical benefits of β-blockers,[7,8] our previous study demonstrated the clinical benefits of β-blockers in the era of primary PCI for STEMI, regardless of the left ventricular ejection fraction (LVEF).[9]

In the previous study, we demonstrated the clinical benefits of β-blockers by analyzing the clinical outcomes between the 2 groups classified according to the use of β-blockers during the period of index STEMI.[9] This data might supported that the treatment with β-blockers should be considered during the period of index STEMI.

As Asian population is more susceptible to the side effects of β-blockers than Caucasians or black Americans due to their β1-receptor sensitivity,[10,11] β-blockers are occasionally discontinued in clinical practice. Reliable data about the clinical

impact of discontinuation of β-blockers in patients with STEMI has been lacking.

The purpose of this study is to assess the impact of discontinuation of β-blockers on long-term clinical outcomes in patients with STEMI.

2. Materials and Methods

To assess the long-term clinical outcomes resulting from discontinuation of β-blockers, we enrolled the STEMI patients from 2003 to 2009, who were followed-up for up to 10 years. We consecutively enrolled 30-day survivors after STEMI who underwent successful revascularization. Successful revascularization was defined as thrombolysis in myocardial infarction trial grade 3 flow and < 30% residual stenosis in infarct related artery after primary PCI. We excluded patents with any of following: history of prior revascularization, predisposing cardiomyopathy, moderate or greater valvular heart disease. Total 901 STEMI patients (716 males, 58 ± 13-year-old) were enrolled. Among the study population, 303 patients (225 males, 61 ± 13-year-old) were not treated with β-blockers. Total 598 patients (491 males, 56 ± 12-year-old) had been treated with β-blockers at the time of discharge from the index STEMI and had continued with β-blockers more than 1month post-discharge. A retrospective review of medical records from enrolled patients was performed. This study was approved by the Ajou University Hospital Institutional Review Board (approval number: AJOUIRB-DB-2023-262).

Total 598 patients, who had been treated with β-blockers at the time of discharge from the index STEMI, were divided into 2 groups according to discontinuation of β-blockers: a continuation of β-blockers group and a discontinuation of β-blockers group. As LV function is one of major prognostic factors,[12,13] the long-term clinical outcomes were reassessed and compared according to the discontinuation of β-blockers after subdividing each group into normal LVEF (≥ 50%) and low LVEF (< 50%).

The end points of the study were major adverse cardiac events (MACEs) during up to 10 years of follow-up, including death, recurrent MI, and target vessel revascularization (TVR). Recurrent MI was defined according to the universal definition of MI.[14] Target vessel revascularization was defined as any repeat percutaneous or surgical revascularization of the index vessel including the target lesion. Follow-up data were obtained by review of medical records and/or telephone interview with patients.

SPSS 18.0 statistical software package (SPSS, Chicago, Illinois) was used for all calculations. Data are shown as the mean ± standard deviation for continuous variables and as percentages for categorical variables. Comparisons were conducted by unpaired Student t test and ANOVA for continuous variables and Pearson chi-square test for categorical variables. Event free survival analysis for patients in these groups was performed using the Kaplan–Meier method. Differences between groups were assessed by log-rank test. The Cox's proportional hazard model was used in the study to assess adjusted relative hazard ratio (HR) of discontinuation of β-blockers in relation to the study end points, taking into account potential variables associated with clinical outcomes. The Cox's proportional hazard model utilized adjusted covariates that are well-known predictors of MACEs, including age, gender, diabetes mellitus, hypertension, smoking, dyslipidemia, Killip classification, LVEF, and discontinuation of β-blockers. The results of Cox's regression analysis were presented as adjusted HRs with corresponding 95% confidence intervals (CI) for clinical outcomes. Multivariate logistic regression analysis was performed to assess the effect discontinuation of β-blockers on clinical outcomes. Null hypotheses of no difference were rejected if P values were < .05.

