Cardiovascular Drugs and Therapy (2019) 33:55–67
https://doi.org/10.1007/s10557-018-6841-7

ORIGINAL ARTICLE

Comparison Between Beta-Blockers with Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers with Angiotensin II Type I Receptor Blockers in ST-Segment Elevation Myocardial Infarction After Successful Percutaneous Coronary Intervention with Drug-Eluting Stents

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Published online: 10 January 2019

Abstract

Background/Aims Limited comparative data concerning long-term clinical outcomes of combination therapy between beta-blockers (BB) with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) therapy in patients with ST-segment elevation myocardial infarction (STEMI) are available. We thought to compare 2-year major clinical outcomes between BB with ACEI and BB with ARB therapy in patients with STEMI after successful percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Methods 13,873 STEMI patients who underwent successful PCI with DES were enrolled and divided into two groups as the BB with ACEI group ($n = 10{,}393$) and the BB with ARB group ($n = 3480$). The clinical endpoint was the occurrence of major adverse cardiac events (MACE) defined as all-cause death, cardiac death (CD), recurrent myocardial infarction (re-MI), total coronary revascularization (target lesion revascularization [TLR], target vessel revascularization [TVR], non-TVR) during the 2-year follow-up period.

Results After propensity score-matched (PSM) analysis, two PSM groups (3296 pairs, $n = 6592$, C-statistic = 0.675) were generated. Although the incidences of re-MI, TLR, and TVR were similar, the incidences of MACE (8.3% vs. 6.8%, log-rank $p = 0.038$, hazard ratio [HR] 1.210, 95% confidence interval [CI] 1.010–1.451, $p = 0.039$), all-cause death, CD, total revascularization, and non-TVR of the BB with ARB group were significantly higher than the BB with ACEI group after PSM. In addition, diabetes and multivessel disease were significant predictors for non-TVR.

Conclusions The combination BB with ACEI may be beneficial for reducing MACE in STEMI patients after successful PCI with DES than the BB with ARB.

Keywords Myocardial infarction · Beta-blocker · Angiotensin-converting enzyme inhibitor · Angiotensin receptor blocker

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Abbreviations

AMI	Acute myocardial infarction
STEMI	ST-segment elevation myocardial infarction
DES	Drug-eluting stent
EES	Everolimus-eluting stent
MACE	Major adverse cardiac event
PCI	Percutaneous coronary intervention
PES	Paclitaxel-eluting stent
SES	Sirolimus-eluting stent
TLR	Target lesion revascularization
TVR	Target vessel revascularization
Non-TVR	Non-target vessel revascularization
ZES	Zotarolimu-eluting stent

Introduction

The ACCF/AHA (American College of Cardiology Foundation/American Heart Association) [1] recommend that oral beta-blocker (BBs) should be initiated in the first 24 h and continued during and after hospitalization in patients with ST-segment elevation myocardial infarction (STEMI) and who do not have contraindications as a class 1 (level of evidence [LOE]: B) recommendation; an angiotensin-converting enzyme inhibitor(s) (ACEI) should be administrated for 24 h to all patients with STEMI without contraindications as a class 1 (LOE: A); and an angiotensin receptor blocker(s) (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACEI (LOE: B). The beneficial role of BB for secondary prevention has been demonstrated in numerous trials, especially in MI patients complicated by hear failure (HF), left ventricular (LV) systolic dysfunction, or ventricular arrhythmia in the pre-reperfusion era [2]. In the modern "reperfusion" era, the European Society of Cardiology guidelines recommended oral BB for all STEMI patients during hospital stay and thereafter without contraindications as a class IIa (LOE: B) [3]. Oral ACEI reduced major adverse cardiac events (MACE) and death following myocardial infarction (MI) [4, 5]. As mentioned, ARB is indicated for ACE inhibitor (ACEI)–intolerant patients. In the VALIANT (Valsartan in Acute Myocardial Infarction) trial, valsartan was found to be statistically non-inferior to captopril [6]. Yang et al. [7] demonstrated that angiotensin II receptor blocker(s) (ARBs) (ARB) may have comparable beneficial effects compared with ACEI in patients with STEMI with preserved LV systolic function. Taken together, current treatment modality suggested the long-term use of a BB (class I, LOE: A, or class IIa, LOE: B) or an ACEI/ARB (class IIa, LOE: A) in patients who survived from a STEMI.

Despite these beneficial roles of BB or ACEI/ARB in STEMI patients, limited data are available concerning long-term major clinical outcomes of combination therapy between BB with ACEI and BB with ARB therapy in patients with STEMI. The aim of the present study was to investigate 2-year major clinical outcomes between BB with ACEI and BB with ARB therapy in patients with STEMI after successful percutaneous coronary intervention (PCI) with drug-eluting stent(s) (DES).

Material and Methods

Study Population

The study population of this study was obtained from the Korean Acute Myocardial Infarction Registry (KAMIR). KAMIR is a nationwide, prospective, observational online registry in South Korea since November 2005. Details of the registry can be found at the KAMIR Web site (http://www.kamir.or.kr). This study was a non-randomized, multicenter, observational, retrospective study. A total of 53,281 AMI patients were evaluated between January 2005 and June 2015 in KAMIR. Among them, patients who had these conditions were excluded:

1. Non-ST-segment elevation myocardial infarction (non-ST-segment elevation myocardial infarction [NSTEMI], $n = 22{,}248$, 41.8%).
2. Uncertainty of diagnosis ($n = 384$, 0.7%), (3) PCI was not done, failed, or suboptimal results ($n = 1240$, 2.3%).
3. Fibrinolysis was done ($n = 1123$, 2.1%).
4. Bare-metal stent(s) (BMS) was (were) deployed ($n = 1475$, 2.8%).
5. Coronary artery bypass graft(s) (CABGs) (CABG) were done ($n = 71$, 0.1%).
6. Follow-up loss or not participated ($n = 2972$, 5.6%).
7. Incomplete laboratory results ($n = 1670$, 3.1%).
8. Contraindications for BB or ACEI or ARB ($n = 3325$, 6.2%).
9. BB only received ($n = 2377$, 4.5%).
10. ACEI only received ($n = 1702$, 3.2%).
11. ARB only received ($n = 750$, 1.4%).
12. ACEI with ARB combination was received ($n = 43$, 0.1%).
13. Triple combination (BB, ACEI, and ARB) was received ($n = 127$, 0.2%).

Finally, 13,873 STEMI patients who underwent successful PCI with DES were enrolled and they were divided into two groups as the BB with ACEI group ($n = 10{,}393$, 74.9%) and the BB with ARB group ($n = 3480$, 25.1%) (Fig. 1). This study protocol was approved by the ethics committee at each participating center, and informed consents were obtained from all individual participants included in the study prior to enrollment. These processes were conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. In this study, all 13,873 patients completed a 2-year clinical follow up by face-to-face interviews, phone calls, or chart review.

