Long-term clinical outcome between beta-blocker with ACEI or ARB in patients with NSTEMI who underwent PCI with drug-eluting stents

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Abstract

Background Because limited comparative data are available, we decided to compare 2-year major clinical outcomes between beta-blockers (BB) with angiotensin converting enzyme inhibitors (ACEI) and BB with angiotensin receptor blockers (ARB) therapy in patients with non-ST-segment elevation myocardial infarction (NSTEMI) after percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Methods A total 11,288 NSTEMI patients who underwent PCI with DES were enrolled and they were divided into two groups, the BB with ACEI group (n = 7600) and the BB with ARB group (n = 3688). The major clinical endpoint was the occurrence of major adverse cardiac events (MACE) defined as all-cause death, recurrent myocardial infarction (re-MI), total revascularization [target lesion revascularization (TLR), target vessel revascularization (TVR), non-TVR] rate during the 2-year follow-up period. Results After propensity score-matched (PSM) analysis, two PSM groups (3317 pairs, n = 6634, C-statistic = 0.695) were generated. Although the cumulative incidences of all-cause death, cardiac death, TLR, and non-TVR were similar between the two groups, MACE (HR = 0.832, 95% CI: 0.704–0.982, P = 0.030), total revascularization rate (HR = 0.767, 95% CI: 0.598–0.984, P = 0.037), and TVR rate (HR = 0.646, 95% CI: 0.470–0.888, P = 0.007) were significantly lower in the BB with ACEI group after PSM.

Conclusions In this study, we suggest that the combination of BB with ACEI may be beneficial for reducing the cumulative incidences of MACE, total revascularization rate, and TVR rather than the BB with ARB after PCI with DES in NSTEMI patients.

Keywords: Angiotensin converting enzyme inhibitor; Angiotensin receptor blocker; Beta-blocker; Myocardial infarction

1 Introduction

Even though there are no randomized controlled trials (RCT) concerning the effectiveness of beta-blockers (BB) therapy in patients with normal left ventricular (LV) systolic function until recently,[1] the current guideline recommends BB were to be continued in patients with normal LV systolic function as Class IIb [Level of Evidence (LoE): C] recommendation.[2] In addition, oral BB also are recommended in the first 24 h in patients with non-ST-segment elevation myocardial infarction (NSTEMI) who do not have contraindications as a Class I (LoE: A).[1,2] Although early intravenous (IV) BB can increase the risk of shock in some patients, BB can decrease myocardial ischemia, reinfarction the incidences of complex ventricular dysrhythmias,[3,4] and it also can increase long-term survival. Therefore, BB are strongly recommended before hospital discharge in patients with LV systolic dysfunction patients [left ventricular ejection fraction (LVEF) < 0.40]. Furthermore, BB should be used cautiously with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) in patients with heart failure (HF). ACEI should be started and continued indefinitely in all patients with decreased LVEF (< 0.40) unless contraindicated as Class I (LoE: A).[5,6] ARB are also indicated in patients with HF or myocardial infarction (MI) combining decreased LVEF (< 0.40) and who are intolerant to ACEI (Class I, LoE: A).[7,8] Despite all of these beneficial roles of BB or ACEI/ARB in acute myocardial infarction (AMI) patients, limited data concerning long-term major clinical outcomes of combination therapy between BB with ACEI and BB with ARB therapy are available in patients with NSTEMI. The authors thought to investigate 2-year major clinical outcomes be-
tween BB with ACEI and BB with ARB therapy in patients with NSTEMI after percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

2 Methods

2.1 Study population and design

The patients from the Korea Acute Myocardial Infarction Registry (KAMIR) are evaluated in this study. The details of this registry can be found at the KAMIR website (http://www.kamir.or.kr). KAMIR is a nationwide, prospective, observational on-line registry in South Korea since November 2005. This study was a non-randomized, multi-center, observational, retrospective study. A total 26,431 AMI patients between November 2005 and June 2015 in the KAMIR registry were investigated. Among them, the patients who had these conditions were excluded: (1) PCI was not done or failed (n = 2372, 9.0%); (2) bare-metal stents (BMS) were deployed (n = 937, 3.5%); (3) coronary artery bypass grafts (CABG) were done (n = 92, 0.3%); (4) follow-up loss or not participated (n = 2926, 11.1%); (5) incomplete laboratory results (n = 1408, 5.3%); (6) contraindications for BB or ACEI or ARB (n = 2803, 10.6%); (7) BB only received (n = 2117, 8.0%); (8) ACEI only received (n = 1381, 5.2%); (9) ARB only received (n = 1018, 3.9%); (10) ACEI with ARB combination was received (n = 132, 0.5%); and (11) triple combination (BB, ACEI, and ARB) was received (n = 115, 0.4%). Finally, a total 11,288 NSTEMI patients underwent PCI with DES were enrolled and they were divided into two groups as the BB with ACEI group (n = 7600, 67.3%) and the BB with ARB group (n = 3688, 32.7%) (Figure 1). In this study, all 11288 patients completed a 2-year clinical follow up by face-to-face interviews, phone calls, or chart review. This study protocol was approved by the ethics committee at each participating centers according to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