3. Results

From 2003 to 2009, total 901 STEMI patients (716 males, 58 ± 13-year-old) were enrolled. Among the study population, 598 patients (491 males, 56 ± 12-year-old) had been treated with β-blockers at the time of discharge from the index STEMI and had continued with β-blockers more than 1-month post-discharge. After 20 ± 29 months (median 11 month) β-blockers treatment, β-blockers were stopped in 188 patients (147 males, 57 ± 11-year-old) for any reason. In the continuation of β-blockers group, 410 patients (344 males, 56 ± 12-year-old) were included.

Table 1

Baseline characteristics according to discontinuation of β-blockers.

Variables	Continuation of β-blockers (n = 410)	Discontinuation of β-blockers (n = 188)	P value
Age, yr	56 ± 12	57 ± 11	.169
Men, No.	344 (84%)	147 (78%)	.106
BMI, kg/m^2	24.8 ± 3.1	24.7 ± 3.4	.773
Prior CABG	1 (0%)	0 (0%)	.617
Prior PCI	32 (7%)	8 (7%)	.991
Medical history			
Hypertension, No.	183 (45%)	74 (39%)	.225
Diabetes mellitus, No.	103 (25%)	33 (18%)	.032
Dyslipidemia, No.	34 (8%)	14 (7%)	.724
Smoking, No.	265 (65%)	122 (65%)	.951
LDL-C, mg/dL	106 ± 32	102 ± 34	.165
LVEF, %	52 ± 11	53 ± 9	.413
WMSI	1.5 ± 0.3	1.5 ± 0.3	.314
Killip class			
Killip class 3, No.	29 (7%)	11 (6%)	.579
Killip class 4, No.	9 (2%)	6 (3%)	.47
Medication, No.			
Aspirin	406 (99%)	187 (100%)	.581
Clopidogrel	380 (93%)	172 (92%)	.612
CCB	45 (11%)	27 (14%)	.238
ACEi or ARB	393 (96%)	174 (93%)	.091
Statins	293 (72%)	128 (68%)	.402
Nitrates	327 (80%)	148 (79%)	.772

ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CCB = calcium channel blocker, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, WMSI = wall motion score index.

Table 2

Baseline angiographic characteristics according to discontinuation of β-blockers.

Variables	Continuation of β-blockers (n = 410)	Discontinuation of β-blockers (n = 188)	P value
Culprit lesion			
LAD, No.	233 (57%)	106 (56%)	.919
LCX, No.	28 (7%)	14 (7%)	.784
RCA, No.	145 (35%)	68 (36%)	.849
Coronary artery disease			
1 Vessel disease, No.	179 (44%)	81 (43%)	.896
2 Vessel Disease, No.	132 (32%)	65 (35%)	.566
3 Vessel Disease, No.	99 (24%)	42 (22%)	.63
Procedural type			
BMS, No.	98 (24%)	45 (24%)	.993
DES, No.	315 (77%)	143 (76%)	.838

BMS = bare metal stent, DES = drug eluting stent, LAD = left anterior descending artery, LCX = left circumflex artery, LM = left main artery, PCI = primary coronary intervention, RCA = right coronary artery.

Baseline characteristics according to the 2 groups are summarized in Table 1. The continuation of β-blockers group had more history of diabetes mellitus (25 vs 18%, P = .032) than the discontinuation of β-blockers group. Global and regional LV function measured by LVEF and wall motion

score index were not significantly different between the 2 groups. There was no significant difference in the distribution of Killip classification, the index of heart failure severity, between the 2 groups. Other variables of medical treatment were not significantly different between the 2 groups. Angiographic and procedural data are summarized in Table 2. Distribution of culprit lesion, number of involved coronary vessels and procedural type were similar between the 2 groups. Baseline characteristics of these 2 groups and the non β-blockers treatment group, who were not treated with β-blockers during the index STEMI, were summarized in Table 3. The non- β blockers group had older age, less males, less hypertension and more Killip class IV compared to other groups. In the present study, no patients needed mechanical circulatory support.

