Atherosclerosis 289 (2019) 109–117

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

A comparison between statin with ACE inhibitor or ARB therapy in STEMI patients who underwent successful PCI with drug-eluting stents

Yong Hoon Kim[a,*,1], Ae-Young Her[a,1], Myung Ho Jeong[b], Byeong-Keuk Kim[c], Sung-Jin Hong[c], Seunghwan Kim[d], Chul-Min Ahn[c], Jung-Sun Kim[c], Young-Guk Ko[c], Donghoon Choi[c], Myeong-Ki Hong[c], Yangsoo Jang[c]

[a] Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, South Korea
[b] Department of Cardiology, Cardiovascular Center, Chonnam National University Hospital, Gwangju, South Korea
[c] Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, South Korea
[d] Division of Cardiology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, South Korea

HIGHLIGHTS

- The beneficial roles of statin and ACEI/ARB in STEMI patients are well-known.
- It is not known which is the better therapy between statin with ACEI or statin with ARB combination.
- Statin with ACEI is better than statin with ARB in reducing mortality rate.
- MACE, MI, and revascularization rates are similar between these two groups.

ARTICLE INFO

Keywords:
Myocardial infarction
Statin
Angiotensin converting enzyme inhibitor
Angiotensin receptor blocker

ABSTRACT

Background and aims: Studies of the comparative clinical outcomes between statin with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in ST-segment elevation myocardial infarction (STEMI) patients are limited. We compared 2-year clinical outcomes between statin with ACEI or ARB therapy in STEMI patients after successful percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Methods: A total of 11,706 STEMI patients were enrolled and separated into two groups: the ACEI group (statin + ACEI, n = 8705) and the ARB group (statin + ARB, n = 3001). The primary endpoint was major adverse cardiac events (MACE) defined as all-cause death, recurrent MI (re-MI), and any coronary revascularization. Secondary endpoints were the individual components of MACE and target vessel failure (TVF).

Results: After propensity score-matched (PSM) analysis, two PSM groups (2729 pairs, n = 5458, C-statistic = 0.675) were generated. The cumulative incidences of MACE, re-MI, and any coronary revascularization were similar between the two groups. However, the cumulative incidences of all-cause death (hazard ratio [HR], 1.548; 95% confidence interval [CI], 1.091–2.197; $p = 0.014$) and cardiac death (HR, 1.850; 95% CI, 1.218–2.811; $p = 0.004$) were significantly higher in the ARB group compared with the ACEI group after PSM analysis.

Conclusions: The combination of statin with ACEI may be the preferred treatment strategy to reduce mortality rates in STEMI patients after successful PCI with DES rather than statin with ARB in this study during a 2-year follow-up period.

1. Introduction

In addition to a substantial capability of statin in reducing serum concentration of low-density lipoprotein (LDL), statin has other favorable effects on endothelial function, plaque stability, vascular remodeling, hemostasis, cardiac muscle, and components of the nervous system [1]. The benefits of statins in secondary prevention have been well demonstrated [2]. Therefore, statins are recommended in all

* Corresponding author. Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, 24289, 156 Baengnyeong Road, Chuncheon City, Gangwon Province, South Korea.
E-mail address: yhkim02@kangwon.ac.kr (Y.H. Kim).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.atherosclerosis.2019.08.018
Received 11 April 2019; Received in revised form 29 June 2019; Accepted 29 August 2019
Available online 29 August 2019
0021-9150/

patients with acute myocardial infarction (AMI), irrespective of cholesterol concentration at presentation [3]. The main beneficial effects of the angiotensin converting enzyme inhibitor (ACEI) are related to bradykinin. Bradykinin exerts numerous beneficial effects on cardiovascular protection, including vasodilation, and stimulation of nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor, as well as tissue plasminogen activator production [4]. The current guidelines recommend the use of ACEI within the first 24 h of ST-segment elevation myocardial infarction (STEMI), especially in patients with heart failure (HF), left ventricular systolic dysfunction, diabetes, or anterior infarction, unless contraindicated (Class IA), and an angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACEI (Class IB) [3,5]. Despite these beneficial roles of statin and ACEI/ARB in STEMI patients, limited data are available concerning long-term major clinical outcomes of combination therapy between statin with ACEI and statin with ARB in patients with STEMI. Therefore, we investigated 2-year major clinical outcomes between statin with ACEI and statin with ARB therapy in patients with STEMI after successful percutaneous coronary intervention (PCI) with drug-eluting stent (DES).

2. Materials and methods

2.1. Study design and population

A total of 18,249 STEMI patients, who underwent successful PCI with DES and who had been prescribed statin in the Korea Myocardial Infarction Registry (KAMIR) from November 2005 to June 2015, were evaluated. The KAMIR is a nationwide, prospective, observational online registry in South Korea since November 2005. Details of the registry can be found at the KAMIR website (http://www.kamir.or.kr). This study was a non-randomized, multicenter, observational, retrospective study. We applied the following exclusion criteria: (1) patients who had not been prescribed ACEI or ARB (n = 3191, 17.5%), (2) patients who had been prescribed the combination therapy of these three drugs (n = 153, 0.8%), (3) patients whose laboratory results were incomplete (n = 2321, 12.7%), (4) patients who were lost to follow-up or did not participate (n = 925, 5.1%). Finally, a total of 11,706 STEMI patients who underwent successful PCI with DES and who had been prescribed statin with ACEI or ARB were enrolled and they were separated into two groups: the ACEI group (statin + ACEI, n = 8705, 74.4%) and the ARB group (statin + ARB, n = 3001, 25.6%) (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 11,706 patients completed a 2-year clinical follow up by face-to-face interviews, phone calls, or chart review.

2.2. PCI procedures and medical treatment

A trans-radial or trans-femoral approach was followed for the diagnostic coronary angiography (CAG) and PCI. All patients' activated clotting times (ACTs) were maintained > 250 s during the procedure. All patients were given loading doses of 200–300 mg aspirin and 300–600 mg clopidogrel, when available. Alternatively, 180 mg ticagrelor or 60 mg prasugrel was given before PCI. When the visually estimated coronary artery diameter stenosis was ≥70% or the patient had typical angina and/or signs of ischemia and ≥50% diameter stenosis, coronary revascularization was considered. After discharge, all patients were instructed to stay on the same medications received during hospitalization. In particular, 100–200 mg/day of aspirin was continued indefinitely, and 75 mg/day of clopidogrel was maintained for ≥12 months. Triple antiplatelet therapy (TAPT) (100 mg cilostazol twice a day were added on to dual antiplatelet therapy) was left to the discretion of the individual operators. The kinds and doses of statin were as follows; 10–40 mg of atorvastatin, 5–10 mg of rosuvastatin, 2–4 mg of pitavastatin, 10–40 mg of simvastatin, 50–100 mg lovastatin, and 80 mg fluvastatin per day.

