Effect of Pre-Procedural Beta-Blocker on Clinical Outcome after Percutaneous Coronary Intervention in Acute Coronary Syndrome

From the 2014 K-PCI Registry

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Summary

The efficacy of pre-procedural beta-blocker use in patients with acute coronary syndrome (ACS) is not well established in the current percutaneous coronary intervention (PCI) era. We investigate the effect of pre-procedural beta-blocker use on clinical outcomes in patients with ACS undergoing PCI. Among 44,967 consecutive cases of PCI enrolled in the nationwide, retrospective, multicenter registry (K-PCI registry), 31,040 patients with ACS were selected and analyzed. We classified patients into pre-procedural beta-blocker group ($n = 8,678$) and pre-procedural no-beta-blocker group ($n = 22,362$) according to the use of beta-blockers at least for two weeks before index PCI. Propensity score-matching analysis was performed and resulted in 7,445 pairs. The primary outcome was in-hospital cardiac death. In propensity score-matched populations, the pre-procedural beta-blocker group had a lower incidence of in-hospital cardiac death compared with the pre-procedural no-beta-blocker group (1.1% versus 2.0%, unadjusted odds ratio [OR]: 0.56, 95% confidence interval [CI]: 0.42-0.73, $P < 0.01$). In subgroup analysis, the pre-procedural beta-blocker group had a lower incidence of in-hospital cardiac death, compared with the pre-procedural no-beta-blocker group in ST-segment elevation myocardial infarction subpopulation (3.1% versus 6.1%, unadjusted OR: 0.49, 95% CI: 0.34-0.71, $P < 0.01$) and non-ST-segment elevation myocardial infarction subpopulation (1.5% versus 2.9%, unadjusted OR: 0.51, 95% CI: 0.33-0.79, $P < 0.01$). However, in unstable angina subpopulation, the in-hospital cardiac death rate was comparable between both groups. In conclusion, the use of pre-procedural beta-blocker was associated with a lower risk of in-hospital cardiac death in patients with ACS undergoing PCI. This result adds to the body of evidence that use of pre-procedural beta-blocker in patients with ACS might be reasonable.

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Key words: Coronary artery disease, Pre-procedural medication, Cardiac death

In recent years, the beneficial effect of beta-blockers in coronary artery disease (CAD) has become controversial, especially in relatively low-risk patients without prior myocardial infarction (MI) or systolic heart failure (HF).¹⁻³ However, historically, beta-blockers have been used one of the standard of care for patients with CAD, including acute MI. Currently, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend early initiation of beta-blocker in

ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndrome (NSTEMI/ACS) patients without contraindication of their use and recommend beta-blocker as initial therapy for relief of symptoms in patients with stable CAD.⁴⁻⁶ Even though clinical evidence support this recommendation derived from studies conducted before the introduction of the current percutaneous coronary intervention (PCI) practice, beta-blockers remain crucial component of optimal medi-

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Figure 1. Schema of group distribution in the registry. PCI indicates percutaneous coronary intervention.

cal therapy in patients with ACS or residual ischemia in the current PCI era.⁷⁻¹¹⁾ In daily use of beta-blockers, clinical uncertainty exists regarding their effectiveness as pre-procedural beta-blocker therapy. Therefore, we investigated clinical outcomes in patients with ACS presentation undergoing PCI according to pre-medication of oral beta-blockers in current PCI practice using nationwide PCI registry.

Methods

Study population: The study population was selected from the K-PCI registry 2014, a retrospective multicenter registry of patients with CAD who underwent PCI during 2014. This registry was sponsored by the Korean Society of Cardiology and the Korean Society of Interventional Cardiology. All consecutive patients were enrolled from 92 high-volume PCI centers in Korea. This registry was an all-comer study with no specific exclusion criteria. The local Institutional Review Board at each center approved this study. Informed consent was waived at all centers, considering the study's retrospective enrollment without clinical follow-up design. Between January 1, 2014 and December 31, 2014, a total of 44,967 consecutive cases of PCI were enrolled in this registry. Clinical, laboratory, and in-hospital outcome data were collected by a trained study coordinator using a standardized case report form and protocol in a web-based reporting system. In the present analysis, for duplicated patients undergoing multiple PCIs, the initial PCI was considered as the index PCI. Patients with cardiogenic shock or cardiopulmonary resuscitation and patients with an uncertain record of beta-blocker medication within last two weeks before the index PCI were excluded. Among the patients included, 11,250 pa-

tients were presented with non-ACS and 31,040 patients with ACS. For the analysis of this study, patients with ACS were divided by use of beta-blockers in the two weeks prior to the index PCI into a pre-procedural beta-blocker group and a pre-procedural no-beta-blocker group. Considering the tolerability of beta-blocker therapy, patients who used beta-blocker medication for more than two weeks before the index PCI were considered as pre-procedural beta-blocker group. The patient flow of the study is shown in Figure 1.