2.2 PCI procedure and medical treatment

Coronary angiography and PCI was performed by standard technique via femoral or radial approach. Patient’s activated clotting time (ACT) was maintained > 250 seconds during the procedure. All patients were given loading doses of 200 to 300mg aspirin and 300 to 600 mg clopidogrel before PCI. When the patient had typical angina and/or signs of ischemia and ≥ 50% diameter stenosis or ≥ 70% diameter stenosis in a coronary artery by visual estimation, coronary artery revascularization was considered. After discharge, the patients were recommended to stay on the same medications that they received during hospitalization;

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Figure 1. Flow chart. ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta-blockers; BMS: bare-metal stent; CABG: coronary artery bypass graft; KAMIR: Korea Acute Myocardial Infarction Registry; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention.
this study was based on the discharge medications. The patients were maintained on 100 to 200 mg aspirin indefinitely, and the combination of aspirin (100 mg/day) and clopidogrel (75 mg/day) was recommended for at least 12 months to patients who had undergone PCI. Triple antiplatelet therapy (TAPT) (100 mg cilostazol twice a day added on to DAPT) was left to the discretion of the individual operators.

2.3 Study definitions and clinical follow-up

If the patients showed absence of persistent ST-segment elevation with increased cardiac biomarkers and clinical context was appropriate, the patients were considered as NSTEMI.[2,9] The major clinical endpoint was the occurrence of major adverse cardiac events (MACE) defined as all-cause death, recurrent myocardial infarction (re-MI), total coronary revascularization during the 2-year follow-up period. All-cause death classified as cardiac death (CD) or non-CD. Recurrent myocardial infarction (re-MI) was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limits or an increase in troponin-T/troponin-I to greater than the 99th percentile of band fraction above the upper normal limits or an increase in the creatine kinase myocardial band fraction.

2.4 Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (SPSS Inc., Chicago, IL, USA). For continuous variables, differences between the groups were evaluated with the unpaired t-test. Data are expressed as mean ± SD. For discrete variables, differences are expressed as counts and percentages, and were analyzed with the χ² test between the groups. To adjust for potential confounders, propensity score-matched (PSM) analysis was performed by using a logistic regression model. We tested all available variables that could be of potential relevance, such as all baseline clinical, angiographic and procedural factors including age, gender (men), LVEF, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, diabetes mellitus (DM), dyslipidemia, previous MI, previous PCI, previous HF, previous cerebrovascular accident (CVA), current smokers, serum creatinine, serum creatine kinase myocardial band (CK-MB), serum troponin-I, N-terminal pro-brain natriuretic peptide (NT-ProBNP), high-sensitivity (hs) C-reactive protein (CRP), serum creatinine, total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, discharge medications [i.e., aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole (Pletal®; Otsuka Pharmaceutical Co., Tokyo, Japan)], calcium channel blockers (CCB), lipid lowering agents, infarct-related artery (IRA) [i.e., left main coronary artery (LMCA), left anterior descending artery (LAD)], left circumflex artery (LCx), right coronary artery (RCA), treated coronary artery (i.e., LMCA, LAD, LCx, RCA), American College of Cardiology/American Heart Association (ACC/AHA) lesion type [i.e., B1, B2 and C], the extent of coronary artery disease [i.e., 1-vessel disease, 2-vessel disease, ≥ 3-vessel disease, and multi-vessel disease (MVD)], the types of deployed DES [i.e., sirolimus-eluting stent (SES), paclitaxel-eluting stents (PES), zotarolimus-eluting stents (ZES), everolimus-eluting stents (EES), biolimus-eluting stents (BES), others], and the diameter, length, and number of stent. The logistic model by which the propensity scores were estimated showed good predictive value (C-statistic = 0.695). Patients in the BB with ACEI group were then one-to-one matched to those in the BB with ARB group according to propensity scores with the nearest available pair matching method. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 3317 well-matched pairs. Cox-proportional hazard models were used to assess the adjusted hazard ratio (HR) comparing the two groups in PSM population. For all analyses, a two sided P < 0.05 was considered statistically significant.