2.3. Study definitions and clinical follow-up

STEMI was defined as the patient who has experienced chest pain with ST-segment elevation in at least 2 contiguous leads of ≥2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women, in leads V2–V3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads, or new onset left bundle branch block on the admission electrocardiogram [2]. A successful PCI was defined as the achievement of an angiographic residual stenosis that was less than 30% and a final Thrombolysis In Myocardial Infarction (TIMI) blood flow grade of three. The primary endpoint was occurrence of MACE, defined as all-cause death, recurrent MI (re-MI), and any coronary revascularization including target lesion revascularization [TLR], target vessel revascularization [TVR], non-TVR during the 2-year follow-up period. The secondary endpoints were the cumulative incidences of the

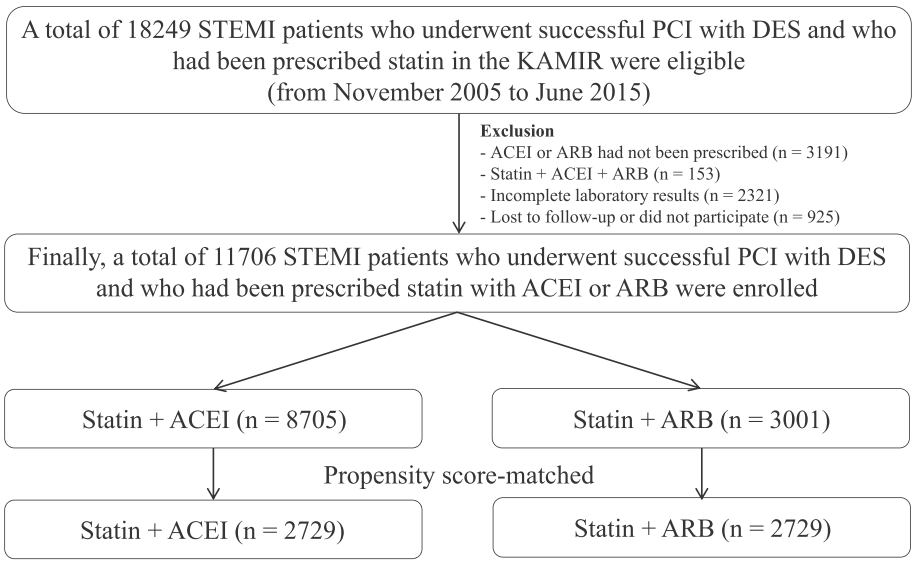

Fig. 1. Flow chart.