Mean follow-up month after index STEMI was 56 ± 28 months. In 132 patients (22%), MACEs were occurred. All the events-free survival rates in the 2 groups were not statistically different (Fig. 1). In the Kaplan–Meier survival curves of patients with normal LVEF, there was no statistical significance between the 2 groups (Fig. 2). Also, there was no significant difference between the 2 groups in the Kaplan–Meier survival curves of patients with low LVEF (Fig. 3). The MACE-free survival and survival rates of the non β-blockers treatment group, who were not treated with β-blockers during the index STEMI, was significantly worse than the discontinuation of β-blockers group (log-rank P = .003 and < 0.001, respectively, Fig. 4). Occurrences of recurrent MI and TVR were similar in these groups.

The results of the Cox's regression analysis for the adverse outcomes are listed in the Table 4. In Cox's proportional hazard model, age (HR = 1.038, 95% CI = 1.018–1.059, P = <.001), diabetes (HR 1.674, 95% CI 1.058–2.649, P = .028) and Killip classification (HR 1.433, 95% CI 1.108–1.854, P = .006) were related to MACEs. Age (HR = 1.038, 95% CI = 1.018–1.059, P = <.001) was related to all cause of death. The discontinuation of β-blockers were not related to MACEs. In a multivariate logistic regression analysis, the adjusted HR of discontinuation of β-blockers for MACEs was 1.006 (95% CI 0.701–1.445, P = .973; all cause of death, HR = 0.942, 95%

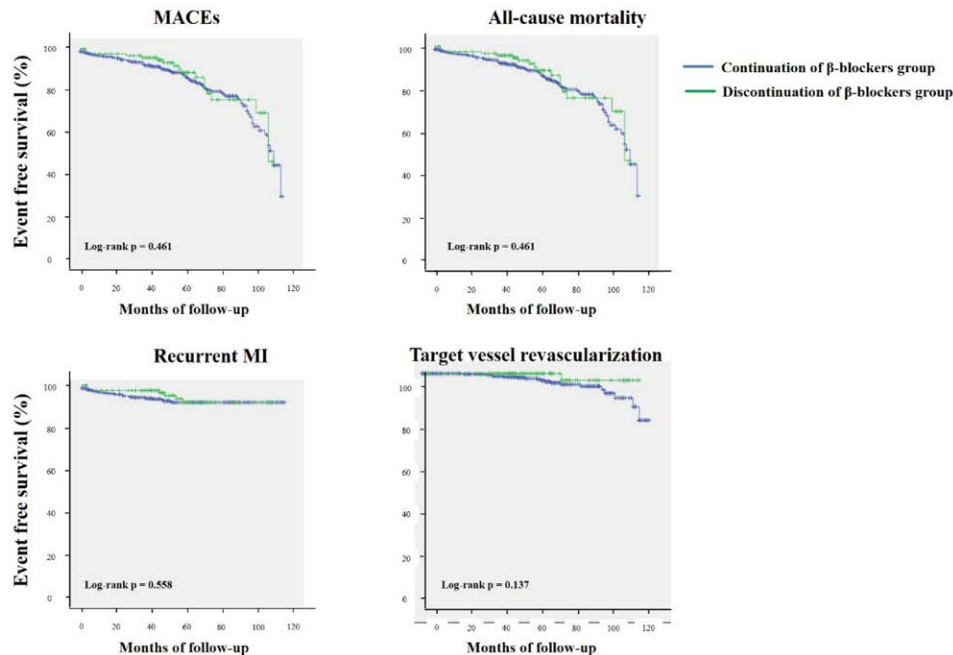**Table 3**

Baseline characteristics according to treatment of β-blockers.