3 Results

3.1 Baseline clinical and angiographic characteristics

Baseline clinical, laboratory, and procedural characteristics of this study population are summarized in Table 1. The mean age of the BB with ARB group was older than the BB with ACEI group (65.4 ± 11.9 vs. 63.5 ± 12.2, P < 0.001). Before PSM, the numbers of men, current smokers and the levels of CK-MB, total cholesterol, HDL-cholesterol, LDL-cholesterol and the prescription rate of clopidogrel and the numbers of ACC/AHA type B1 and C, ≥ 3-vessel disease, and MVD were higher in the BB with ACEI group than the BB with ARB group. In contrast, the BB with ARB group showed higher numbers of hypertension, DM, and previous history of MI, PCI, HF, and CVA and the level of serum NT-ProBNP, hs-CRP, and serum creatinine, ticagrelor,
Table 1. Baseline clinical, laboratory, angiographic and procedural characteristics.

| Variables | Entire patients | Propensity score-matched patients |
|-----------|----------------|----------------------------------|
|           | BB+ACEI (n = 7600) | BB+ARB (n = 3688) | P-value | BB+ACEI (n = 3317) | BB+ARB (n = 3317) | P-value |
| Age, yrs  | 63.5 ± 12.2 | 65.4 ± 11.9 | < 0.001 | 65.2 ± 11.9 | 65.1 ± 12.0 | 0.612 |
| Men       | 5323 (70.0%) | 2437 (66.1%) | < 0.001 | 2231 (67.3%) | 2226 (67.1%) | 0.896 |
| LVEF      | 53.8% ± 10.9% | 54.7% ± 11.5% | < 0.001 | 54.2% ± 11.0% | 54.6% ± 11.5% | 0.235 |
| BMI, kg/m²| 24.1 ± 3.0 | 24.3 ± 3.3 | 0.017 | 24.3 ± 3.1 | 24.2 ± 3.3 | 0.744 |
| SBP, mmHg | 136.1 ± 26.4 | 135.5 ± 26.5 | 0.223 | 136.1 ± 26.3 | 135.9 ± 26.6 | 0.759 |
| DBP, mmHg | 81.3 ± 15.3 | 81.5 ± 15.4 | 0.550 | 81.5 ± 15.1 | 81.5 ± 15.5 | 0.814 |
| Hypertension | 3843 (50.6%) | 2356 (63.9%) | < 0.001 | 2048 (61.7%) | 2029 (61.2%) | 0.632 |
| Diabetes mellitus | 1016 (13.4%) | 467 (12.7%) | 0.298 | 419 (12.6%) | 423 (12.8%) | 0.883 |
| Dyslipidemia | 300 (0.9%) | 43 (1.2%) | 0.171 | 39 (1.2%) | 38 (1.1%) | 0.909 |
| Previous MI | 340 (4.5%) | 266 (7.2%) | < 0.001 | 220 (6.6%) | 205 (6.2%) | 0.452 |
| Previous PCI | 520 (6.8%) | 441 (12.0%) | < 0.001 | 318 (9.6%) | 332 (10.0%) | 0.563 |
| Previous CABG | 68 (0.9%) | 43 (1.2%) | 0.171 | 39 (1.2%) | 38 (1.1%) | 0.909 |
| Previous HF | 136 (1.8%) | 95 (2.6%) | < 0.001 | 76 (2.3%) | 76 (2.3%) | 1.000 |
| Current smokers | 2965 (39.0%) | 1162 (31.5%) | < 0.001 | 1107 (33.4%) | 1092 (32.9%) | 0.696 |
| CK-MB, mg/dL | 64.6 ± 178.5 | 53.2 ± 87.6 | < 0.001 | 57.0 ± 125.4 | 55.1 ± 90.4 | 0.471 |
| Troponin-I, ng/mL | 19.1 ± 14.7 | 19.1 ± 14.5 | 0.962 | 19.4 ± 14.4 | 19.4 ± 14.8 | 0.964 |
| NT-ProBNP, pg/mL | 2209.0 ± 4063.7 | 3294.2 ± 6062.1 | < 0.001 | 2801.3 ± 5352.4 | 2741.4 ± 4411.1 | 0.619 |
| hs-CRP, mg/dL | 9.8 ± 45.5 | 12.2 ± 52.2 | 0.014 | 12.3 ± 57.3 | 11.2 ± 39.6 | 0.365 |
| Serum creatinine, mg/L | 134.0 ± 14.7 | 129.5 ± 14.5 | < 0.001 | 134.0 ± 14.5 | 129.5 ± 14.5 | 0.840 |
| Total cholesterol, mg/dL | 185.0 ± 46.6 | 177.6 ± 45.8 | < 0.001 | 179.7 ± 45.5 | 179.5 ± 45.6 | 0.840 |
| Triglyceride, mg/L | 134.9 ± 105.5 | 136.3 ± 111.3 | 0.529 | 136.3 ± 114.4 | 135.5 ± 105.1 | 0.750 |
| HDL cholesterol, mg/L | 44.5 ± 18.3 | 42.4 ± 12.2 | < 0.001 | 43.0 ± 11.3 | 42.9 ± 12.2 | 0.686 |
| LDL cholesterol, mg/L | 117.1 ± 39.3 | 111.9 ± 43.5 | < 0.001 | 112.9 ± 39.4 | 112.9 ± 38.5 | 0.998 |