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

Variables	Total study population			Propensity score-matched patients		
	Statin + ACEI (n = 8705)	Statin + ARB (n = 3001)	*p* value	Statin + ACEI (n = 2729)	Statin + ARB (n = 2729)	*p* value
Age (years)	61.2 ± 12.5	62.8 ± 12.3	< 0.001	62.2 ± 12.4	62.5 ± 12.4	0.310
Men, n (%)	6835 (78.5)	2224 (74.1)	< 0.001	2073 (76.0)	2042 (74.8)	0.330
LVEF (%)	51.2 ± 10.8	52.2 ± 10.9	< 0.001	52.1 ± 10.7	52.0 ± 10.9	0.931
BMI (kg/m^2)	24.2 ± 3.1	24.3 ± 3.2	0.095	24.3 ± 3.01	24.3 ± 3.1	0.673
SBP (mmHg)	129.3 ± 27.2	129.0 ± 28.1	0.647	128.9 ± 26.9	129.4 ± 28.2	0.507
DBP (mmHg)	79.3 ± 16.6	79.3 ± 16.8	0.927	79.0 ± 16.2	79.5 ± 16.8	0.283
Cardiogenic shock, n (%)	425 (4.9)	151 (5.0)	0.744	128 (4.7)	130 (4.8)	0.898
CPR on admission, n (%)	227 (2.6)	127 (4.2)	< 0.001	82 (3.0)	108 (4.0)	0.055
Primary PCI, n (%)	8046 (92.4)	2853 (95.1)	< 0.001	2581(94.6)	2582 (94.6)	0.952
Door-to-balloon time (min)	60.6 ± 38.4	57.9 ± 34.7	0.109	59.4 ± 37.1	58.1 ± 38.4	0.355
Hypertension, n (%)	3849 (44.2)	1572 (52.4)	< 0.001	1394 (51.1)	1383 (50.7)	0.766
Diabetes mellitus, n (%)	1961 (22.5)	819 (27.3)	< 0.001	689 (25.2)	721 (26.4)	0.322
Dyslipidemia, n (%)	950 (10.9)	315 (10.5)	0.526	279 (10.2)	281 (10.3)	0.847
Metabolic syndrome, n (%)	2192 (25.2)	823 (27.4)	0.015	698 (25.6)	737 (27.0)	0.230
Previous MI, n (%)	186 (2.1)	107 (3.6)	< 0.001	92 (3.4)	83 (3.0)	0.489
Previous PCI, n (%)	281 (3.2)	186 (6.2)	< 0.001	149 (5.5)	150 (5.5)	0.853
Previous CABG, n (%)	26 (0.3)	9 (0.3)	0.992	11 (0.4)	8 (0.3)	0.491
Previous HF, n (%)	39 (0.4)	27(0.9)	0.004	22 (0.8)	21 (0.8)	0.878
Previous CVA, n (%)	428 (4.9)	158 (5.3)	0.451	143 (5.2)	139 (5.1)	0.807
Current smokers, n (%)	4411 (50.7)	1294 (43.1)	< 0.001	1195 (43.8)	1190 (43.6)	0.889
CK-MB (mg/dL)	174.1 ± 216.5	168.1 ± 208.4	0.176	172.4 ± 254.9	169.7 ± 201.8	0.663
Troponin-I (ng/mL)	62.5 ± 143.7	62.2 ± 82.3	0.882	62.4 ± 103.2	62.3 ± 83.7	0.960
NT-ProBNP (pg/mL)	1193.7 ± 2586.8	1479.9 ± 3246.1	< 0.001	1429.9 ± 3479.2	1418.9 ± 3012.7	0.901
hs-CRP (mg/dL)	10.0 ± 46.9	11.7 ± 53.9	0.103	12.1 ± 57.8	11.4 ± 53.3	0.666
Serum creatinine (mg/L)	1.04 ± 1.03	1.08 ± 1.23	0.111	1.08 ± 1.34	1.08 ± 1.22	0.981
Blood glucose (mg/dL)	170.0 ± 72.0	175.8 ± 75.8	< 0.001	173.7 ± 77.5	174.1 ± 74.5	0.822
Total cholesterol (mg/dL)	188.2 ± 43.4	184.3 ± 44.5	< 0.001	184.8 ± 43.1	185.5 ± 44.5	0.583
Triglyceride (mg/L)	136.9 ± 113.6	135.4 ± 108.2	0.825	132.2 ± 97.3	137.0 ± 110.2	0.083
HDL cholesterol (mg/L)	44.7 ± 20.2	43.6 ± 18.4	0.005	43.7 ± 13.4	43.9 ± 18.9	0.667
LDL cholesterol (mg/L)	119.7 ± 38.2	118.0 ± 43.6	0.060	118.2 ± 39.1	118.1 ± 38.6	0.963
Discharge medications						
Aspirin, n (%)	8663 (99.5)	2987 (99.5)	0.913	2716 (99.5)	2716 (99.5)	1.000
Clopidogrel, n (%)	7940 (91.2)	2544 (84.8)	< 0.001	2374 (87.0)	2371 (86.9)	0.904
Ticagrelor, n (%)	443 (5.1)	244 (8.1)	< 0.001	202 (7.4)	209 (7.7)	0.720
Prasugrel, n (%)	236 (2.7)	178 (5.9)	< 0.001	120 (4.4)	123 (4.5)	0.844
Cilostazole, n (%)	2220 (25.5)	738 (24.6)	0.322	635 (23.3)	665 (24.4)	0.340
Beta-blockers, n (%)	7631 (87.7)	2509 (83.6)	< 0.001	2359 (83.2)	2379 (83.9)	0.474
CCBs, n (%)	343 (3.9)	178 (5.9)	< 0.001	163 (6.0)	160 (5.9)	0.863
Angiographic & procedural characteristics						
Infarct-related artery						
Left main, n (%)	82 (0.9)	46 (1.5)	0.007	34 (1.2)	38 (1.4)	0.635
Left anterior descending, n (%)	4632 (53.2)	1598 (53.2)	0.971	1462 (53.6)	1450 (53.1)	0.745
Left circumflex, n (%)	788 (9.1)	267 (8.9)	0.798	254 (9.3)	241 (8.8)	0.540
Right coronary artery, n (%)	3192 (36.7)	1086 (36.2)	0.637	977 (35.8)	997 (36.5)	0.573
Treated vessel						
Left main, n (%)	129 (1.5)	72 (2.4)	0.001	58 (2.1)	59 (2.2)	0.926
Left anterior descending, n (%)	5192 (59.6)	1865 (62.1)	0.016	1660 (60.8)	1677 (61.5)	0.637
Left circumflex, n (%)	1351 (15.5)	541 (18.0)	0.001	481 (17.6)	480 (17.6)	0.972
Right coronary artery, n (%)	3593 (41.3)	1250 (41.7)	0.717	1107 (40.6)	1143 (41.9)	0.322
ACC/AHA lesion type						
Type B1, n (%)	1269 (14.6)	379 (12.6)	0.008	346 (12.7)	367 (13.4)	0.399
Type B2, n (%)	2248 (25.8)	1200 (40.0)	< 0.001	971 (35.6)	986 (36.1)	0.672
Type C, n (%)	4401 (50.6)	1127 (37.6)	< 0.001	1115 (40.9)	1089 (39.9)	0.473
Extent of coronary artery disease						
1-vessel, n (%)	4493 (51.6)	1648 (54.9)	0.002	1472 (53.9)	1482 (54.3)	0.786
2-vessel, n (%)	2605 (29.9)	862 (28.7)	0.214	785 (28.8)	790 (28.9)	0.881
≥3-vessel, n (%)	1607 (18.5)	491 (16.4)	0.010	472 (17.3)	457 (16.7)	0.589
Multi-vessel disease, n (%)	4212 (48.4)	1353 (45.1)	0.002	1257 (46.1)	1247 (45.7)	0.786
Drug-eluting stents						
SES, n (%)	1595 (18.3)	364 (12.1)	< 0.001	373 (13.7)	362 (13.3)	0.663
PES, n (%)	1344 (15.4)	341 (11.4)	< 0.001	365 (13.4)	336 (12.3)	0.241
ZES, n (%)	2084 (23.9)	706 (23.5)	0.646	638 (23.4)	656 (24.0)	0.567
EES, n (%)	2542 (29.2)	1009 (33.6)	< 0.001	900 (33.0)	919 (33.7)	0.585
BES, n (%)	620 (7.1)	401 (13.4)	< 0.001	300 (11.0)	295 (10.8)	0.828
Others, n (%)	176 (2.0)	100 (3.3)	< 0.001	82 (3.0)	79 (2.9)	0.810
IVUS, n (%)	1201 (13.8)	476 (15.9)	0.005	447 (16.4)	441 (16.2)	0.826
OCT, n (%)	18 (0.2)	8 (0.3)	0.548	3 (0.1)	5 (0.2)	0.479
FFR, n (%)	74 (0.9)	7 (0.2)	< 0.001	6 (0.2)	5 (0.2)	0.763
Statins						
Atorvastatin, n (%)	3185 (36.6)	1189 (39.6)	0.003	1043 (38.2)	1061 (38.9)	0.548
Rosuvastatin, n (%)	2010 (23.1)	699 (23.3)	0.821	677 (24.8)	684 (25.1)	0.827
Pitavastatin, n (%)	378 (4.3)	366 (12.2)	< 0.001	243 (8.9)	226 (8.3)	0.412

(*continued on next page*)

Table 1 (*continued*)

Variables	Total study population			Propensity score-matched patients		
	Statin + ACEI (n = 8705)	Statin + ARB (n = 3001)	*p* value	Statin + ACEI (n = 2729)	Statin + ARB (n = 2729)	*p* value
Simvastatin, n (%)	491 (5.6)	115 (3.8)	< 0.001	118 (4.3)	113 (4.1)	0.737
Other[a], n (%)	294 (3.4)	50 (1.7)	< 0.001	49 (1.8)	49 (1.8)	1.000
Stent diameter (mm)	3.19 ± 0.40	3.18 ± 0.41	0.066	3.18 ± 0.40	3.18 ± 0.41	0.931
Stent length (mm)	26.3 ± 8.9	26.4 ± 9.9	0.530	26.1 ± 9.4	26.43 ± 9.8	0.241
Number of stent	1.39 ± 0.70	1.45 ± 0.74	< 0.001	1.44 ± 0.75	1.43 ± 0.72	0.883

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

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction, BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass graft; CVA, cerebrovascular accidents; 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 blocker; ACC/AHA, American College of Cardiology/American Heart Association; BMS, bare-metal stents; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; ZES, zotarolimus-eluting stents; EES, everolimus-eluting stents; BES, biolimus-eluting stents.