Variables	Continuation of β-blockers (n = 410)	Discontinuation of β-blockers (n = 188)	Non β-blockers treatment (n = 303)	P value
Age, yr	56 ± 12	57 ± 11	61 ± 13	<.001
Men, No.	344 (84%)	147 (78%)	225 (68%)	.002
BMI, kg/m2	24.8 ± 3.1	24.7 ± 3.4	23.9 ± 4.3	.006
Prior CABG	1 (0%)	0 (0%)	1 (0%)	.809
Prior PCI	32 (7%)	8 (7%)	25 (8)	.71
Medical history				
Hypertension, No.	183 (45%)	74 (39%)	104 (34%)	.044
Diabetes Mellitus, No.	103 (25%)	33 (18%)	61 (20%)	.213
Dyslipidemia, No.	34 (8%)	14 (7%)	19 (6%)	.604
Smoking, No.	265 (65%)	122 (65%)	197 (65%)	.737
LDL-C, mg/dL	106 ± 32	102 ± 34	101 ± 36	.041
LVEF, %	52 ± 11	53 ± 9	49 ± 12	<.001
WMSI	1.5 ± 0.3	1.5 ± 0.3	1.6 ± 0.3	.366
Killip class				
Killip class 3, No.	29 (7%)	11 (6%)	30 (10%)	.186
Killip class 4, No.	9 (2%)	6 (3%)	24 (8%)	.001
Medication, No.				
Aspirin	406 (99%)	187 (100%)	301 (99%)	.958
Clopidogrel	380 (93%)	172 (92%)	268 (88%)	.048
CCB	45 (11%)	27 (14%)	87 (29%)	<.001