PCI Procedure and Medical Treatment

A diagnostic coronary angiography and PCI were done through either the femoral or the radial artery after an administration of unfractionated heparin (50–100 IU/kg). Patient's activated clotting time (ACT) was maintained > 250 s during the procedure. All patients were given loading doses of 200 to 300 mg aspirin and 300 to 600 mg clopidogrel before PCI. Revascularization was considered clinically indicated when the patient had typical angina and/or signs of ischemia and ≥ 50% diameter restenosis (stenosis) or ≥ 70% diameter

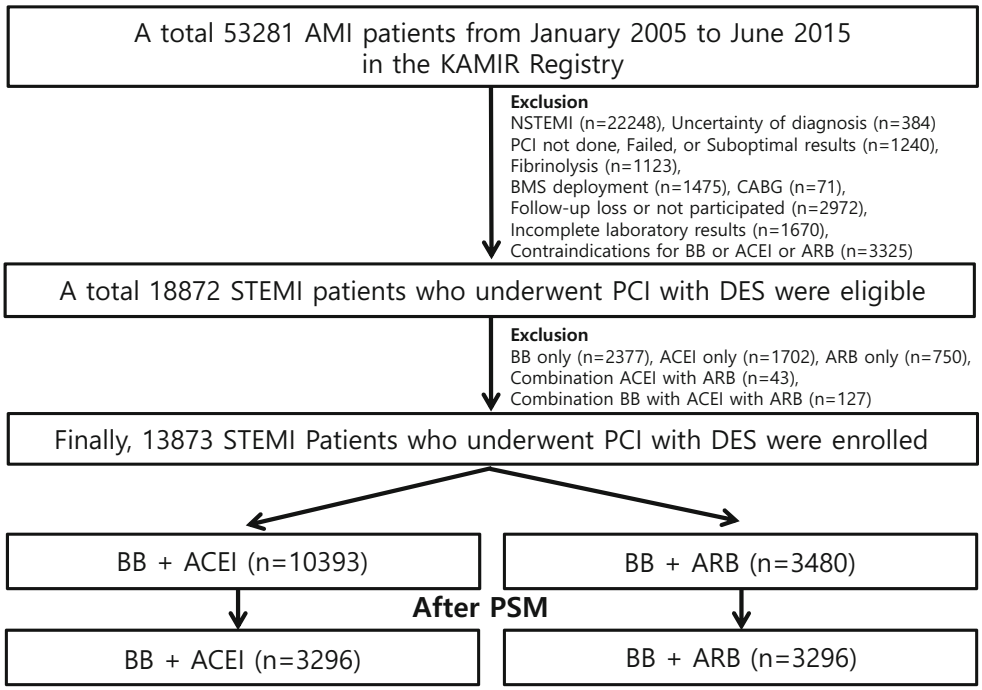

Fig. 1 Flowchart. AMI acute myocardial infarction, KAMIR Korea Acute Myocardial Infarction Registry, PCI percutaneous coronary intervention, BMS bare-metal stent(s), CABG coronary artery bypass graft(s), DES drug-eluting stent(s), BB beta-blocker, ACEI angiotensin-converting enzyme inhibitor(s), ARB angiotensin receptor blocker(s), PSM propensity score-matched analysis

restenosis (stenosis) in a coronary artery by visual estimation. A successful PCI was defined as the achievement of an angiographic residual stenosis was less than 30% and final thrombolysis in myocardial infarction (TIMI) blood flow grade was 3. After discharge, the patients were recommended to stay on the same medications they received during hospitalization, including any kind of antiplatelet agent (aspirin, clopidogrel, ticagrelor and/or prasugrel), BB, ACEI, ARB and lipid lowering agents. Especially, the total duration of dual antiplatelet therapy (DAPT, the combination of aspirin [100 mg/day] and clopidogrel [75 mg/day]) was recommended for more than 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.

Study Definitions and Clinical Outcomes

The major clinical endpoint was the occurrence of MACE defined as all-cause death, cardiac death (CD), recurrent myocardial infarction (re-MI), and total coronary revascularization during the 2-year follow-up period. All-cause death classified as CD or non-CD. 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 the upper normal limit [8] after index PCI. Total coronary revascularization was defined as a revascularization of the target vessel or non-target vessels. Target lesion revascularization (TLR) was defined as a revascularization of the target lesion due to restenosis or reocclusion within the stent or 5 mm in and adjacent of the distal or proximal segment. Target vessel revascularization (TVR) was defined as a revascularization of the target vessel or any segment of the coronary artery containing the target lesion. Non-TVR was defined as a revascularization of any segment of the non-target coronary artery.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 20 (SPSS Inc., Chicago, IL, USA). For continuous variables, differences between groups were evaluated with the unpaired t test. Data are expressed as mean ± standard deviations. For discrete variables, differences are expressed as counts and percentages and were analyzed with χ^2 test between the groups. To adjust for potential confounders, propensity score-marched analysis (PSM) was performed 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. The C-statistics for PSM was 0.675 in this study. 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 3296 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.

Table 1 Baseline clinical, laboratory, angiographic, and procedural characteristics