Discharge medications

| Aspirin | 7492 (98.6%) | 3626 (98.3%) | 0.287 | 3260 (98.3%) | 3261 (98.3%) | 0.924 |
| Clopidogrel | 6948 (91.4%) | 3166 (84.4%) | 0.014 | 2910 (87.7%) | 2898 (87.4%) | 0.655 |
| Ticagrel | 300 (3.9%) | 272 (74.8%) | < 0.001 | 209 (63.6%) | 207 (62.9%) | 0.919 |
| Prasugrel | 163 (2.1%) | 165 (4.5%) | < 0.001 | 118 (3.6%) | 130 (3.9%) | 0.437 |
| Cilostazol | 1712 (22.5%) | 781 (21.2%) | 0.105 | 664 (20.0%) | 700 (21.1%) | 0.274 |
| CCB | 463 (6.1%) | 428 (11.6%) | < 0.001 | 341 (10.3%) | 337 (10.2%) | 0.871 |
| Lipid lowering agents | 6367 (83.8%) | 3141 (84.4%) | 0.370 | 2784 (83.9%) | 2794 (84.2%) | 0.737 |

Angiographic & procedural characteristics

Infarct-related artery

| Left main | 161 (2.1%) | 101 (2.7%) | 0.040 | 85 (2.6%) | 84 (2.5%) | 0.938 |
| Left anterior descending | 3044 (40.1%) | 1436 (38.9%) | 0.256 | 1302 (39.3%) | 1295 (39.0%) | 0.821 |
| Left circumflex | 1878 (24.7%) | 924 (25.1%) | 0.692 | 820 (24.7%) | 836 (25.2%) | 0.650 |
| Right coronary artery | 1781 (23.4%) | 928 (25.2%) | 0.044 | 812 (24.5%) | 812 (24.5%) | 1.000 |

Treated vessel

| Left main | 243 (3.2%) | 137 (3.7%) | 0.153 | 122 (3.7%) | 116 (3.5%) | 0.962 |
| Left anterior descending | 3738 (49.2%) | 1811 (49.1%) | 0.937 | 1618 (49.8%) | 1627 (49.1%) | 0.825 |
| Left circumflex | 2561 (33.7%) | 1321 (35.8%) | 0.026 | 1171 (35.3%) | 1183 (35.7%) | 0.758 |
| Right coronary artery | 2277 (30.0%) | 1229 (33.3%) | 0.001 | 1053 (31.7%) | 1075 (32.4%) | 0.563 |

ACC/AHA lesion type

| Type B1 | 1103 (14.5%) | 469 (12.7%) | 0.010 | 455 (13.7%) | 433 (13.1%) | 0.428 |
| Type B2 | 2040 (26.8%) | 1570 (42.6%) | < 0.001 | 1282 (38.6%) | 1277 (38.5%) | 0.900 |
| Type C | 3005 (39.5%) | 1032 (28.0%) | < 0.001 | 979 (29.5%) | 1008 (30.4%) | 0.437 |
Data are presented as means ± SD or n (%). The P-values for continuous data were obtained from the analysis of the unpaired t-test, the P-values for categorical data were obtained from the chi-square test. ACC: American College of Cardiology; ACEI: angiotensin converting enzyme inhibitors; AHA: American Heart Association; ARB: angiotensin receptor blockers; BB: beta-blockers; BES: biolimus-eluting stents; BMI: body mass index; CABG: coronary artery bypass graft; CCB: calcium channel blockers; CK-MB: creatine kinase myocardial band; CVA: cerebrovascular accidents; DBP: diastolic blood pressure; EES: everolimus-eluting stents; HF: heart failure; hs-CRP: high sensitivity-C-reactive protein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NT-ProBNP: N-terminal pro-brain natriuretic peptide; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stents; SBP: systolic blood pressure; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stents.