[a] Includes lovastatin, fluvastatin, fibrate, and ezetimibe.

individual components of MACE (all-cause death, cardiac death, re-MI, any coronary revascularization, TLR, TVR, and non-TVR) and target vessel failure (TVF). All-cause death was classified as cardiac death (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 after the index PCI [6]. Any coronary revascularization was defined as a revascularization of the target vessel or non-target vessels. TVF was defined as a composite of death related to the target vessel, myocardial infarction, or clinically driven TVR. The definition of TLR, TVR, and non-TVR was previously published [7]. In this study, the definition of hypertension was based on the interviews and/or admission notes and/or history of antihypertensive treatment. In addition, hypertension was defined as values ≥ 140 mmHg systolic blood pressure (SBP) and/or ≥ 90 mmHg diastolic blood pressure (DBP) based on the current guidelines [8,9]. The presence of dyslipidemia was defined as positive history of dyslipidemia regardless of the presence or absence of lipid-lowering agents treatment or lipid-lowering agents treatment regardless of the presence or absence of history of dyslipidemia. Although patients did not have a previous history of dyslipidemia or did not receive lipid-lowering agents, their laboratory results were compatible with the diagnostic criteria of dyslipidemia and they were considered as dyslipidemic patients in this study [10]. Because the definition of dyslipidemia is different according to the guidelines and race, we defined dyslipidemia according to the Asian guidelines [11] such as patients whose 12-h fasting serum LDL-cholesterol concentrations were at least 140 mg/dL, high-density lipoprotein (HDL)-cholesterol concentrations < 40 mg/dL, and triglyceride (TG) concentrations were ≥150 mg/dL.

2.4. Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (IBM; Armonk, NY, 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 groups. To adjust for potential confounders, propensity score-matched (PSM) analysis was performed using a logistic regression model. We tested all available variables that could be of potential relevance: age, men, left ventricular ejection fraction (LVEF), body mass index (BMI), SBP, DBP, incidences of cardiogenic shock, cardiopulmonary resuscitation (CPR) on admission, primary PCI, hypertension, diabetes mellitus (DM), dyslipidemia, previous cardiovascular risk factors (previous MI, previous PCI, previous coronary artery bypass graft, previous cerebrovascular accidents, previous HF), current smoker, values of serum creatine kinase myocardial band, serum troponin-I, N-terminal pro-brain natriuretic peptide (NT-ProBNP), high-sensitivity C-reactive protein, serum creatinine, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, discharge medications (aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, beta-blockers, calcium channel blockers), incidence of IRA, treated vessel, American College of Cardiology/American Heart Association type B1, B2 and C lesion, extent of coronary artery disease, and the kinds of DES, number of stent, length of stent, and diameter of stent. The C-statistics for PSM was 0.680 in this study. Patients in the ACEI group were then one-to-one matched to those in the 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 2729 matched pairs. Cox-proportional hazard models were used to assess the adjusted hazard ratio (HR) comparing the two groups in the PSM population. For all analyses, a two sided $p < 0.05$ was considered statistically significant (Supplementary Data).

3. Results

3.1. Baseline clinical, laboratory, angiographic and procedural characteristics

Baseline clinical, laboratory, and procedural characteristics of this study population are summarized in Table 1. In the total study population, the mean age of the patients enrolled in the ARB was older than the ACEI group (62.8 ± 12.3 year *vs.* 61.2 ± 12.5 year, $p < 0.001$). The number of men among the total study population was higher in the ACEI group than the ARB group (78.5% *vs.* 74.1%, $p < 0.001$). Because the mean value of LVEF in this study population was 51.4 ± 10.8%, this study population was composed of patients who had relatively well-preserved LVEFs. However, the mean value of LVEF was higher in the ARB group than in the ACEI group (52.2 ± 10.9% *vs.* 51.2 ± 10.8%, $p < 0.001$). The incidence of cardiovascular risk factors (hypertension, DM, previous MI, previous PCI, and previous HF) and the serum levels of NT-ProBNP and blood glucose were higher in the ARB than the ACEI group. Despite these negative baseline conditions, the prescription rates of newly developed antiplatelet agents (ticagrelor and prasugrel) as discharge medications, the frequency of second-generation DES (everolimus eluting stents [EES] and biolimus-eluting stents [BES]) deployment, and the use of intravascular ultrasound (IVUS) were higher in the ARB group than in the ACEI group. In contrast, the numbers of current smokers, the number of American College of Cardiology/American Heart Association (ACC) type C lesions, and the frequency of first-generation DES (sirolimus-eluting