	Entire patients			Propensity score-matched patients		
Variables	BB+ACEI ($n = 10,393$)	BB+ARB ($n = 3480$)	p value	BB+ACEI ($n = 3296$)	BB+ARB ($n = 3296$)	p value
Age (years)	61.1 ± 12.5	62.4 ± 12.4	< 0.001	62.4 ± 12.4	62.3 ± 12.4	0.674
Men, *n* (%)	8109 (78.0)	2596 (74.6)	< 0.001	2465 (74.8)	2470 (74.9)	0.887
LVEF (%)	51.1 ± 10.4	52.1 ± 10.6	< 0.001	51.9 ± 10.4	52.0 ± 10.6	0.680
BMI (kg/m^2)	24.2 ± 3.1	24.2 ± 3.1	0.293	24.3 ± 3.1	24.2 ± 3.1	0.670
SBP (mmHg)	129.8 ± 27.3	129.4 ± 28.5	0.445	129.6 ± 27.6	129.7 ± 28.3	0.906
DBP (mmHg)	79.7 ± 16.5	79.3 ± 17.0	0.301	79.3 ± 16.6	79.5 ± 16.9	0.586
Primary PCI, *n* (%)	9383 (90.3)	3248 (93.3)	< 0.001	3065 (93.0)	3071 (93.2)	0.771
Hypertension, *n* (%)	4595 (44.2)	1813 (52.1)	< 0.001	1663 (50.5)	1671 (50.7)	0.844
Diabetes mellitus, *n* (%)	2378 (22.9)	958 (27.5)	< 0.001	889 (27.0)	870 (26.4)	0.597
Dyslipidemia, *n* (%)	1092 (10.5)	342 (9.8)	0.254	319 (9.7)	328 (10.0)	0.709
Previous MI, *n* (%)	290 (2.8)	146 (4.2)	< 0.001	129 (3.9)	120 (3.6)	0.561
Previous PCI, *n* (%)	448 (4.3)	273 (7.8)	< 0.001	219 (6.6)	217 (6.6)	0.921
Previous CABG, *n* (%)	34 (0.3)	17 (0.5)	0.173	18 (0.5)	16 (0.5)	0.731
Previous CVA, *n* (%)	527 (5.1)	191 (5.5)	0.336	181 (5.5)	177 (5.4)	0.828
Previous HF, *n* (%)	68 (0.7)	39 (1.1)	0.006	38 (1.2)	30 (0.9)	0.329
Current smokers, *n* (%)	5170 (49.7)	1485 (42.7)	< 0.001	1416 (43.0)	1437 (43.6)	0.602
CK-MB (mg/dL)	169.8 ± 243.5	162.3 ± 228.0	0.096	164.8 ± 233.4	164.1 ± 232.6	0.899
Troponin-I (ng/mL)	59.8 ± 136.4	60.5 ± 80.8	0.791	59.0 ± 94.1	60.6 ± 81.9	0.451
NT-ProBNP (pg/mL)	1229.0 ± 2867.3	1610.3 ± 3756.5	< 0.001	1500.6 ± 3586.4	1531.4 ± 3315.7	0.717
hs-CRP (mg/dL)	9.2 ± 51.3	10.9 ± 50.1	0.099	10.0 ± 49.8	10.9 ± 50.7	0.459
Serum creatinine (mg/L)	1.06 ± 1.39	1.08 ± 1.16	0.497	1.06 ± 0.95	1.08 ± 1.17	0.573
Total cholesterol (mg/dL)	186.5 ± 44.6	182.5 ± 45.0	< 0.001	183.2 ± 44.2	183.2 ± 45.1	0.998
Triglyceride (mg/L)	136.4 ± 111.2	137.1 ± 115.5	0.770	137.7 ± 108.8	136.5 ± 111.8	0.668
HDL cholesterol (mg/L)	44.6 ± 19.4	43.8 ± 17.8	0.017	44.1 ± 23.1	43.9 ± 18.0	0.752
LDL cholesterol (mg/L)	118.2 ± 38.5	116.4 ± 43.1	0.036	116.5 ± 40.4	116.5 ± 38.9	0.954
Discharge medications						
Aspirin, *n* (%)	10,310 (99.2)	3451 (99.2)	0.843	3260 (98.9)	3270 (99.2)	0.202
Clopidogrel, *n* (%)	9536 (91.8)	2987 (85.8)	< 0.001	2868 (87.0)	2879 (87.3)	0.685
Ticagrelor, *n* (%)	463 (4.5)	231 (6.6)	< 0.001	206 (6.3)	206 (6.3)	1.000
Prasugrel, *n* (%)	249 (2.4)	185 (5.3)	< 0.001	151 (4.6)	146 (4.4)	0.767
Cilostazole, *n* (%)	2646 (25.6)	834 (24.0)	0.078	803 (24.4)	797 (24.2)	0.863
CCB, *n* (%)	318 (3.1)	181 (5.2)	< 0.001	163 (4.9)	154 (4.7)	0.604
Lipid-lowering agents	8707 (83.8)	2901 (83.4)	0.566	2739 (83.1)	2749 (83.4)	0.742
Angiographic and procedural characteristics						
Infarct-related artery						
Left main, *n* (%)	102 (1.0)	47 (1.4)	0.067	42 (1.3)	41 (1.2)	0.912
Left anterior descending, *n* (%)	5339 (51.4)	1816 (52.2)	0.406	1728 (52.4)	1717 (52.1)	0.786
Left circumflex, *n* (%)	975 (9.4)	298 (8.6)	0.148	266 (8.1)	286 (8.7)	0.374
Right coronary artery, *n* (%)	3592 (34.6)	1165 (33.5)	0.243	1121 (34.0)	1107 (33.6)	0.715
Treated vessel						
Left main, *n* (%)	154 (1.5)	74 (2.1)	0.010	64 (1.9)	66 (2.0)	0.859
Left anterior descending, *n* (%)	5905 (56.8)	2070 (59.5)	0.006	1963 (59.6)	1951 (59.2)	0.763
Left circumflex, *n* (%)	1590 (15.3)	587 (16.9)	0.028	533 (16.2)	542 (16.4)	0.764
Right coronary artery, *n* (%)	3990 (38.4)	1346 (38.7)	0.763	1267 (38.4)	1272 (38.6)	0.899

Table 1 (continued)

Variables	Entire patients			Propensity score-matched patients		
	BB+ACEI ($n = 10,393$)	BB+ARB ($n = 3480$)	p value	BB+ACEI ($n = 3296$)	BB+ARB ($n = 3296$)	p value
ACC/AHA lesion type						
Type B1, *n* (%)	1449 (13.9)	443 (12.7)	0.071	449 (13.6)	437 (13.3)	0.665
Type B2, *n* (%)	2568 (24.7)	1328 (38.2)	< 0.001	1169 (35.5)	1182 (35.9)	0.738
Type C, *n* (%)	4960 (47.7)	1205 (34.6)	< 0.001	1191 (36.1)	1193 (36.2)	0.959
Extent of coronary artery disease						
1-vessel, *n* (%)	5143 (49.5)	1835 (52.7)	0.001	1724 (52.3)	1728 (52.4)	0.921
2-vessel, *n* (%)	2915 (28.0)	961 (27.6)	0.622	941 (28.5)	911 (27.6)	0.411
≥ 3-vessel, *n* (%)	1894 (18.2)	532 (15.3)	< 0.001	488 (14.8)	512 (15.5)	0.410
Multivessel disease, *n* (%)	4809 (46.3)	1493 (42.9)	0.001	1429 (43.4)	1423 (43.2)	0.881
Drug-eluting stents						
SES, *n* (%)	1775 (17.1)	346 (9.9)	< 0.001	371 (11.3)	344 (10.4)	0.285
PES, *n* (%)	1490 (14.3)	351 (10.1)	< 0.001	364 (11.0)	350 (10.6)	0.579
ZES, *n* (%)	2220 (21.4)	749 (21.5)	0.840	694 (21.1)	721 (21.9)	0.418
EES, *n* (%)	2722 (26.2)	1079 (31.0)	< 0.001	1015 (30.8)	1020 (30.9)	0.894
BES, *n* (%)	641 (6.2)	417 (12.0)	< 0.001	356 (10.8)	341 (10.3)	0.548
Others, *n* (%)	187 (1.8)	107 (3.1)	< 0.001	89 (2.7)	99 (3.0)_	0.459
Stent diameter (mm)	3.20 ± 0.38	3.18 ± 0.39	0.048	3.19 ± 0.39	3.18 ± 0.39	0.645
Stent length (mm)	26.1 ± 8.3	26.1 ± 8.9	0.925	26.2 ± 8.9	26.0 ± 8.7	0.453
Number of stent	1.37 ± 0.67	1.40 ± 0.72	0.018	1.39 ± 0.70	1.39 ± 0.72	0.946

Values are mean ± SD or *n* (%). The *p* value for continuous data from analysis of the unpaired *t* test. The *p* value for categorical data from chi-square test