ACEi or ARB	393 (96%)	174 (93%)	273 (90%)	.03
Statins	293 (72%)	128 (68%)	176 (58%)	.001
Nitrates	327 (80%)	148 (79%)	234 (77%)	.435

ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CCB = calcium channel blocker, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, WMSI = wall motion score index.

Figure 1. Kaplan–Meier survival curves for free of adverse outcomes in the continuation of β-blockers group and the discontinuation of β-blockers group. MACEs = major adverse cardiovascular events, MI = myocardial infarction.
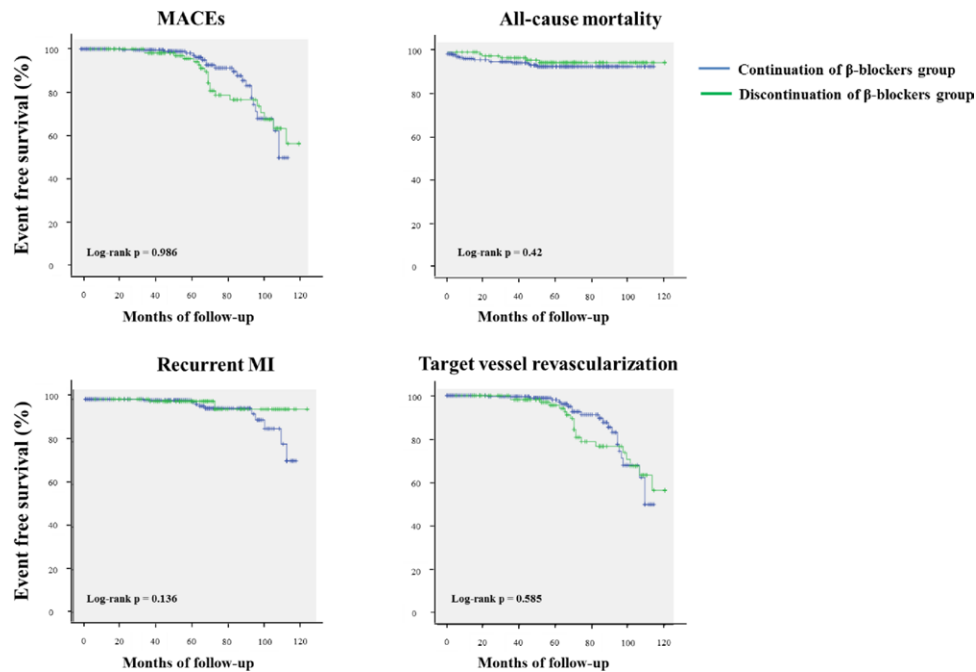
Figure 2. Kaplan–Meier survival curves for free of adverse outcomes between two groups (the continuation of β-blockers group and the discontinuation of β-blockers group) with a left ventricular ejection fraction of 50% or higher. MACEs = major adverse cardiovascular events, MI = myocardial infarction.
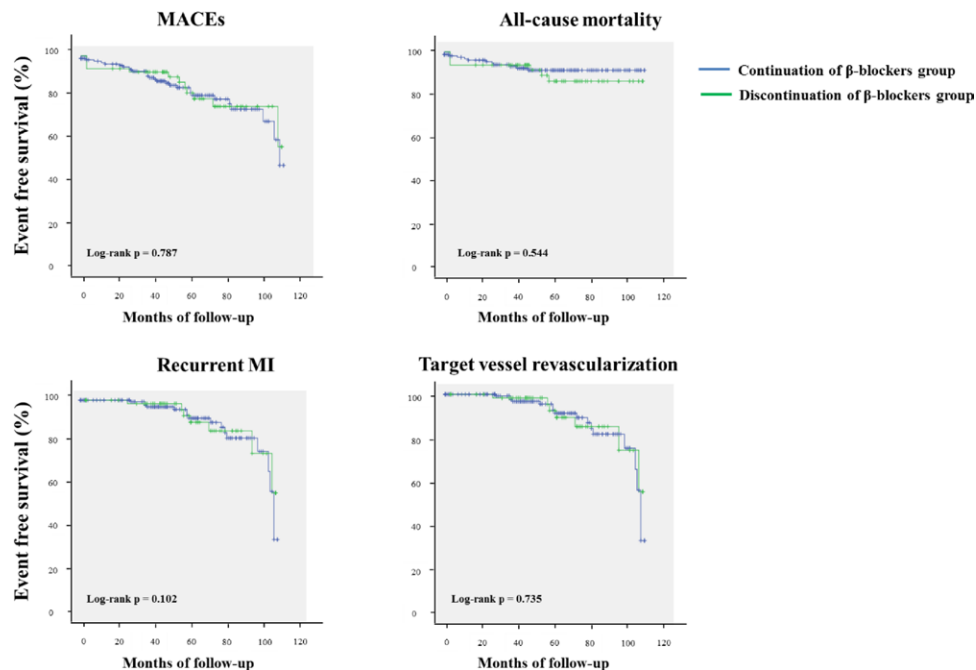