### Table 1. Cont.

| Variables                   | Entire patients | Propensity score-matched patients |
|-----------------------------|-----------------|-----------------------------------|
|                             | BB+ACEI (n = 7600) | BB+ARB (n = 3688) | P-value | BB+ACEI (n = 3317) | BB+ARB (n = 3317) | P-value |
| Extent of coronary artery disease |                 |                     |         |                   |                     |         |
| 1-vessel                    | 2930 (38.6%)    | 1569 (42.5%)        | < 0.001 | 1353 (40.7%)      | 1381 (41.6%)       | 0.485   |
| 2-vessel                    | 2263 (29.8%)    | 1101 (29.9%)        | 0.933   | 1018 (30.7%)      | 980 (29.5%)        | 0.309   |
| ≥ 3-vessel                  | 1674 (22.0%)    | 716 (19.4%)         | 0.001   | 642 (19.4%)       | 663 (20.0%)        | 0.517   |
| Multi-vessel disease        | 3937 (51.8%)    | 1817 (49.3%)        | 0.019   | 1660 (50.0%)      | 1643 (49.5%)       | 0.303   |
| Drug-eluting stents         |                 |                     |         |                   |                     |         |
| SES                         | 1448 (18.9%)    | 445 (12.1%)         | < 0.001 | 421 (12.7%)       | 415 (12.5%)        | 0.831   |
| PES                         | 1220 (16.1%)    | 348 (9.4%)          | < 0.001 | 332 (10.0%)       | 342 (10.3%)        | 0.659   |
| ZES                         | 1685 (22.2%)    | 752 (20.4%)         | 0.599   | 732 (22.1%)       | 732 (22.1%)        | 1.000   |
| EES                         | 2255 (29.7%)    | 1430 (38.8%)        | < 0.001 | 1360 (41.0%)      | 1354 (40.8%)       | 0.812   |
| BES                         | 612 (8.1%)      | 585 (15.9%)         | < 0.001 | 381 (11.5%)       | 384 (11.6%)        | 0.986   |
| Others                      | 405 (5.3%)      | 129 (3.5%)          | < 0.001 | 110 (3.3%)        | 115 (3.5%)         | 0.761   |
| Stent diameter, mm          | 3.09 ± 0.37     | 3.08 ± 0.37         | 0.069   | 3.08 ± 0.37       | 3.08 ± 0.36        | 0.703   |
| Stent length, mm            | 26.8 ± 9.6      | 26.4 ± 10.4         | 0.045   | 26.5 ± 9.9        | 26.4 ± 10.3        | 0.668   |
| Number of stent             | 1.56 ± 0.80     | 1.56 ± 0.84         | 0.856   | 1.56 ± 0.80       | 1.56 ± 0.83        | 0.996   |

3.2 Clinical outcomes

Table 2 shows the cumulative clinical outcomes by Kaplan-Meier analysis and Cox-proportional hazard ratio (HR) analysis up to 2 years for the two groups. In entire patients, the cumulative incidence of MACE (7.7% vs. 10.4%, Log-rank \( P < 0.001 \), HR = 0.739, 95% CI: 0.647–0.844, \( P < 0.001 \); Figure 2A), all-cause death (2.9% vs. 4.6%, Log-rank \( P < 0.001 \), HR = 0.629, 95% CI: 0.512–0.773, \( P < 0.001 \)), prasugrel, and CCB were more frequently prescribed and LCx and RCA were more frequently treated in the BB with ARB group. ACC/AHA type B2 and 1-vessel disease were higher in the BB with ARB group. The first-generation DES (SES and PES) were more frequently deployed in the BB with ACEI group and the second-generation DES (EES and BES) were more frequently deployed in the BB with ARB group. The number of deployed ZES was similar between the two groups. Although, the number of deployed stents and the diameter of deployed stents were similar between the two groups, the length of deployed stents was higher in the BB with ACEI group than BB with ARB group (26.8 ± 9.6 vs. 26.4 ± 10.4 mm, \( P = 0.045 \)). However, these baseline differences between the two groups were well balanced after PSM.