BB beta-blockers, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *LVEF* left ventricular ejection fraction, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *STEMI* ST-segment elevation myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *PCI* percutaneous coronary intervention, *MI* myocardial infarction, *CABG* coronary artery bypass grafts, *CVA* cerebrovascular accident, *HF* heart failure, *CK-MB* creatine kinase myocardial band, *NT-ProBNP* N-terminal pro-brain natriuretic peptide, *hs-CRP* high sensitivity-C-reactive protein, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CCB* calcium channel blockers, *ACC/AHA* American College of Cardiology/American Heart Association, *SES* sirolimus-eluting stents (stent), *PES* paclitaxel-eluting stent, *ZES* zotarolimus-eluting stent(s), *EES* everolimus-eluting stent(s), *BES* biolimus-eluting stent(s)

Results

Baseline Clinical, Laboratory, Angiographic, and Procedural 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 (62.4 ± 12.4 vs. 61.1 ± 12.5, $p < 0.001$). Before PSM, the numbers of men, dyslipidemia, and current smokers; the levels of total cholesterol, HDL-cholesterol, and LDL-cholesterol; the prescription rate of clopidogrel; and the numbers of ACC/AHA type C, ≥ 3-vessel disease, and multivessel disease (MVD) were higher in the BB with ACEI group than the BB with ARB group. By contrast, the BB with ARB group showed higher numbers of primary PCI, hypertension, DM, and previous history of MI, PCI, and HF and the level of serum NT-ProBNP. In addition, the numbers of ACC/AHA type 2, and one-vessel disease were higher in the BB with ARB group. The fist-generation DESs (siroliumus-eluting stent and paclitaxel-eluting stent) were more frequently deployed in the BB with ACEI group, and the second-generation DESs (everolimus-eluting stent and biolimus-eluting stent) were more frequently deployed in the BB with ARB group. The zotarolimus-eluting stent was similarly deployed between the two groups. Even though the length of deployed stents were similar between the two groups, the number of deployed stents was higher in the BB with ARB group than BB with ACEI group (1.40 ± 0.72 mm vs. 1.37 ± 0.67 mm, $p = 0.018$) and the diameter of deployed stents were larger in the BB with ACEI group than the BB with ARB group (3.20 ± 0.38 mm vs. 3.18 ± 0.39 mm, $p = 0.048$). However, these baseline differences between the two groups were well balanced after PSM.

Clinical Outcomes

Clinical outcomes at 30 days, 1 year, and 2 years are shown in Table 2. During 30 days after index PCI, major clinical outcomes were similar between the two groups. At 1 year, the incidences of all-cause death (2.2% vs. 1.2%, $p < 0.001$) and CD (1.9% vs. 0.9%, $p < 0.001$) were significantly higher in the

Table 2 Clinical outcomes at 30 days, 1 year, and 2 years

	Entire patients				Propensity score-matched patients		
	Total (n = 13,873)	BB+ACEI (n = 10,393)	BB+ARB (n = 3480)	p value	BB+ACEI (n = 3296)	BB+ARB (n = 3296)	p value
30 days							
MACE	202 (1.5)	147 (1.4)	55 (1.6)	0.479	60 (1.8)	49 (1.5)	0.334
All-cause death, n (%)	104 (0.7)	73 (0.7)	31 (0.9)	0.265	25 (0.8)	30 (0.9)	0.503
Cardiac death, n (%)	95 (0.7)	65 (0.6)	30 (0.9)	0.143	22 (0.7)	29 (0.9)	0.399
Re-MI, n (%)	169 (1.2)	120 (1.2)	49 (1.4)	0.238	50 (1.5)	44 (1.3)	0.604
Total revascularization, n (%)	33 (0.2)	23 (0.2)	10 (0.3)	0.489	8 (0.2)	9 (0.3)	0.808
TLR, n (%)	9 (0.1)	6 (0.1)	3 (0.1)	0.567	2 (0.1)	3 (0.1)	0.655
TVR, n (%)	16 (0.1)	10 (0.1)	6 (0.2)	0.252	5 (0.2)	5 (0.2)	1.000
Non-TVR, n (%)	17 (0.1)	13 (0.1)	4 (0.1)	0.882	3 (0.1)	4 (0.1)	0.705
1 year							
MACE, n (%)	731 (5.3)	514 (4.9)	217 (6.2)	0.003	178 (5.4)	204 (6.2)	0.171
All-cause death, n (%)	203 (1.5)	127 (1.2)	76 (2.2)	< 0.001	44 (1.3)	72 (2.2)	0.011
Cardiac death, n (%)	158 (1.1)	93 (0.9)	65 (1.9)	< 0.001	32 (1.0)	62 (1.9)	0.002
Re-MI, n (%)	238 (1.7)	175 (1.7)	63 (1.8)	0.619	74 (2.2)	56 (1.7)	0.112
Total revascularization, n (%)	417 (3.0)	296 (2.8)	121 (3.5)	0.060	91 (2.8)	115 (3.5)	0.103
TLR, n (%)	138 (1.0)	102 (1.0)	36 (1.0)	0.785	33 (1.0)	34 (1.0)	0.902
TVR, n (%)	233 (1.7)	162 (1.6)	71 (2.0)	0.056	55 (1.7)	65 (2.0)	0.407
Non-TVR, n (%)	188 (1.4)	137 (1.3)	51 (1.5)	0.515	36 (1.1)	51 (1.5)	0.107
2 years							
MACE, n (%)	897 (6.5)	625 (6.0)	272 (7.8)	< 0.001	215 (6.5)	257 (7.8)	0.045
All-cause death, n (%)	250 (1.8)	155 (1.5)	95 (2.7)	< 0.001	56 (1.7)	90 (2.7)	0.004
Cardiac death, n (%)	185 (1.3)	109 (1.0)	76 (2.2)	< 0.001	40 (1.2)	72 (2.2)	0.003
Re-MI, n (%)	278 (2.0)	197 (1.9)	81 (2.3)	0.115	84 (2.5)	74 (2.2)	0.422
Total revascularization, n (%)	520 (3.7)	365 (3.5)	155 (4.5)	0.011	111 (3.4)	148 (4.5)	0.022
TLR, n (%)	156 (1.1)	116 (1.1)	40 (1.1)	0.872	39 1.2)	38 (1.2)	0.909
TVR, n (%)	294 (2.1)	204 (2.0)	90 (2.6)	0.027	71 (2.2)	84 (2.5)	0.329
Non-TVR, n (%)	235 (1.7)	167 (1.6)	68 (2.0)	0.170	41 (1.2)	66 (2.0)	0.019

Values are numbers and percentages. The p value for categorical data from chi-square test

BB beta-blockers, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *MACE* major adverse cardiac events, *re-MI* recurrent myocardial infarction, *TLR* target lesion revascularization, *TVR* target vessel revascularization