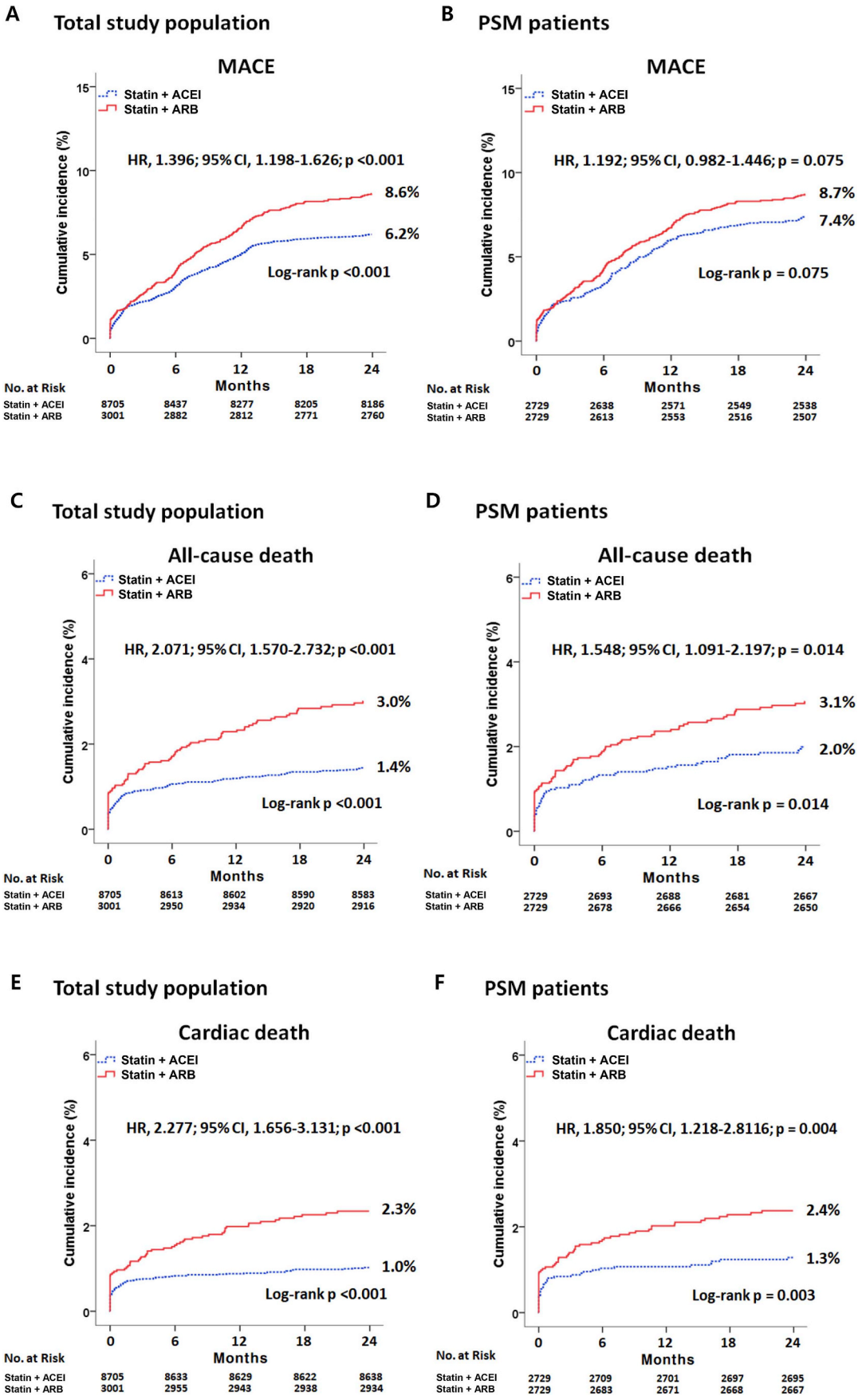

Fig. 2. Kaplan-Meier curved analysis for MACE (A, B), all-cause death (C, D), and cardiac death (E, F).

stents [SES] and paclitaxel-eluting stents [PES]) deployment were higher in the ACEI group than the ARB group. Additionally, the incidence of metabolic syndrome was significantly different between the two groups (25.2% *vs.* 27.4%, $p = 0.015$). After PSM, the incidence of metabolic syndrome was similar between the two groups (25.6% *vs.* 27.0%, $p = 0.230$).

3.2. Clinical outcomes

In the total study population, the cumulative incidences of MACE (8.6% *vs.* 6.2%, Log-rank $p < 0.001$; hazard ratio [HR], 1.396; 95% confidence interval [CI], 1.198–1.626; $p < 0.001$), all-cause death (3.0% *vs.* 1.4%, Log-rank $p < 0.001$; HR, 2.071; 95% CI, 1.570–2.732; $p < 0.001$), and CD (2.3% *vs.* 1.0%, Log-rank $p < 0.001$; HR, 2.277; 95% CI, 1.656–3.131; $p < 0.001$) (Fig. 2), TVR (2.9% *vs.* 2.1%, Log-rank $p = 0.021$; HR, 1.372; 95% CI, 1.048–1.796; $p = 0.021$), and TVF (6.9% *vs.* 4.6%, Log-rank $p < 0.001$; HR, 1.490; 95% CI, 1.252–1.774; $p < 0.001$) were significantly higher in the ARB group than the ACEI group A (Table 2). After PSM analysis, the cumulative incidences of all-cause death (3.1% *vs.* 2.0%, Log-rank $p = 0.014$; HR, 1.548; 95% CI, 1.091–2.197; $p = 0.014$) and CD (2.4% *vs.* 1.3%, Log-rank $p = 0.003$; HR, 1.850; 95% CI, 1.218–2.811; $p = 0.004$) were significantly higher in the ARB compared with the ACEI group (Table 2). However, the cumulative incidences of MACE, re-MI, any revascularization, TLR, TVR, and TVF were similar between the two groups. Fig. 3 shows the subgroup analysis for MACE at 2 years. Regarding the patients who were not in a state of cardiogenic shock, the ACEI group showed a more beneficial effect on MACE compared with the ARB group. In the ACEI group, the use of ZES showed better outcomes for MACE than the ARB group. In addition, older patients (≥65 years) and female gender, patients who had decreased LVEF (< 50%), and were hypertensive and diabetic, patients who were in a state of cardiogenic shock, who were managed with CPR on admission, and had the total length of the deployed stent of more than 28 mm, were common predictors for both all-cause death and CD in this study (Supplementary Data 1).

4. Discussion

The main findings of this study are as follows: first, the cumulative incidences of MACE, re-MI, any revascularization, TLR, TVR, and TVF were similar between the two groups. Second, the cumulative incidence of all-cause death and CD was significantly lower in statin with ACEI group compared with statin with ARB group.

Statins are well-known first-line evidence-based drugs for the management of dyslipidemia and reduction of the risk of cardiovascular events [2,12,13]. In the Swedish registry, it was demonstrated that initiation of statin treatment, at or before hospital discharge, in survivors of AMI is associated with a reduced 1-year mortality rate [14]. Myauchi et al. [15] reported that early statin treatment stabilized the vulnerable plaque and improved the prognosis in patients with acute coronary syndrome. Kim et al. [16] reported statin could reduce the cumulative incidences of MACE, all-cause death, and CD more than in statin non-user after PCI in AMI patients who underwent PCI with new-generation DES regardless of the presence or absence of dyslipidemia. Even though the beneficial roles of ACEI and ARB in STEMI patients are well-known [3.5], the relative superiority on long-term clinical outcomes between ACEI and ARB is still debatable [17,18]. Long-term comparative studies between statin with ACEI or statin with ARB therapy in patients with STEMI after DES implantation are scarce. Terry et al. suggested that treatment with ACEI is beneficial following AMI [19]. Statin and ACEI or ARB mechanism of action overlaps especially in the activation of NO synthase [20]. ACEI catalyze the breakdown of bradykinin to inactive peptides and this process leads to accumulation of bradykinin. Bradykinin exerts numerous beneficial effects on cardiovascular protection including vasodilation and stimulation of NO [4]. Ferrari et al. suggested that the intrinsic effect on bradykinin is increased by ACEI and not by ARB in some meta-anlayses [21]. The cholesterol-independent or “pleiotropic” effects of statins include the upregulation and activation of endothelial NO synthase, especially in the presence of hypoxia [22,23]. One meta-analysis study [24] demonstrated that the percentage of patients on statin therapy showed no significant relationship with the reduction in outcomes due to ACEI. In addition, in the ARB trials, no statistical significance was found in terms of outcome and percentage of patients on statin therapy. Therefore, regarding the differences of the cumulative incidence of all-cause death and CD between the two groups in this study, we can conclude that the main determinant factor for this mortality difference was the attribution of the beneficial effect of ACEI on cardiovascular mortality reduction itself. Hence, we cautiously suggest that ACEI may be the preferred drugs for reducing mortality compared with ARB in patients with STEMI after DES. This suggestion may be supported by the fact that ARB are involved in selective blockage of the angiotensin II type 1