Figure 3. Kaplan–Meier survival curves for free of adverse outcomes between two groups (the continuation of β-blockers group and the discontinuation of β-blockers group) with a left ventricular ejection fraction of <50%. MACEs = major adverse cardiovascular events, MI = myocardial infarction.

CI = 0.547–1.622, P = .828; recurrent MI, HR = 0.476, 95% CI = 0.179–1.262, P = .136, and TVR, HR = 1.417, 95% CI = 0.865–2.321, P = .166, respectively, Table 5). The discontinuation of β-blockers was not independently associated with increased risk for MACEs.

4. Discussion and conclusion

In the present study, discontinuation of β-blockers after index STEMI was not associated with adverse clinical outcomes, irrespective of LVEF. Compared with the patients who were not treated with β-blockers during the index STEMI, the patients, who were treated with β-blockers during the index STEMI but not continued treatment of β-blockers, had better prognosis.

As the lack of reperfusion resulted in severe LV dysfunction and extensive myocardial scarring, providing a substrate for reentrant circuits and fatal ventricular arrhythmias in the pre-reperfusion era, the role of β-blockers was crucial for short and long-terms clinical outcomes.[3–5] In the reperfusion era, the
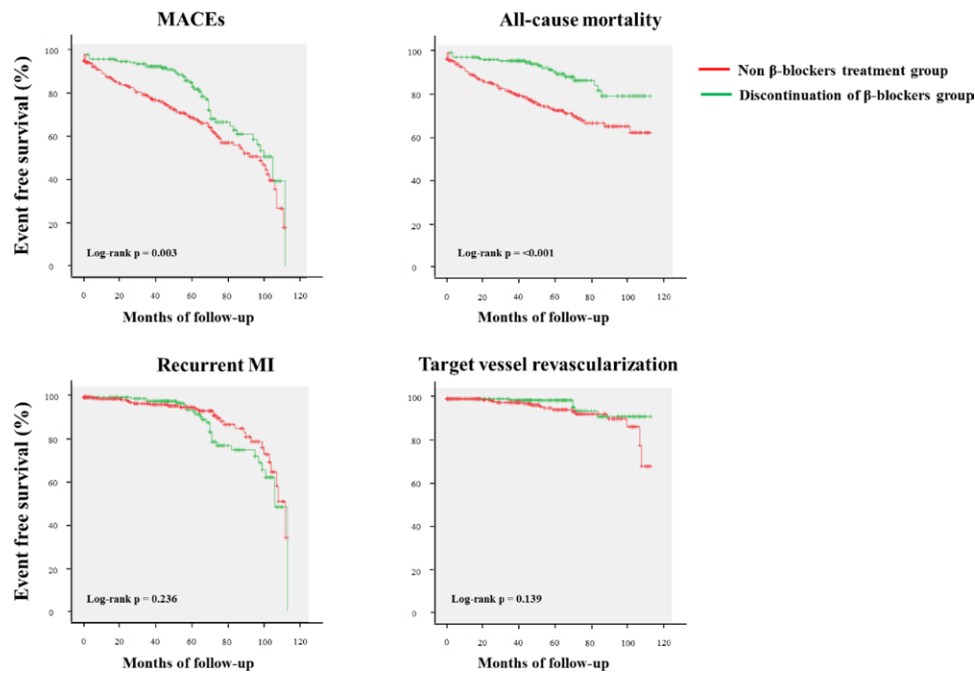
Figure 4. Kaplan–Meier survival curves for free of adverse outcomes in the discontinuation of β-blockers group and the non β-blockers treatment group. MACEs = major adverse cardiovascular events, MI = myocardial infarction.

incidence of mechanical complications of acute MI, LV dysfunction or extensive myocardial scarring has notably decreased after STEMI.[15] In the present study, there was no patient with mechanical complications of acute MI or LVEF of <40%. With this changing patient population, the role of β-blockers may have also changed. Some data demonstrated that β-blockers have no short term mortality benefit particularly in patients without heart failure.[7,8] In the present study, as the patients were treated with β-blockers during the index STEMI and discontinued, we can conclude only that the discontinuation of β-blockers might not be associated with adverse clinical outcomes. There is still controversy over the required duration of β-blockers treatment following STEMI.

Consistent with our previous study,[9] the present study further supported the clinical benefits of initial β-blockers treatment during the index STEMI. After acute MI, early use of β-blockers attenuated serum C-reactive protein (CRP), a marker of the acute inflammatory response.[16] In acute phase of MI, serum CRP is elevated in response to stimulation by cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α. During and immediately after acute MI, the increase in plasma IL-6 level was caused by spillover from cardiac tissue, the site of inflammation, and the spillover of IL-6 was facilitated by catecholamine stimulation.[17,18] Patients with high plasma IL-6 levels during the acute phase of STEMI had worse clinical outcomes.[19] By suppressing both inflammatory and adrenergic system in the myocardium, initial β-blockers treatment may have beneficial role even in the reperfusion era.

During the chronic phase following STEMI in the pre-reperfusion era, the role of β-blockers was primarily focused on their anti-arrhythmic effect and their preventive role in ventricular remodeling. With the changing patient population in the reperfusion era, the magnitude of these effects of β-blockers appears to be diminishing. As inflammation is essential in all stages of coronary artery disease, β-blockers, which can suppress both inflammatory and adrenergic system, may have potential to influence disease progression in chronic phase following STEMI. Although the level of plasma IL-6 tends to decrease at 4 months following STEMI, small number of patients with sustained high plasma IL-6 level during this period demonstrated

worse clinical outcomes.[19] During the chronic phase following STEMI, the role of β-blockers might have changed to manage residual inflammation in the reperfusion era.