PCI procedure and pre-procedural medication: Antiplatelet medications before the PCI and coronary interventions were performed according to the current standard procedural guideline. Anticoagulation therapy during PCI was performed according to current practice guideline by the Korean Society of Interventional Cardiology. The treatment strategies during PCI were all left to the operator's discretion. The pre-procedural antianginal medications, including beta-blockers, calcium-channel blockers, long-acting nitrates, nicorandil, or trimetazidine, were considered that patients has taken or has been oral medication within the two weeks prior to index PCI.

Definition and outcomes: Clinical presentation at procedure were classified into five categories by an attending physician in each hospital based on the following criteria: 1) Silent ischemia was defined in patients with no symptoms or symptoms that were unlikely to be ischemic pain; 2) Stable angina was defined in patients with angina symptoms that did not change in frequency or pattern in the six weeks prior to the index PCI or that were controlled by rest and/or oral antianginal medications; 3) Unstable angina was defined in patients with rest angina (occurring during rest and prolonged, usually > 20 minutes) or new-onset angina (within the past two months, of at

Table I. Baseline Clinical and Angiographic Characteristics

	Overall population			Propensity score-matched population		
	Pre-procedural Beta-Blocker group (n = 8678)	Pre-procedural No-Beta-Blocker group (n = 22362)	Absolute Standardized Difference	Pre-procedural Beta-Blocker group (n = 7445)	Pre-procedural No-Beta-Blocker group (n = 7445)	Absolute Standardized Difference
Demographic characteristics						
Age (years)	66.0 ± 11.6	64.8 ± 12.2	−0.101	66.1 ± 11.7	66.4 ± 11.5	0.027
Age > 75 years	1995 (23.0)	4831 (21.6)	−0.033	1750 (23.5)	1782 (23.9)	0.010
Male	5968 (68.8)	15846 (70.9)	0.046	5127 (68.9)	5111 (68.7)	−0.005
Hypertension	6047 (69.7)	12487 (55.9)	−0.289	5098 (68.5)	5287 (71.0)	0.055
Diabetes	3426 (39.5)	7287 (32.6)	−0.144	2873 (38.6)	2892 (38.8)	0.005
Dyslipidemia	4516 (52.1)	7040 (31.5)	−0.426	3710 (49.8)	3648 (49.0)	−0.017
Chronic kidney disease	754 (8.7)	1257 (5.6)	−0.119	619 (8.3)	648 (8.7)	0.014
Current Smoking	2109 (24.6)	6834 (30.6)	0.135	1864 (25.0)	1812 (24.3)	−0.016
Family history of CAD	480 (5.9)	1160 (5.3)	−0.025	437 (5.9)	463 (6.2)	0.015
Previous history of MI	1463 (16.9)	1139 (5.1)	−0.383	1099 (14.8)	1030 (13.8)	−0.027
Previous history of PCI	3199 (36.9)	2989 (13.4)	−0.563	2509 (33.7)	2550 (34.3)	0.012
Previous CABG	198 (2.3)	190 (0.9)	−0.115	163 (2.2)	151 (2.0)	−0.011
Previous CVA	757 (8.7)	1808 (8.1)	−0.023	661 (8.9)	670 (9.0)	0.004
Peripheral arterial disease	230 (2.7)	416 (1.9)	−0.053	193 (2.6)	210 (2.8)	0.014
Clinical diagnosis at procedure						0.048
Unstable angina	4773 (55.0)	10572 (47.3)	−0.210	3984 (53.5)	4274 (57.4)	
NSTEMI	2387 (27.5)	5849 (26.2)		2108 (28.3)	1804 (24.2)	
STEMI	1518 (17.5)	5941 (26.6)		1353 (18.2)	1367 (18.4)	
Anti-Anginal meds at procedure						
Ca-Channel-Blocker	2001 (23.1)	3702 (16.6)	−0.164	1622 (21.8)	1778 (23.9)	0.050
Long-Acting Nitrates	1592 (18.4)	1410 (6.3)	−0.373	1141 (15.3)	1120 (15.0)	−0.008
Nicorandil	2231 (25.7)	1736 (7.8)	−0.495	1566 (21.0)	1501 (20.2)	−0.022
Trimetazidine	1099 (12.7)	1167 (5.2)	−0.263	760 (10.2)	806 (10.8)	0.020
Angiographic characteristics						
1 vessel disease	3132 (36.2)	8273 (37.1)	0.001	2636 (35.4)	2706 (36.4)	0.001
2 vessel disease	2780 (32.2)	6771 (30.4)		2405 (32.3)	2271 (30.5)	
3 vessel disease	2735 (31.6)	7248 (32.5)		2404 (32.3)	2468 (33.2)	
Left main disease	583 (6.7)	1621 (7.3)	0.021	528 (7.1)	545 (7.3)	0.009
Proximal LAD lesion	3455 (39.8)	9623 (43.0)	0.065	3024 (40.6)	3021 (40.6)	0.001
PCI status			−0.128			0.063
Elective PCI	5327 (61.4)	12317 (55.1)		4574 (61.4)	4802 (64.5)	
Non-elective PCI	3351 (38.6)	10045 (44.9)		2871 (38.6)	2643 (35.5)	
Arterial access site for PCI						
Femoral	3953 (45.6)	11080 (49.6)	−0.080	3516 (47.2)	3422 (46.0)	−0.025
Radial	4835 (55.7)	11586 (51.8)	0.078	4025 (54.1)	4099 (55.1)	0.020