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

Outcomes	Cumulative events at 2 years (%)				
	Statin + ACEI	Statin + ARB	Log-rank	Hazard ratio (95% CI)	*p* value
Total study population					
MACE	519 (6.2)	241 (8.6)	< 0.001	1.396 (1.198–1.626)	< 0.001
All-cause death	122 (1.4)	85 (3.0)	< 0.001	2.071 (1.570–2.732)	< 0.001
Cardiac death	87 (1.0)	67 (2.3)	< 0.001	2.277 (1.656–3.131)	< 0.001
Re-MI	115 (1.4)	50 (1.9)	0.117	1.303 (0.935–1.816)	0.118
Any repeat revascularization	313 (3.8)	134 (4.9)	0.012	1.297 (1.509–1.587)	0.012
TLR	94 (1.1)	40 (1.5)	0.188	1.281 (0.885–1.855)	0.189
TVR	170 (2.1)	77 (2.9)	0.021	1.372 (1.048–1.796)	0.021
Non-TVR	149 (1.8)	60 (2.2)	0.203	1.214 (0.900–1.639)	0.204
TVF	382 (4.6)	189 (6.9)	< 0.001	1.490 (1.252–1.774)	< 0.001
Propensity score-matched patients					
MACE	191 (7.4)	222 (8.7)	0.075	1.192 (0.982–1.446)	0.075
All-cause death	52 (2.0)	79 (3.1)	0.014	1.548 (1.091–2.197)	0.014
Cardiac death	34 (1.3)	62 (2.4)	0.003	1.850 (1.218–2.811)	0.004
Re-MI	50 (1.9)	43 (1.8)	0.535	0.879 (0.585–1.322)	0.536
Any repeat revascularization	102 (4.0)	126 (5.1)	0.064	1.279 (0.985–1.660)	0.065
TLR	30 (1.2)	40 (1.6)	0.185	1.375 (0.857–2.208)	0.187
TVR	59 (2.3)	71 (2.9)	0.213	1.245 (0.882–1.758)	0.213
Non-TVR	47 (1.8)	57 (2.3)	0.258	1.249 (0.849–1.838)	0.259
TVF	150 (5.9)	172 (6.9)	0.148	1.175 (0.944–1.463)	0.149

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; MACE, major adverse cardiac events; Re-MI, recurrent myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; TVF, target vessel failure.

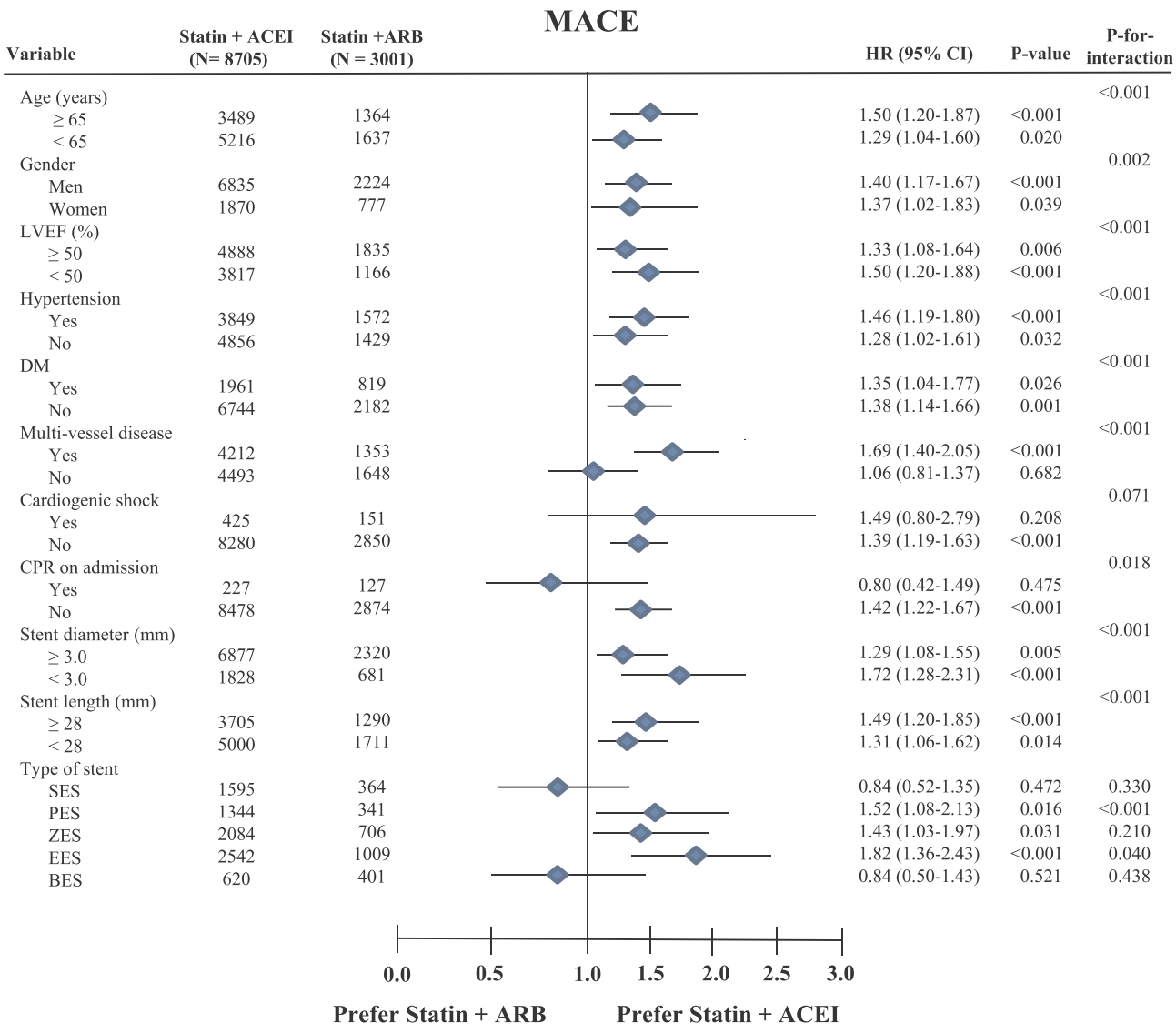

Fig. 3. Subgroup analysis for MACE.