This study has several limitations. First, the results of the study did not demonstrate that β-blockers treatment could be stopped in all the patients with STEMI. Although the incidence of high-risk patients after STEMI has been getting decreased, some patients should be treated with β-blockers for better prognosis. Before decision of discontinuation of β-blockers, risk stratification should be considered. As the myocardial structural and functional alterations beyond LVEF could affect the adverse clinical outcomes, other imaging modalities, such as speckle-tracking echocardiography or cardiac magnetic resonance imaging, might be needed for more detailed risk stratification. Second, the extent of residual inflammation could not be estimated in the chronic phase following STEMI. Although the result logically implied that initial β-blockers treatment has beneficial role by attenuating the acute inflammation, the duration of persistent inflammation remains difficult to determine in the chronic phase following STEMI. In patients with residual inflammation, β-blockers treatment should be continued for improving clinical outcomes. As the present study was not designed to evaluate the inflammation and the effect of β-blockers treatment, inflammatory markers, such as CRP or plasma IL-6, were not controlled in the statistics. To prove this, further studies might be needed. Third, the required duration of β-blockers treatment after STEMI could not be estimated from the present study. As the present study was observational study, the maintenance duration of β-blockers was not controlled for analysis. In the present study, the discontinuation of β-blockers group that had received β-blocker treatment for 20 ± 29 months (median 11month) after index STEMI was not independently associated with increased risk for MACEs. Additionally, chronic inflammation tends to decrease at 4 months following STEMI.[19] Although these results might suggest that β-blockers treatment could be stopped after at least 11 months, randomized controlled trials might be needed to evaluate the required duration of β-blockers treatment after STEMI. From the present study, it can just be concluded that β-blockers treatment should be considered during the index STEMI.

Table 4

Cox's regression analysis for the adverse outcomes.

Variables	Adjusted hazard ratio (95% CI)	P value
MACEs		
Age	1.038 (1.018–1.059)	<.001
Gender	0.819 (0.443–1.513)	.819
Hypertension	1.191 (0.778–1.822)	.422
Diabetes	1.674 (1.058–2.649)	.028
Dyslipidemia	0.515 (0.195–1.356)	.179
Smoking	0.661 (0.404–1.08)	.099
Killip classification	1.433 (1.108–1.854)	.006
LVEF	0.992 (0.972–1.012)	.416
Discontinuation of β-blockers	0.874 (0.568–1.345)	.541
All cause mortality		
Age	1.116 (0.991–1.256)	.07
Gender	0.734 (0.041–13.272)	.734
Hypertension	2.866 (0.276–29.733)	.378
Diabetes	0.697 (0.065–7.5)	.765
Dyslipidemia	0 (0)	.998
Smoking	0.399 (0.031–5.102)	.48
Killip classification	0.936 (0.224–3.91)	.928
LVEF	0.949 (0.834–1.08)	.425
Discontinuation of β-blockers	0.405 (0.05–3.28)	.397
Recurrent MI		
Age	0.993 (0.954–1.032)	.712
Gender	1.219 (0.288–5.16)	.788
Hypertension	1.909 (0.761–4.786)	.168
Diabetes	1.053 (0.378–2.932)	.921
Dyslipidemia	0.469 (0.061—3.617)	.469
Smoking	0.492 (0.156–1.549)	.492
Killip classification	0.756 (0.364–1.569)	.453
LVEF	1.027 (0.988–1.068)	.177
Discontinuation of β-blockers	2.172 (0.793–5.946)	.131
TVR		
Age	0.997 (0.972–1.023)	.823
Gender	0.811 (0.339—1.942)	.639
Hypertension	1.364 (0.775–2.398)	.281
Diabetes	0.648 (0.354–1.187)	.648
Dyslipidemia	0.865 (0.294–2.546)	.865
Smoking	0.755 (0.39–1.46)	.403
Killip classification	1.335 (0.961–1.855)	.085
LVEF	1.01 (0.984–1.035)	.461
Discontinuation of β-blockers	0.669 (0.384–1.163)	.154

CI = confidence interval, LVEF = left ventricular ejection fraction, MACEs = major adverse cardiovascular events, MI = myocardial infarction, TVR = target vessel revascularization.