Values are mean ± standard deviation or n (%). CABG indicates coronary bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular accident; LAD, left anterior descending artery; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

least Canadian Cardiovascular Society [CCS] Class III severity) or increasing angina (previously diagnosed angina that has become distinctly more frequent, longer in duration, or increased by one or more CCS class to at least CCS III severity); 4) non-ST-elevation MI (NSTEMI) was defined as cardiac biomarkers (creatinine kinase-myocardial band [CK-MB], Troponin T or I) that exceed the upper limit of normal according to the individual hospital's laboratory parameters, with clinical presentation consistent or suggestive of ischemia, and an absence of electrocardiogram changes diagnostic of STEMI; 5) STEMI was defined as new or presumed new ST-segment elevation or a new bundle branch block not able to be resolved within 20 minutes and cardiac biomarkers (CK-MB, Troponin T or I) that exceed the upper limit of normal according to the individual hospital's laboratory pa-

rameters with clinical presentation, which is consistent or suggestive of ischemia.¹²⁾ Silent ischemia and stable angina were classified as non-ACS and unstable angina, NSTEMI and STEMI were classified as ACS. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) lower than 60 mL/minute/1.73 m² using the Modified Diet in Renal Disease equation. The primary outcome was cardiac death during hospitalization. The secondary outcomes were all-cause death, non-fatal MI, urgent PCI, and stroke. All-cause death was defined as any death during hospitalization after index PCI. Cardiac death was defined as any death due to a proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), death from an unknown cause, and all procedure-related deaths. Non-fatal MI was defined as a new occurrence of a cardiac biomarker after index PCI in

Baseline characteristics: In the overall included populations, 31,040 patients were presented with ACS and pre-procedural beta-blockers were prescribed in 8,678 patients (27.9%), and not in 22,362 patients (72.1%). Baseline clinical and angiographic characteristics are shown in Table I. Overall, patients in the pre-procedural beta-blocker group had multiple comorbidities. Compared with patients in the pre-procedural no-beta-blocker group, those in the pre-procedural beta-blocker group had a higher prevalence of hypertension, diabetes, dyslipidemia, CKD, previous history of MI, previous history of PCI, previous coronary artery bypass graft, unstable angina as clinical diagnosis at procedure, and elective PCI. In addition, patients in the pre-procedural beta-blocker group were older and more likely to receive other antianginal medications and elective PCI, but they had a lower prevalence of STEMI as a clinical diagnosis at procedure, current smoking, and non-elective PCI. After performing propensity score-matching for the entire population, a total of 7,445 matched pair pa-

Figure 2. Comparative unadjusted odds ratio of cardiac death according to clinical diagnosis subgroup at the time of the procedure in the overall and propensity score-matched populations in acute coronary syndrome. CI indicates confidence interval; NSTEMI, non-ST-elevation myocardial infarction; and STEMI, ST-elevation myocardial infarction.

tients were created. The C-statistic for the propensity score model was 0.78, and an absolute standardized difference of all variables between the pre-procedural beta-blocker group and the pre-procedural no-beta-blocker group was less than 0.1 (10.0%).