(AT1) receptor, which leads to unwanted elevation of circulating angiotensin II levels through unopposed stimulation of angiotensin II type 2 (AT2) receptor. Because angiotensin II has a positive inotropic activity, sustained activation of angiotensin II increases myocardial oxygen demand, but causes vasoconstriction of the coronary vasculatures simultaneously. Hence, this leads to further exacerbation of oxygen imbalance and myocardial ischemia after MI, and may result in irreversible myocardial damage [25]. In addition, angiotensin II is related to accelerated initiation and progression of atherosclerosis and increased incidences of cardiac inflammatory plaque instability and thrombus formation compared with ACEI [26,27]. Plaque rupture is the most common type of plaque complication, accounting for about 70% of fatal AMI and/or sudden coronary deaths [28]. Most recently, Magnoni et al. [29] demonstrated that the combination of ACEI and statin (but not ARB) was associated with decresed prevalence of plaque neovascularization in sixty-six patients with asymptomatic carotid artery stetnosis of intermediate severity assessed by contrast-enhanced ultrasound.

Furthermore, the toxic effects of angiotensin II on myocytes cause loss of myoctes and trigger abnormal deposition of fibrillar collagen in the heart [30]. The suggestion that elevated plasma AT2 activity is an important independent predictor for MACE in patients with obstructive coronary artery disease is a well-known acceptable concept [31,32]. Dézsi et al. speculated that the beneficial effect of ARB on coronary events is difficult to elucidate and ARB has failed to demonstrate the same or better clinical outcome shown by ACEI [33].

Recently, Kim et al. [34] demonstrated that the combination of beta-blockers with ACEI was more beneficial than beta-blockers with ARB in reducing the cumulative incidences of MACE, all-cause death, CD, total revascularization, and non-TVR in STEMI patients after successful PCI during a 2-year follow-up period. There were some differences in major clinical outcomes between the former (Kim group) study and this study. Compared to the previous study, the cumulative incidences of MACE, total revascularization, and TVR were similar between the ACEI group and the ARB group in this study. Therefore, the different clinical outcomes in this study may be related to the "pleotropic" effects of statin compared with beta-blockers. Mainly, the increased cumulative incidence of MACE and total revascularization in the previous Kim study were related to increased cumulative incidence of non-TVR. Athyros et al. [35] reported that statins exert their beneficial effects on non-TVR after PCI reducing inflammation (early benefit) and LDL-cholesterol level (in the long run). Regarding non-TVR, the clinical benefit of statin therapy in AMI patients may include decreased inflammation, oxidative stress and monocyte adhesion in the ischemic myocardium [36] and this effect can be interpreted as a statin-related cardioprotective effect very early in the course of AMI [37].

Long-term lipid-lowering effects may be obtained by stabilizing the plaque of the culprit lesion and other site plaques leading to a reduction of new fatal coronary events [38].

In view of drug-drug interaction, ticagrelor is metabolized mainly by cytochrome P450 (CYP) isoenzyme, CYP3A4 [39]. CYP3A4 isoenzyme metabolizes atorvastatin, simvastatin, and lovastatin. Thus, in combination with statins, ticagrelor increases the effectiveness of atorvastatin, simvastatin, and lovastatin due to inhibition of CYP3A4. In this study, we tried to minimize the influence of these drug-drug interactions through PSM analysis. Even though we tried to match according to the kinds of statins between the two groups, many different statins had been prescribed and we could not match the dose of each drug.

Currently, there is no clear evidence that either of these combination therapies is better than the other in patients with STEMI. Therefore, this topic is currently widely debated. Even though this is a retrospective cohort study, more than fifty high-volume University or community hospitals with facilities for primary PCI and onsite cardiac surgery in Korea participated in this study. In addition, this registry reflects the results of “real-world” clinical practice. Furthermore, the published data focusing on this topic was very limited, and in this study, the study population was not small. According to the current guidelines, most interventional cardiologists use the combination therapy either statin with ACEI or ARB in patients with STEMI after PCI even if the information of these combination therapies is limited. Therefore, we think that this comparative study may provide meaningful information to interventional cardiologists. Taken together, the present study confirms that statin with ACEI was better than statin with ARB in STEMI patients after DES deployment in reducing mortality rates. However, this result may be more precisely defined by other well-designed, prospective, randomized studies in the future.

In this study, there are several limitations. First, there may be some under-reporting and/or missed data because the study is non-randomized. Second, this registry data did not include complete information concerning the presence or absence of change in any prescription dose of each drugs, change during the follow-up period, and long-term drug compliance (especially, crossover between ACEI and ARB), and drug-related adverse events (because this study was based on discharge medications), which may be an important bias. Third, the selection of treatment strategies of either statin with ACEI or BB with ARB after PCI was left to the physicians’ preferences; this may be another important selection bias. Fourth, although we adopted PSM analysis for adjusting numerous confounding factors, we could not match individual dose and drug. Fifth, 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. Sixth, in this study, we defined hypertension according to the current guidelines, however, the blood pressure of the patients was abnormally elevated or decreased under STEMI. Seventh, there may be a sample selection bias, because the total numbers of dyslipidemic patients in this study (1265/11,706, 10.8%) was relatively lower than a previous landmark trial (41%–42%) [40]. Eighth, the potential effects of ACEI and ARB on the causes of non-CD (i.e., cancer, diabetes) are important. Unfortunately, due to limits of our database, we could not provide full information concerning the causes of non-CD. Finally, the use of anti-arrhythmic agents and digoxin is another important determinant factor for long-term clinical outcomes. However, we could not provide the prescription status of these agents due to lack of information in this registry database.

In conclusion, the combination of statin with ACEI may be the preferred treatment strategy for reducing the mortality rates in STEMI patients after successful PCI with DES over statin with ARB.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

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

Acknowledgements

We would like to acknowledge Dr. Malcom Neill Allison (oallison@msn.com) for editorial assistance.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.08.018.