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Table 2. Clinical outcomes by Kaplan-Meier analysis and Cox-proportional hazard ratio analysis up to two years.

| Outcomes                  | BB+ACEI | BB+ARB | Log-rank | Hazard ratio (95% CI) | P-value |
|---------------------------|---------|--------|----------|-----------------------|---------|
| Entire Patients           |         |        |          |                       |         |
| MACE                      | 565 (7.7%) | 354 (10.4%) | <0.001   | 0.739 (0.647–0.844)   | <0.001  |
| All-cause death           | 213 (2.9%) | 158 (4.6%) | <0.001   | 0.629 (0.512–0.773)   | <0.001  |
| Cardiac death             | 145 (2.0%) | 113 (3.3%) | <0.001   | 0.602 (0.470–0.769)   | <0.001  |
| Re-MI                     | 120 (1.7%) | 78 (2.4%) | 0.020    | 0.714 (0.537–0.949)   | 0.021   |
| Total revascularization   | 266 (3.7%) | 164 (5.0%) | 0.003    | 0.746 (0.614–0.906)   | 0.003   |
| TLR                       | 72 (1.0%) | 36 (1.1%) | 0.724    | 0.930 (0.624–1.388)   | 0.724   |
| TVR                       | 138 (1.9%) | 113 (3.5%) | <0.001   | 0.561 (0.437–0.719)   | <0.001  |
| Non-TVR                   | 135 (1.9%) | 52 (1.6%) | 0.264    | 1.200 (0.871–1.652)   | 0.265   |
| Propensity score matched Patients |         |        |          |                       |         |
| MACE                      | 256 (8.2%) | 301 (9.7%) | 0.030    | 0.832 (0.704–0.982)   | 0.030   |
| All-cause death           | 106 (3.4%) | 129 (4.1%) | 0.106    | 0.809 (0.626–1.047)   | 0.107   |
| Cardiac death             | 72 (2.3%) | 92 (2.9%) | 0.099    | 0.772 (0.567–1.051)   | 0.101   |
| Re-MI                     | 56 (1.8%) | 67 (2.3%) | 0.266    | 0.818 (0.574–1.166)   | 0.267   |
| Total revascularization   | 111 (3.6%) | 141 (4.7%) | 0.036    | 0.767 (0.598–0.984)   | 0.037   |
| TLR                       | 31 (1.0%) | 34 (1.1%) | 0.653    | 0.895 (0.550–1.455)   | 0.654   |
| TVR                       | 63 (2.1%) | 95 (3.2%) | 0.007    | 0.646 (0.470–0.888)   | 0.007   |
| Non-TVR                   | 51 (1.7%) | 47 (1.6%) | 0.758    | 1.064 (0.716–1.582)   | 0.759   |

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta-blockers; CI: confidence interval; MACE: major adverse cardiac events; Non-TVR: non-target vessel revascularization; Re-MI: re-myocardial infarction; TLR: target lesion revascularization; TVR: target vessel revascularization.

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**Figure 3.** Subgroup analysis for MACE in the entire (A) and in the PSM (B) patients. ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta-blockers; CI: confidence interval; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention; PSM: propensity score-matched.

**Table 3.** Multivariate Cox-proportional regression analysis for predictors of TVR in PSM patients.

| Variables                         | Unadjusted |          |          | Adjusted   |          |          |
|-----------------------------------|------------|----------|----------|------------|----------|----------|
|                                   | Hazard ratio | P-value  | Hazard ratio | P-value  | Hazard ratio | P-value  |
|                                   | (95% CI)    |          | (95% CI)  |          | (95% CI)  |          |
| Age, ≥ 65 yrs                     | 1.104 (0.862–1.415) | 0.433    | 1.437 (1.067–2.018) | 0.016    |
| Men                               | 1.052 (0.808–1.371) | 0.705    | 1.005 (0.721–1.400) | 0.979    |
| LVEF, < 50%                       | 0.876 (0.671–1.143) | 0.330    | 0.883 (0.629–1.239) | 0.471    |
| Hypertension                      | 0.862 (0.671–1.108) | 0.246    | 0.978 (0.709–1.348) | 0.890    |
| Diabetes mellitus                 | 0.733 (0.568–0.946) | 0.017    | 0.654 (0.478–0.895) | 0.008    |
| Dyslipidemia                      | 1.007 (0.698–1.452) | 0.972    | 1.070 (0.663–1.728) | 0.782    |
| Previous myocardial infarction    | 0.532 (0.346–0.816) | 0.004    | 0.401 (0.256–0.630) | <0.001   |
| Multi-vessel disease              | 0.577 (0.445–0.747) | <0.001   | 0.598 (0.433–0.826) | 0.002    |
| Current smokers                   | 1.328 (1.016–1.737) | 0.038    | 1.116 (0.797–1.563) | 0.523    |
| ACC/AHA type B2/C                 | 0.471 (0.344–0.664) | <0.001   | 0.459 (0.307–0.687) | <0.001   |
| Stent diameter, < 3.0 mm          | 0.823 (0.627–1.080) | 0.159    | 1.196 (0.852–1.679) | 0.300    |
| Stent length, ≥ 28 mm             | 0.634 (0.495–0.813) | <0.001   | 0.596 (0.435–0.815) | 0.001    |
| IRA-LAD                           | 1.096 (0.849–1.415) | 0.482    | 0.938 (0.683–1.289) | 0.693    |
| IRA-LCx                           | 0.989 (0.743–1.315) | 0.938    | 1.263 (0.860–1.853) | 0.234    |
| IRA-RCA                           | 0.666 (0.511–0.868) | 0.003    | 0.713 (0.509–0.999) | 0.053    |
| Treated vessel-LAD                | 0.780 (0.609–1.001) | 0.051    | 0.730 (0.533–1.000) | 0.049    |
| Treated vessel-LCx                | 0.688 (0.536–0.884) | 0.003    | 0.826 (0.601–1.136) | 0.239    |
| Treated vessel-RCA                | 0.658 (0.511–0.847) | 0.025    | 0.703 (0.511–0.967) | 0.060    |