BB with ARB group compared with the BB with ACEI group. Therefore, the incidence of MACE were also higher in the BB with ARB group (6.2% vs. 4.9%, $p = 0.003$). The cumulative incidence of clinical outcomes by Kaplan–Meier and Cox proportional hazard ratio (HR) analysis at 2-year are summarized in Table 3. The incidence of MACE was significantly higher in the BB with ARB group than the BB with ACEI groups before (8.3% vs. 6.2%, log-rank $p < 0.001$, HR 1.337, 95% confidence interval [CI] 1.160–1.542, $p < 0.001$, Fig. 2a) and after PSM analysis (8.3% vs. 6.8%, log-rank $p = 0.0038$, HR 1.210, 95% CI 1.010–1.451, $p = 0.039$, Fig. 2b). In all patients, the incidences of all-cause death, CD, total coronary revascularization, and TVR were significantly higher in the BB with ARB group compared with the BB with ACEI group. After PSM analysis, the incidences of all-cause death (2.9% vs. 1.8%, log-rank $p = 0.004$, HR 1.622, 95% CI 1.162–2.264, $p = 0.005$, Fig. 3a), CD (2.3% vs. 1.3%, log-rank $p = 0.002$, HR 1.814, 95% CI 1.233–2.670, $p = 0.003$, Fig. 3b), total coronary revascularization (4.9% vs. 3.6%, log-rank $p = 0.014$, HR 1.360, 95% CI 1.063–1.739, $p = 0.014$), and non-TVR (2.2% vs. 1.3%, log-rank $p = 0.012$, HR 1.638, 95% CI 1.109–2.418, $p = 0.013$, Fig. 3d) were significantly higher in the BB with ARB group compared with the BB with ACEI group. Figure 4 shows subgroup analysis for MACE at 2 years. In cases of DM and MVD, the choice of BB with ACEI may be prefer rather than BB with ARB to reduce MACE after PCI for STEMI patients. Table 4 shows multivariate Cox proportional regression analysis for predictors of non-TVR of PSM patients. DM and MVD were also significant predictors for non-TVR in this study.

Table 3 Clinical outcomes by Kaplan–Meier analysis and Cox proportional hazard ratio analysis at 2 years

Outcomes	Cumulative events at 2 years (%)				
	BB+ACEI	BB+ARB	Log-rank	Hazard ratio (95% CI)	*p* value
Entire patients					
MACE	625 (6.2)	272 (8.3)	< 0.001	1.337 (1.160–1.542)	< 0.001
All-cause death	155 (1.5)	95 (2.9)	< 0.001	1.867 (1.446–2.410)	< 0.001
Cardiac death	109 (1.1)	76 (2.3)	< 0.001	2.116 (1.578–2.836)	< 0.001
Re-MI	197 (1.9)	81 (2.5)	0.092	1.248 (0.963–1.616)	0.093
Total revascularization	365 (3.7)	155 (4.8)	0.004	1.313 (1.088–1.584)	0.005
TLR	116 (1.2)	40 (1.2)	0.757	1.058 (0.739–1.516)	0.757
TVR	204 (2.1)	90 (2.8)	0.014	1.363 (1.064–1.747)	0.014
Non-TVR	167 (1.7)	68 (2.1)	0.116	1.253 (0.945–1.662)	0.116
Propensity score-matched patients					
MACE	215 (6.8)	257 (8.3)	0.038	1.210 (1.010–1.451)	0.039
All-cause death	56 (1.8)	90 (2.9)	0.004	1.622 (1.162–2.264)	0.005
Cardiac death	40 (1.3)	72 (2.3)	0.002	1.814 (1.233–2.670)	0.003
Re-MI	84 (2.6)	74 (2.4)	0.443	0.885 (0.647–1.210)	0.444
Total revascularization	111 (3.6)	148 (4.9)	0.014	1.360 (1.063–1.739)	0.014
TLR	39 (1.3)	38 (1.2)	0.953	0.987 (0.631–1.542)	0.953
TVR	71 (2.3)	84 (2.8)	0.254	1.201 (1.876–1.648)	0.255
Non-TVR	41 (1.3)	66 (2.2)	0.012	1.638 (1.109–2.418)	0.013

BB beta-blockers, *ACE* angiotensin-converting enzyme inhibitor(s), *ARB* angiotensin receptor blocker(s), *CI* confidence interval, *MACE* major adverse cardiac event(s), *Re-MI* re-myocardial infarction, *TLR* target lesion revascularization, *TVR* target vessel revascularization, *Non-TVR* non-target vessel revascularization

Discussion

After PSM analysis, our analysis showed that the following: (1) the cumulative incidence of MACE was higher in the BB with ARB group compared with the BB with ACEI group. (2) The cumulative incidences of all-cause death, CD, total coronary revascularization, and non-TVR were higher in the BB with ARB group than BB with ACEI group. (3) In addition,

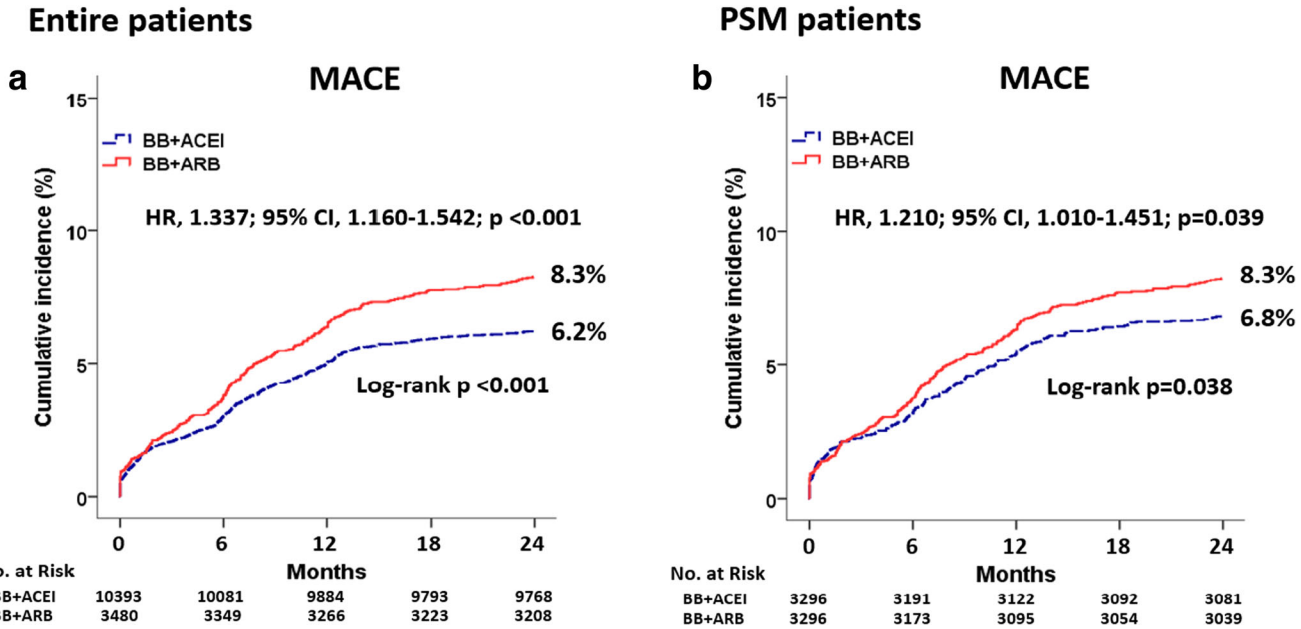

Fig. 2 Kaplan–Meier curved analysis for MACE before (**a**) and after (**b**) PSM. PSM propensity score-matched analysis, MACE major adverse cardiac event, HR hazard ratio, CI confidence interval, BB beta-blocker, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker

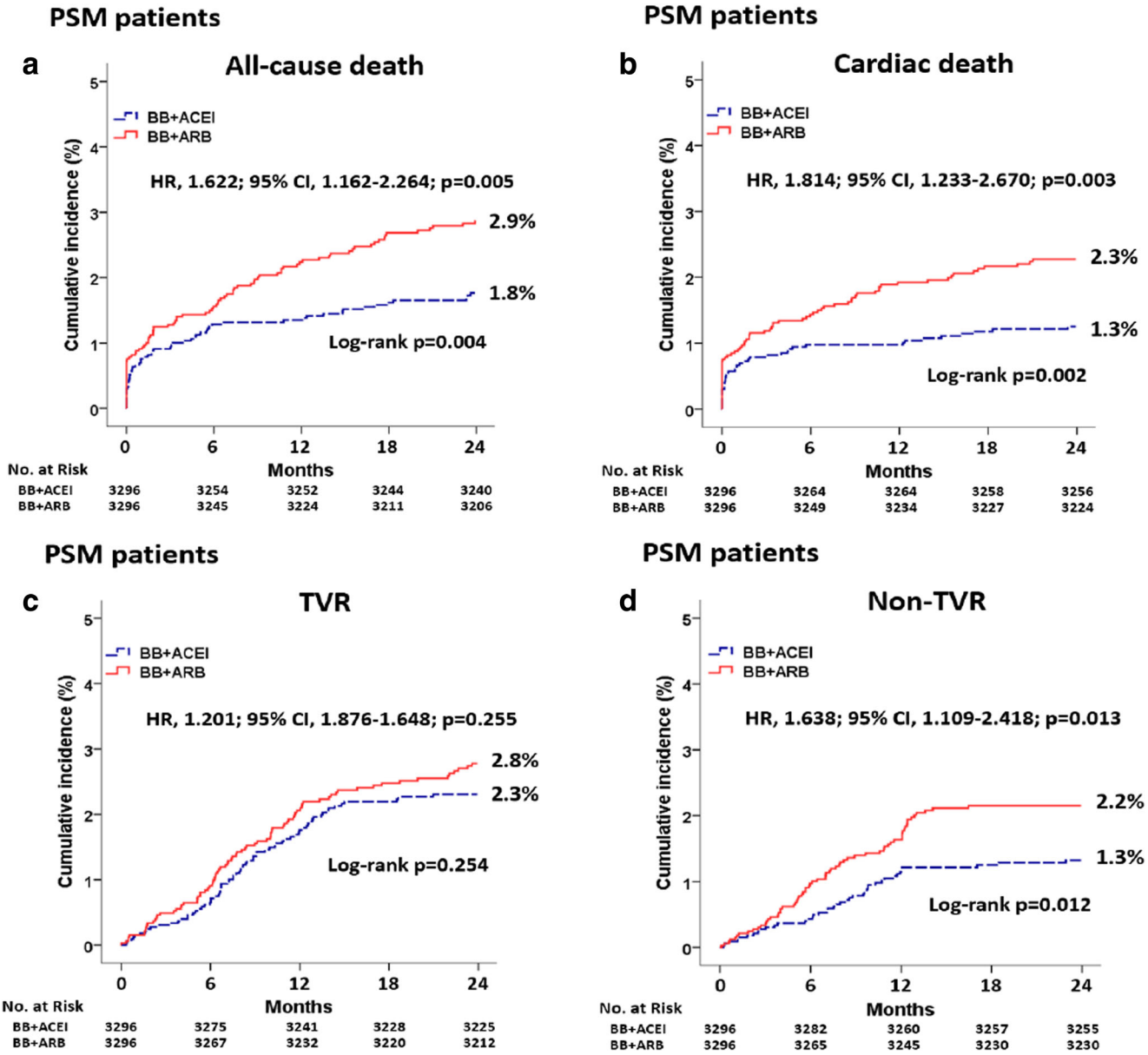

Fig. 3 Kaplan–Meier curved analysis for all-cause death (**a**), cardiac death (**b**), TVR (**c**), and non-TVR (**d**) during 2-year follow-up period. PSM propensity score-matched, HR hazard ratio, CI confidence interval, BB beta-blocker(s), ACEI angiotensin-converting enzyme inhibitor(s), ARB angiotensin receptor blocker(s), TVR target vessel revascularization, Non-TVR non-target vessel revascularization

DM and MVD were significant predictors for non-TVR of PSM patients. (4) However, the cumulative incidences of re-MI, TLR, and TVR were not significantly different between the two groups.

BBs are helpful in reducing arrhythmia, hypertension, and considered a useful therapeutic agent for acute coronary syndrome (ACS) or HF [9, 10]. In the COMMIT trial (Clopidogrel and Metoprolol in Myocardial Infarction Trial), early intravenous (IV) metoprolol increased the risk of cardiogenic shock (5.0% vs. 3.9%; OR, 1.30; 95% CI, 1.19–1.41; $p < 0.00001$) [11]. Therefore, potential harmful effects of early IV BB therapy rather than oral BB in AMI were suggested [12]. By contrast, long-term beneficial effects of BB after STEMI are well established [2]. Andersson et al. [13] found that BB were associated with a lower risk of cardiac events in patients with newly diagnosed heart disease combining a recent MI during 3.7 years of follow-up period. However, the optimal duration of BB treatment is not known. Because ACEI reduce both MI and mortality in patients with symptomatic HF or asymptomatic LV systolic dysfunction, ACEI is recommended in patients with lowered LVEF (≤ 40%) or who have experienced HF [14–16]. ACEI are (is) concerned with the conversion of angiotensin I to angiotensin II formation and catalyze the breakdown of bradykinin to inactive peptides, and this process leads to accumulation of bradykinin. Bradykinin exerts numerous beneficial effects on cardiovascular