Table 5

Multivariate logistic regression analysis of discontinuation of β-blockers for adverse clinical outcomes.

Variables	Hazard ratio (95% CI)	P value
MACEs	1.006 (0.701–1.445)	.973
All-cause mortality	0.942 (0.547–1.622)	.828
Recurrent MI	0.476 (0.179–1.262)	.136
TVR	1.417 (0.865–2.321)	.166

CI = confidence interval, MACEs = major adverse cardiovascular events, MI = myocardial infarction, TVR = target vessel revascularization.

5. Conclusion

Discontinuation of β-blockers was not associated with adverse cardiovascular outcomes after STEMI. The beneficial effect of β-blockers on clinical outcomes may persist in patients with initial β-blockers treatment at index STEMI.

Author contributions

Conceptualization: Joon-Han Shin.
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Methodology: Jin-Sun Park.
Supervision: Seung-Jea Tahk, Joon-Han Shin.
Writing – original draft: Jin-Sun Park.
Writing – review & editing: Joon-Han Shin.

References

[1] Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–77.

[2] O'Gara PT, Kushner FG, Ascheim DD, et al. Circulation. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;127:e362–425.

[3] Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med. 1981;304:801–7.

[4] A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA. 1982;247:1707–14.

[5] Hjalmarson A, Herlitz J, Holmberg S, et al. The Göteborg metoprolol trial. Effects on mortality and morbidity in acute myocardial infarction. Circulation. 1983;67:I26–32.

[6] Puymirat E, Simon T, Steg PG, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA. 2012;308:998–1006.

[7] Dondo TB, Hall M, West RM, et al. Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. J Am Coll Cardiol. 2017;69:2710–20.

[8] Bangalore S, Makani H, Radford M, et al. Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med. 2014;127:939–53.

[9] Lee YH, Park JS, Tahk SJ, et al. β-blocker therapy in the era of primary percutaneous intervention for ST elevation myocardial infarction. Cardiology. 2015;132:91–100.

[10] Hori M, Sasayama S, Kitabatake A, et al. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the multicenter carvedilol heart failure dose assessment (MUCHA) trial. Am Heart J. 2004;147:324–30.

[11] Xie HG, Kim RB, Wood AJ, et al. Molecular basis of ethnic differences in drug disposition and response. Annu Rev Pharmacol Toxicol. 2001;41:815–50.

[12] Ng VG, Lansky AJ, Meller S, et al. The prognostic importance of left ventricular function in patients with ST-segment elevation myocardial infarction: the HORIZONS-AMI trial. Eur Heart J Acute Cardiovasc Care. 2014;3:67–77.

[13] Michaels AD, Goldschlager N. Risk stratification after acute myocardial infarction in the reperfusion era. Prog Cardiovasc Dis. 2000;42:273–309.

[14] Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation. 2007;116:2634–53.

[15] Gueret P, Khalife K, Jobic Y, et al. Echocardiographic assessment of the incidence of mechanical complications during the early phase of myocardial infarction in the reperfusion era: a French multicentre prospective registry. Arch Cardiovasc Dis. 2008;101:41–7.

[16] Anzai T, Yoshikawa T, Takahashi T, et al. Early use of beta-blockers is associated with attenuation of serum C-reactive protein elevation and favorable short-term prognosis after acute myocardial infarction. Cardiology. 2003;99:47–53.

[17] Murray DR, Prabhu SD, Chandrasekar B. Chronic beta-adrenergic stimulation induces myocardial proinflammatory cytokine expression. Circulation. 2000;101:2338–41.

[18] Bürger A, Benicke M, Deten A, et al. Catecholamines stimulate interleukin-6 synthesis in rat cardiac fibroblasts. Am J Physiol Heart Circ Physiol. 2001;281:H14–21.

[19] Tollefsen IM, Shetelig C, Seljeflot I, et al. High levels of interleukin-6 are associated with final infarct size and adverse clinical events in patients with STEMI. Open Heart. 2021;8:e001869.