ACC: American College of Cardiology; AHA: American Heart Association; CI: confidence interval; IRA: infarct-related artery; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LVEF: left ventricular ejection fraction; PSM: propensity score-matched; RCA: right coronary artery; TVR: target vessel revascularization.
presence of ACC/AHA type B2/C lesion (HR = 0.459, 95% CI: 0.307–0.687, P < 0.001), who received long-length DES (stent length ≥ 28 mm, HR = 0.596, 95% CI: 0.435–0.815, P = 0.001) and who received PCI in the LAD, (HR = 0.730, 95% CI: 0.533–1.000, P = 0.049) were significant predictors for TVR in this study.

4 Discussion

Our analysis showed that: (1) the cumulative incidences MACE, total revascularization and TVR were significantly lower in the BB with ACEI group than the BB with ARB group before and after PSM; (2) the cumulative incidences of all-cause death, CD, TLR, and non-TVTR were not significantly different between the BB with ACEI group and the BB with ARB group after PSM; and (3) in addition, old age (≥ 65 years), diabetes, history of previous MI, MVD, ACC/AHA type B2/C lesion, long-length DES, PCI in the LAD were significant predictors for TVR in PSM patients.

A large randomized BB trial demonstrated that there was no benefit of early intravenous metoprolol followed by 4 weeks of oral treatment compared with placebo. Recently, oral BB shows no association between BB and all-cause mortality in post-AMI patients with low prevalence of HF and/or reduced LVEF. In contrast, another registry study showed the risks of cardiogenic shock or death were significantly increased in patients receiving BB within 24 hours of hospital admission in STEMI or NSTEMI patients. Therefore, they suggested early BB treatment should be avoided in patients with AMI. The current European guideline recommend early administration of BB should be avoided in these patients if the ventricular function is unknown, and also, it suggested that BB are recommended in patients with reduced LV systolic function (LVEF ≤ 40%) in the absence of contraindication in the aspect of long-term management. This recommendation is similar with the AHA/ACC guideline. According to the both, the European and the AHA/ACC guidelines, ACEI should be started and continued indefinitely in all patients with decreased LVEF (< 40%) and ARB are alternative treatment modality to ACEI in patients who are intolerable to ACEI. The treatment of ACEI leads to accumulation of bradykinin and this has some important beneficial effects including vasodilation, and stimulation of nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor, and tissue plasminogen activator production. Furthermore, ACEI is associated with enhancement of endothelial function, cardiovascular remodeling, and reducing the progression of atherosclerosis in the AIRE study. Compared to the ACEI, the ARB’s unwanted effect was related with elevation of the circulating angiotensin II level through unopposed stimulation of angiotensin II type 2 (AT2) receptor which can accelerate, and the process of cardiac myocyte hypertrophy apoptosis. In addition, this AT2 receptor activation leads to plaque instability and thrombus formation.

In this study, the main causes of difference in the cumulative incidence of MACE between the two groups were related to an increased incidence of revascularization in the BB with ARB group. According to the previous reports, the increased revascularization rate in this study may be related to the adverse effects of increased serum levels of angiotensin II in the BB with ARB group.