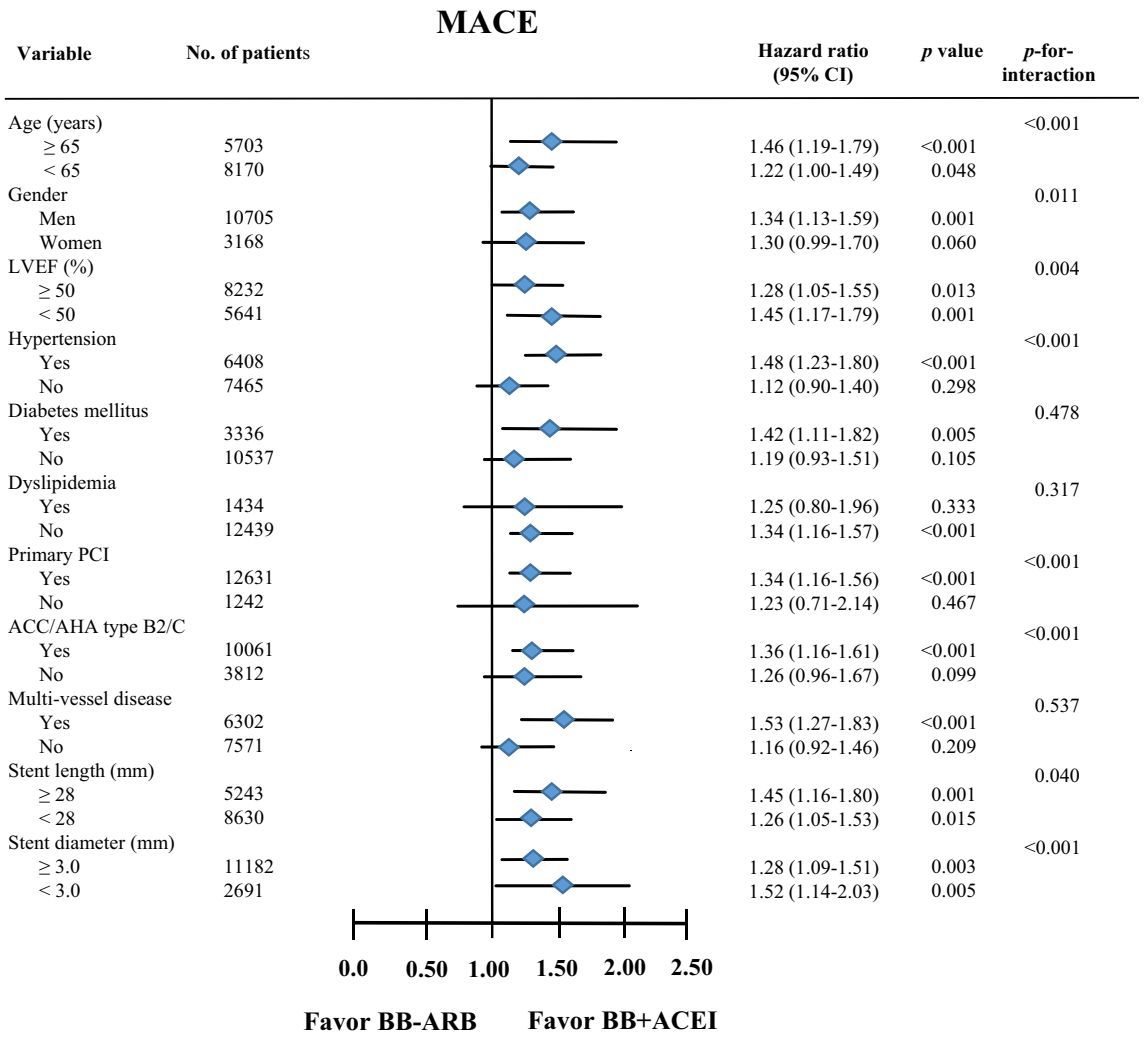

Fig. 4 Subgroup analysis for MACE. MACE major adverse cardiac event, LVEF left ventricular ejection fraction, PCI percutaneous coronary intervention, ACC/AHA American College of Cardiology/American Heart Association

protection including vasodilation and stimulation of nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor, and tissue plasminogen activator production [17]. ACEI can enhance endothelial function, cardiovascular remodeling, and reduce the progression of atherosclerosis in addition to its blood pressure lowering effect, and this leads to beneficial effect on cardiovascular outcomes such as MI or HF [18, 19]. ARBs (ARB) are (is) also involved in selective blockage of the angiotensin II type 1 (AT1) receptor. However, this blockage evokes unwanted elevation of circulating angiotensin II level through unopposed stimulation of angiotensin II type 2 (AT2) receptor, and this results in increased incidences of cardiac myocyte hypertrophy, apoptosis, and inflammation. This phenomenon was suggested in some animal studies [20, 21]. Furthermore, this AT2 receptor activation leads to plaque instability and thrombus formation [20]. Elevated serum level of angiotensin II due to activation of renin-angiotensin system (RAS) plays an important role in the pathogenesis of coronary artery disease (CAD) [22]. Park et al. [23] reported that RAS inhibitor users showed improved 1-year incidences of CD and MI compared with non-users after successful late PCI in patients with STEMI (HR 0.34, 95% CI 0.199–0.588, $p = 0.001$).

Although both BB and RAS inhibitors are effective agents for improving the prognosis of STEMI, there are limited studies comparing their additive effects in STEMI patients who underwent successful PCI with DES, and the basic detailed mechanisms of these beneficial effects of combination therapy of BB with RAS inhibitors were not well known. In hypertensive patients, one possible suggested beneficial effect of BB is renin reduction, which decreases the angiotensin I levels [24]. Konishi et al. [25] reported that combination BB with RAS inhibitors is more effective for patients after AMI than RAS inhibitors alone through suppression of matrix metalloproteinase (MMP)-2 and MMP-9 level. One meta-analysis [26] demonstrated that only ACEI reduced the risk of all-cause death not ARB in 108,212 patients without HF. However, Lee at al. [27] demonstrated isolated BB therapy (HR 0.98, 95% CI 0.80–

Table 4 Multivariate Cox proportional regression analysis for predictors of non-TVR in PSM patients

Variables	Univariate analysis HR (95% CI)	*p* value	Multivariate analysis HR (95% CI)	*p* value
Age, ≥ 65 years	0.866 (0.588–1.275)	0.466	0.683 (0.443–1.052)	0.083
Gender, men	1.009 (0.652–1.560)	0.970	0.928 (0.568–1.517)	0.767
LVEF, < 50%	1.002 (0.772–1.300)	0.990	1.295 (0.866–1.938)	0.208
Hypertension	1.303 (0.889–1.911)	0.175	1.109 (0.740–1.660)	0.616
Diabetes mellitus	2.019 (1.376–2.964)	< 0.001	1.896 (1.273–2.825)	0.002
Dyslipidemia	0.751 (0.365–1.543)	0.436	0.682 (0.330–1.408)	0.300
Previous myocardial infarction	0.497 (0.123–2.014)	0.328	0.424 (0.104–1.729)	0.232
Primary PCI	1.571 (0.640–3.856)	0.324	1.550 (0.618–3.885)	0.350
Multivessel disease	2.477 (1.663–3.689)	< 0.001	2.707 (1.754–4.178)	< 0.001
Current smokers	0.835 (0.566–1.231)	0.363	0.808 (0.523–1.247)	0.336
ACC/AHA type B2/C	0.971 (0.642–1.468)	0.888	0.876 (0.562–1.365)	0.559
Stent diameter, < 3.0 mm	0.922 (0.565–1.505)	0.746	1.002 (0.625–1.607)	0.993
Stent length, ≥ 28 mm	1.151 (0.781–1.696)	0.479	1.058 (0.707–1.583)	0.784
IRA-LAD	0.770 (0.526–1.126)	0.178	1.008 (0.323–3.147)	0.990
IRA-LCx	1.656 (0.944–2.904)	0.079	1.563 (0.445–5.496)	0.486
IRA-RCA	1.137 (0.767–1.685)	0.524	1.524 (0.413–5.624)	0.527
Treated vessel-LAD	0.813 (0.556–1.189)	0.285	0.635 (0.325–1.240)	0.183
Treated vessel-LCx	1.432 (0.903–2.271)	0.127	0.755 (0.385–1.481)	0.414
Treated vessel-RCA	1.090 (0.741–1.604)	0.662	0.501 (0.207–1.211)	0.125

PSM propensity score-matched, *HR* hazard ratio, *CI* confidence interval, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *ACC/AHA* American College of Cardiology/American Heart Association, *IRA* infarct-related artery, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery, *RCA* right coronary artery

1.21, $p = 0.856$) or combination with ACEI/ARB (HR 1.03, 95% CI 0.89–1.19, $p = 0.727$) had similar adjusted risk of all-cause death in unselected AMI patients who survived at least 30 days during a median follow-up of 2.4 years.