Clinical outcomes: In the overall included populations, the pre-procedural beta-blocker group had a significantly lower incidence of cardiac death (pre-procedural beta-blocker group versus pre-procedural no-beta-blocker group: 1.1% versus 2.3%, unadjusted odds ratio [OR]: 0.49, 95% confidence interval [CI]: 0.39-0.61, $P < 0.01$), all-cause death (1.8% versus 3.2%, unadjusted OR: 0.56, 95% CI: 0.47-0.67, $P < 0.01$), non-fatal MI (1.1% versus 2.1%, unadjusted OR: 0.54, 95% CI: 0.44-0.67, $P < 0.01$), and stroke (0.1% versus 0.3%, unadjusted OR: 0.50, 95% CI: 0.27-0.93, $P = 0.03$). The incidence of urgent PCI was similar between the pre-procedural beta-blocker group and the pre-procedural no-beta-blocker group (0.3% versus 0.3%, unadjusted OR: 1.08, 95% CI: 0.66-1.76, $P = 0.76$). In propensity score-matched populations, the pre-procedural beta-blocker group still had a lower incidence of cardiac death (1.1% versus 2.0%, adjusted OR: 0.52, 95% CI: 0.40-0.69, $P < 0.01$), all-cause death (1.8% versus 2.8%, adjusted OR: 0.62, 95% CI: 0.50-0.78, $P < 0.01$), and non-fatal MI (1.2% versus 1.8%, adjusted OR: 0.64, 95% CI: 0.49-0.85, $P < 0.01$). There were no differences between the two groups in the rate of stroke (0.2% versus 0.2%, adjusted OR: 0.75, 95% CI: 0.34-1.63, $P = 0.46$) and urgent PCI (0.3% versus 0.3%, adjusted OR: 1.14,

95% CI: 0.62-2.11, $P = 0.68$) (Table II).

Subgroup analysis: In the overall included populations, the pre-procedural beta-blocker group had a significantly lower incidence of cardiac death, compared with the pre-procedural no-beta-blocker group in the STEMI subpopulation (3.1% versus 5.7%, unadjusted OR: 0.53, 95% CI: 0.39-0.72, $P < 0.01$) and NSTEMI subpopulation (1.6% versus 2.4%, unadjusted OR: 0.65, 95% CI: 0.45-0.93, $P = 0.02$). In propensity score-matched populations, the pre-procedural beta-blocker group still had a lower incidence of cardiac death, compared with the pre-procedural no-beta-blocker group in STEMI subpopulation (3.1% versus 6.1%, unadjusted OR: 0.49, 95% CI: 0.34-0.71, $P < 0.01$) and NSTEMI subpopulation (1.5% versus 2.9%, unadjusted OR: 0.51, 95% CI: 0.33-0.79, $P < 0.01$). However, in unstable angina subpopulation, the incidence of cardiac death between the pre-procedural beta-blocker group and pre-procedural no-beta-blocker group was not different in both the overall and propensity score-matched populations (Figure 2). In the analysis of the unadjusted OR for cardiac death in other subgroups, the association of a better outcome with pre-procedural beta-blocker use was consistent across various subgroups in the overall and propensity score-matched populations (Figures 3, 4).

Discussion

In the present study, we investigated the effect of pre-procedural beta-blocker use on clinical outcomes in

Figure 3. Comparative unadjusted odds ratio of cardiac death for subgroups in the overall population in acute coronary syndrome. CI indicates confidence interval; LAD, left anterior descending artery; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

patients with ACS who underwent PCI, using data from a nationwide multicenter registry in the Republic of Korea. The use of pre-procedural beta-blockers in ACS was associated with a lower rate of cardiac death and all-cause death in the overall population, and this result was consistent in the propensity score-matched population. The incidence of cardiac death was significantly lower in the pre-procedural beta-blocker group than the pre-procedural no-beta-blocker group, especially in patients with STEMI and NSTEMI. However, in patients with unstable angina, the incidence of cardiac death was not different between the two groups.