Although BB and renin-angiotensin system (RAS) inhibitors, both are effective agents for improving the prognosis of AMI, there are limited data concerning comparative effectiveness of combination BB with ACEI or ARB in NSTEMI patients who underwent PCI with DES and the basic detailed possible mechanisms of beneficial effects of combination therapy of BB with RAS inhibitors were not well known. Konishi, et al. reported that compared to RAS inhibitors alone, the combined use of BB with RAS inhibitors is more effective for reducing MACE in patients with AMI (36.3% vs. 15.8%, P < 0.0001). However, the use of ACEI/ARB at hospital discharge is independently associated with long-term survival benefit in patients with AMI already treated with BB and antiplatelet agents had demonstrated in other study.

In this study, the BB with ACEI group showed similar 2-year all-cause death, CD, re-MI, TLR, and non-TVTR except for MACE, total revascularization, and TVR. However, the comparative efficacy and safety between ACEI and ARB on cardiovascular disease may be somewhat debatable. In the previous study, losartan showed a significant increase in cardiovascular mortality as compared to captopril, and it showed ARB was as effective as ACEI in reducing the incidence of death or MI or angina or revascularization or stroke in other study. However, other study suggested that the survival rate was better in the ACEI group than the ARB group in AMI patients. Other meta-analysis for the ACEI and the ARB, head-to-head comparison in hypertensive patients demonstrated that the ACEI and the ARB had the same effect on all outcomes. In our study, the mean value of LVEF (before PSM: 53.8% ± 10.9% vs. 54.7% ± 11.5%; after PSM: 54.2% ± 11.0% vs. 54.6% ± 11.5%) was more than 50% and the number of patients showing lower LVEF (< 50%) was about 29% (3278/11288). Therefore, the study population of this study had relatively well-preserved LV systolic function. There is absence of randomized controlled trial concerning the efficacy of BB in contemporary AMI without reduced LVEF or HF.
More recent data showed that BB on LV remodeling was uncertain in 114 AMI patients with preserved LVEF. In one small-scaled study, ARB treatment suppressed stromal cell-derived factor-1α, a pro-inflammatory cytokine, release from the infarcted myocardial region and improved left ventricular function and adverse remodeling in 50 AMI survivors who had preserved LVEF. The authors published the data concerning the comparative impact of RAS inhibitors between ST-segment MI and NSTEMI. 

The study population of this comparative study was some different from this study, because of the study population of that comparative study was confined to the patients who received the RAS inhibitors. In contrast, the enrolled patients were received BB and RAS inhibitors in this study. And the enrolled period was also some different between that study and this study. Taken together, if the impact of BB on long-term outcome in patients who had preserved LVEF, the major determinant for long-term outcome could be the ACEI or the ARB. In this situation, we suggest that the ACEI is better than the BB in reducing MACE in this study.

The result of subgroup analysis for MACE in our study showed the BB with ACEI was the preferred choice rather than the BB with ARB regardless of LVEF (Figure 3B), especially in case of old age (≥65 years), MVD, long-length DES (≥28 mm). The other main finding of this study was the cumulative incidence of TVR between the two groups. Because of the paucity of previous comparative RCT or registry data concerned with combined use of the BB with ACEI or ARB, we could not precisely explain the main causes of the different rate of TVR. Before the DES era, the TLR rates were higher in the ACEI group than the ARB group, and angiotensin II stimulates hypertrophic growth of vascular smooth muscle cells and they were related to restenosis after angioplasty. Deftereos, et al. found out ACEI inhibits in-stent restenosis by stimulating apoptosis. In this study, the BB with ACEI group showed numerically reduced incidences of TLR compared with the BB with ARB group. However, this difference was not statistically significant. In this study, the predictors of TVR in PSM patients were as follow, old age (≥65 years), diabetes, history of previous MI, MVD, the presence of ACC/AHA type B2/C lesions, long-length DES (≥28 mm), the PCI in the LAD during multivariate Cox-proportional multivariate regression analysis (Table 3).

Finally, we think that the combination BB with ACEI may be beneficial for reducing MACE, total revascularization, and TVR rates in NSTEMI patients after PCI with DES than the BB with ARB. Taken together, the results of this study may provide useful information to the interventional cardiologist during or after PCI, these also help select the appropriate combination between BB and ACEI or ARB to reduce the incidences of MACE, total revascularization, and TVR.

In conclusion, even though the cumulative incidence of all-cause death, CD, TLR, and non-TVR were not significantly different between the two groups; the cumulative incidences of MACE, total revascularization, and TVR were significantly higher in the BB with ARB group before and after PSM. Therefore, in this study, we suggest that the combination of BB with ACEI may be beneficial for reducing the cumulative incidences of MACE, total revascularization rate, and TVR rather than the BB with ARB after PCI with DES in NSTEMI patients. However, to confirm these results further large-scaled study is needed.

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