In this study, BB with ACEI group showed better 2-year clinical outcomes. These results may be somewhat different compared with previous reports [7, 23, 27, 28]. The main causes of these different results may be originated from the differences in composition of study population and the types of BB or ACE or ARB used. Although the mean value of LVEF was higher in the BB with ARB group, the mean value of the entire patient population was more than 50%. Hence, the enrolled patients in this study had relatively preserved LVEF. Although we could not precisely explain the causes of these results, we can assume that the main causative factor of these results is maybe that ACEI can reduce the level of serum angiotensin and activate the bradykinin system and ARB may cause prolonged elevated level of angiotensin II and upregulation of angiotensin I. Another possible factor may be drug interactions between BB with ACEI and BB with ARB. Because of the limitations of our study, we could not evaluate these drug interactions in this study. However, the results of this study may give some meaningful message to interventional cardiologist during or after PCI to select better combination between BB and ACEI or ARB to reduce the incidence of MACE.

One of the meaningful messages of this study is that the combination of BB with ACEI reduced the incidence of non-TVR compared with the BB with ARB during 2-year follow-up period in STEMI patients after successful PCI. CAD progression involves the entire coronary vasculature and could be responsible for adverse events in areas remote from the culprit vessel [29]. Hong et al. [30] performed three-vessel intravascular ultrasound (IVUS) examination in 235 patients and reported culprit lesion plaque rupture, secondary remote plaque ruptures, and multiple plaque rupture were more common in AMI patients compared with stable angina patients. They also mentioned that the only independent predictor of multiple plaque rupture was AMI (odds ratio 3.752; 95% CI 1.546–9.105; $p = 0.003$). Stone et al. [31] found that MACE rate were equally contributable to recurrence at the site of culprit lesions and to non-culprit lesions in patients with acute coronary syndrome (ACS) after PCI. In our study, the cumulative incidence of non-TVR between the two groups was more prominent 1-year after index PCI (Fig. 2d). During the initial 1 year after PCI, even when considering that the

cumulative incidence of non-TVR was numerically lower in the BB with ACEI group, this difference of incidence rate was not statistically significant. With regard to prognostic factors, in the present study, we found that DM and MVD appeared to be independent predictors of non-TVR (Table 4). Diabetes is a well-known risk factor of CAD and plays an important role in stent restenosis and re-MI after PCI during follow-up period [32], and acts as a negative prognostic factor for non-TVR [33]. MVD was associated with poor short- and long-term prognoses following PCI compared with single vessel CAD especially in patients with STEMI or AMI [29, 34, 35]. Taken together, the results of our study provide a similar message concerning the importance of non-TVR in STEMI patients as reported in previous studies. However, the interpretation of this result requires some caution due to several limitations described below.

In this study, there were several limitations. First, because the present study was non-randomized, there may be some under-reporting and/or missed data. Second, because this registry data did not include the full data concerning the prescription doses, long-term drug compliance, drug-related adverse events, and the kinds of BB, ACEI, and ARB, this study was based on discharge medications and we could not precisely estimate diverse drug interactions among these drugs, so these factors may act as important bias in this study. Third, the selection of specific combination either BB with ACEI or BB with ARB after PCI was left to physicians' preferences; this may be another important selection bias. Fourth, the total mortality rate (1.8%) of this study was relatively low. This result can be affected by selection bias including the low proportion of patients with a history of HF and the many patients who were excluded due to loss of follow-up or refusal to participate. Fifth, even though we adopted PSM analysis for adjusting numerous confounding factors, a large-scale randomized controlled trial may be needed. Sixth, the 2-year follow-up period of this study was relatively short to determine the long-term major clinical outcomes and a longer follow-up period data is needed. Finally, a high c-statistic in the propensity model is neither necessary nor sufficient for control of confounding. Moreover, the use of the c-statistic as a guide in constructing propensity scores may result in less overlap in propensity scores between treated and untreated subjects; this may require to restrict populations for inference. Such restrictions may reduce precision of estimates and change the population to which the estimate applies. Variable selection based on prior knowledge of subject matter, empirical observation, and sensitivity analysis is preferable and avoids many of these problems [36]. In addition, in the patients who were not matched at enrollment, many clinical variables are very likely not accounted for and these may lead to bias not adjusted by propensity score matching.

In conclusion, the combination of BB with ACEI may be more beneficial for reducing MACE rate in STEMI patients after successful PCI with DES than the BB with ARB. In addition, DM and MVD were statistically significant predictors for non-TVR.

Acknowledgements Korea Acute Myocardial infarction Registry (KAMIR) investigators.

Myung Ho Jeong, MD; Youngkeun Ahn, MD; Sung Chul Chae, MD; Jong Hyun Kim, MD; Seung-Ho Hur, MD; Young Jo Kim, MD; In Whan Seong, MD; Donghoon Choi, MD; Jei Keon Chae, MD; Taek Jong Hong, MD; Jae Young Rhew, MD; Doo-Il Kim, MD; In-Ho Chae, MD; Jung Han Yoon, MD; Bon-Kwon Koo, MD; Byung-Ok Kim, MD; Myoung Yong Lee, MD; Kee-Sik Kim, MD; Jin-Yong Hwang, MD; Myeong Chan Cho, MD; Seok Kyu Oh, MD; Nae-Hee Lee, MD; Kyoung Tae Jeong, MD; Seung-Jea Tahk, MD; Jang-Ho Bae, MD; Seung-Woon Rha, MD; Keum-Soo Park, MD; Chong Jin Kim, MD; Kyoo-Rok Han, MD; Tae Hoon Ahn, MD; Moo-Hyun Kim, MD; Ki Bae Seung, MD; Wook Sung Chung, MD; Ju-Young Yang, MD; Chong Yun Rhim, MD; Hyeon-Cheol Gwon, MD; Seong-Wook Park, MD; Young-Youp Koh, MD; Seung Jae Joo, MD; Soo-Joong Kim, MD; Dong Kyu Jin, MD; Jin Man Cho, MD; Sang-Wook Kim, MD; Jeong Kyung Kim, MD; Tae Ik Kim, MD; Deug Young Nah, MD; Si Hoon Park, MD; Sang Hyun Lee, MD; Seung Uk Lee, MD; Hang-Jae Chung, MD; Jang-Hyun Cho, MD; Seung Won Jin, MD; Myeong-Ki Hong, MD; Yangsoo Jang, MD; Jeong Gwan Cho, MD; Hyo-Soo Kim, MD; and Seung Jung Park, MD.

Funding This research was supported by a fund (2016-ER6304-02) by Research of Korea Centers for Disease Control and Prevention.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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