Beta-blockers have shown consistent improvement of clinical outcome in patients with cardiovascular disease, including survival in patients with CAD and MI or systolic HF.^{10,13-15} The presumed mechanisms of the beneficial effects of beta-blockers include a decrease in oxygen demand with the negative inotropic and chronotropic effects, decrease in left ventricular (LV) wall stress, decrease in ventricular arrhythmias, and reduced LV remodeling.¹⁶⁻¹⁹ Based on this evidence and hypotheses, current guidelines recommend initiation of an oral beta-blocker within 24 hours after STEMI or NSTEMI-ACS.⁵ However, the evidence of these recommendations is based on studies in the pre-PCI era, and studies focused on the use of pre-procedural beta-blockers are limited and inconsistent in

the current PCI era.^{17,20-22} In a recent randomized study of patients with STEMI undergoing primary PCI, the pre-procedural effect of metoprolol in cardioprotection during an acute myocardial infarction (METOCARD-CNIC) trial showed that intravenous metoprolol administered before primary PCI reduced infarct size and preserved LV function in selected patients (anterior STEMI presenting < 6 hours from symptom onset).²³ In another study, the early beta-blocker administration before primary PCI in patients with ST-elevation myocardial infarction (EARLY-BAMI) trial, the use of beta-blockers was not associated with a reduction in infarct size or 30 day adverse cardiac events. However, the use of beta-blockers reduced the incidence of malignant arrhythmia in the acute phase.²⁴ In registry data, regarding patients with STEMI undergoing primary PCI, beta-blocker therapy was associated with improved survival regardless of risk profile.¹⁰ In the present study, pre-procedural beta-blocker therapy was associated with a low risk of cardiac death in the STEMI and NSTEMI subpopulation during hospitalization. According to previous studies, one plausible explanation of the in-hospital mortality benefit in the confined the STEMI and NSTEMI subpopulation is the antiarrhythmic property of pre-procedural beta-blockers in the acute phase of MI. However, for patients with unstable angina in this study, pre-procedural beta-blocker therapy was not associated with a

Figure 4. Comparative unadjusted odds ratio of cardiac death for subgroups in the propensity score-matched population in acute coronary syndrome. Abbreviations are as in Figure 3.

benefit in cardiac death. The insufficient effect of beta-blockers in this particular subset appears counterintuitive and may be based on multiple reasons. As previously demonstrated by the Conduit Artery Functional End Point (CAFÉ) trial investigators, pharmacologically induced bradycardia with beta-blockers leads to increased central aortic pressure with consequently worse cardiovascular outcomes.²⁵⁾ These agents are also poor at achieving optimal control of essential hypertension, resulting in a downgrade of their role as a first-line agent in current hypertension guidelines.²⁶⁻²⁸⁾ In the subgroup analysis of the present study, the association of pre-procedural beta-blocker use with benefit of cardiac death was consistent across variable subgroups, and there was no significant interaction between pre-procedural beta-blocker and cardiac death. Although beta-blockers have currently been downgraded to secondary agents in patients with hypertension, we emphasize that beta-blockers are still recommended for patient with ACS, and it might be reasonable to consider beta-blocker in primary prevention for high-risk patients, such as patient with CAD concomitant with hypertension or diabetes, for improved mortality when those patients develop ACS. Further prospective evaluation of the preventive role of beta-blockers may be necessary for patients with various cardiovascular diseases.

Study limitations: There were some limitations to the

present study. First, the study design was non-randomized, retrospective, and observational, which may have significantly affected the results owing to confounding factors. Although we performed a propensity score-matching analysis to adjust for potential confounding factors, we were not able to correct for unmeasured variables. In particular, we did not have detailed information of stability or severity in patient with acute MI, such as time of symptom onset to PCI, pre/post PCI Thrombolysis in Myocardial Infarction flow grade or Killip class on admission according to use of pre-procedural beta-blocker, the present data could have selection bias. Second, even if we use another pre-procedural or intra-procedural medication following current standard procedural guidelines, because of the limited design of data collection in this registry, we did not have detailed information on all the medications, such as antiplatelet medications, statins, or glycoprotein IIb/IIIa receptor inhibitors. Third, in the present study, we found that pre-procedural beta-blockers had beneficial effects on cardiac death in the confined acute MI subgroup, but there was no information on the specific cause of cardiac death, such as fatal arrhythmia, HF, or various procedural complications, because of the retrospective analysis with our registry. Hence, it was difficult to determine which clinical effects of beta-blockers may lead to difference in mortality rates. Fourth, due to retrospective and

registry study design, we do not have any detailed data regarding specific types and dose of beta-blockers and prescribed duration after index PCI.

Conclusion

The use of pre-procedural beta-blockers was associated with a lower risk of in-hospital cardiac death in patients with ACS undergoing PCI and the benefit of pre-procedural beta-blocker use was remarkable in patients with acute MI. This result adds to the body of evidence that use of pre-procedural beta-blocker in patients with ACS might be reasonable.

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Disclosure

Conflicts of interest: None declared.

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