References

[1] M.S. Kostapanos, H.J. Milionis, M.S. Elisaf, An overview of the extra-lipid effects of rosuvastatin, J. Cardiovasc. Pharmacol. Ther. 13 (2008) 157–174.
[2] C. Baigent, A. Keech, P.M. Kearney, et al., Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet 366 (2005) 1267–1278.
[3] B. Ibanez, S. James, S. Agewall, et al., ESC Scientific Document Group, 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 39 (2018) 119–177.
[4] J.L. Probstfield, K.D. O'Brien, Progression of cardiovascular damage: the role of renin-angiotensin system blockade, Am. J. Cardiol. 105 (2010) 10A–20A.
[5] P.T. O'Gara, F.G. Kushner, D.D. Ascheim, et al., 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology foundation/American heart association task force on practice guidelines, J. Am. Coll. Cardiol. 61 (2013) e78–e140.
[6] P.T. O'Gara, F.G. Kushner, D.D. Ascheim, et al., American College of Cardiology foundation/American heart association task force on practice guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology foundation/American heart association task force on practice guidelines, Circulation 127 (2013) e362–425.
[7] Y.H. Kim, A.Y. Her, M.H. Jeong, et al., Impact of renin-angiotensin system inhibitors on long-term clinical outcomes in patients with acute myocardial infarction treated with successful percutaneous coronary intervention with drug-eluting stents: comparison between STEMI and NSTEMI, Atherosclerosis 280 (2019) 166–173.
[8] G. Mancia, R. Fagard, K. Narkiewicz, et al., 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the european society of hypertension [ESH] and of the european society of Cardiology (ESC), Eur. Heart J. 34 (2013) 2159–2219.
[9] P.A. James, S. Oparil, B.L. Carter, et al., 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8), J. Am. Med. Assoc. 311 (2014) 507–520.
[10] Y.H. Kim, A.Y. Her, M.H. Jeong, et al., Two-year clinical outcomes of zotarolimus- and everolimus-eluting durable-polymer-coated stents versus biolimus-eluting biodegradable-polymer-coated stent in patients with acute myocardial infarction with dyslipidemia after percutaneous coronary intervention: data from the KAMIR, Heart

Vessel. 34 (2019) 237–250.
[11] T. Teramoto, J. Sasaki, S. Ishibashi, S. Birou, H. Daida, S. Dohi, et al., Japan Atherosclerosis Society, Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version, J. Atheroscler. Thromb. 20 (2013) 517–523.
[12] W.B. Hillegass, G.K. Alam, High-dose atorvastatin was superior to standard-dose pravastatin for reducing death or major cardiovascular events in acute coronary syndromes, ACP J. Club 141 (2004) 33.
[13] G.G. Schwartz, A.G. Olsson, M.D. Ezekowitz, et al., Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial, J. Am. Med. Assoc. 285 (2001) 1711–1718.
[14] U. Stenestrand, L. Wallentin, Swedish Register of Cardiac Intensive Care (RIKS-HIA). Early statin treatment following acute myocardial infarction and 1-year survival, J. Am. Med. Assoc. 285 (2001) 430–436.
[15] K. Miyauchi, T. Kimura, T. Morimoto, et al., Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome (Japan-ACS): rationale and design, Circ. J. 70 (2006) 1624–1628.
[16] Y.H. Kim, A.Y. Her, M.H. Jeong, et al., Two-year outcomes of statin therapy in patients with acute myocardial infarction with or without dyslipidemia after percutaneous coronary intervention in the era of new-generation drug-eluting stents within Korean population: data from the Korea Acute Myocardial Infarction Registry, Cathet. Cardiovasc. Interv. (2018), https://doi.org/10.1002/ccd.27985 Nov 25.
[17] K. Dickstein, J. KjekshusOPTIMAAL Steering Committee of the OPTIMAAL Study Group, Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan, Lancet 360 (2002) 752–760.
[18] J. McMurray, S. Solomon, K. Pieper, et al., The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), J. Am. Coll. Cardiol. 47 (2006) 726–733.
[19] T.K. Ma, K.K. Kam, B.P. Yan, et al., Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status, Br. J. Pharmacol. 160 (2010) 1273–1292.
[20] X. Zhang, Y.W. Xie, A. Nasjletti, et al., ACE inhibitors promote nitric oxide accumulation to modulate myocardial oxygen consumption, Circulation 95 (1997) 176–182.
[21] R. Ferrari, G.M. Rosano, Not just numbers, but years of science: putting the ACE inhibitor-ARB meta-analyses into context, Int. J. Cardiol. 166 (2013) 286–288.
[22] U. Laufs, V. La Fata, J. Plutzky, et al., Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors, Circulation 97 (1998) 1129–1135.
[23] U. Laufs, V.L. Fata, J.K. Liao, Inhibition of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase blocks hypoxia-mediated down-regulation of endothelial nitric oxide synthase, J. Biol. Chem. 272 (1997) 31725–31729.
[24] V. Hoang, M. Alam, D. Addison, et al., Efficacy of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in coronary artery disease without heart failure in the modern statin era: a meta-analysis of randomized-controlled trials, Cardiovasc. Drugs Ther. 30 (2016) 189–198.
[25] R. Perondi, A. Saino, R.A. Tio, et al., ACE inhibition attenuates sympathetic coronary vasoconstriction in patients with coronary artery disease, Circulation 85 (1992) 2004–2013.
[26] M.H. Strauss, A.S. Hall, Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox, Circulation 114 (2006) 838–854.
[27] A.R. da Silva, R.A. Fraga-Silva, N. Stergiopulos, et al., Update on the role of angiotensin in the pathophysiology of coronary atherothrombosis, Eur. J. Clin. Investig. 45 (2015) 274–287.
[28] M. Naghavi, P. Libby, E. Falk, et al., From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I, Circulation 108 (2003) 1664–1672.
[29] M. Magnoni, E. Ammirati, F. Moroni, Impact of cardiovascular risk factors and pharmacologic treatments on carotid intraplaque neovascularization detected by contrast-enhanced ultrasound, J. Am. Soc. Echocardiogr. 32 (2019) 113–120.
[30] K.T. Weber, C.G. Brilla, Pathological hypertrophy and cardiac interstitium. Fibrosis and renin–angiotensin–aldosterone system, Circulation 83 (1991) 1849–1865.
[31] J. Ramchand, S.K. Patel, P.M. Srivastava, et al., Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease, PLoS One 13 (2018) e0198144.
[32] J.T. Ortiz-Pérez, M. Riera, X. Bosch, et al., Role of circulating angiotensin converting enzyme 2 in left ventricular remodeling following myocardial infarction: a prospective controlled study, PLoS One 8 (2013) e61695.
[33] C.A. Dézsi, Differences in the clinical effects of angiotensin-converting enzyme inhibitors and Angiotensin receptor blockers: a critical review of the evidence, Am. J. Cardiovasc. Drugs 2014 (2014) 167–173.
[34] Y.H. Kim, A.Y. Her, M.H. Jeong, et al., 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, Cardiovasc. Drugs Ther. 33 (2019) 55–67.
[35] V.G. Athyros, K. Tziomalos, M. Florentin, et al., Statin loading in patients undergoing percutaneous coronary intervention for acute coronary syndromes: a new pleiotropic effect? Curr. Med. Res. Opin. 26 (2010) 839–842.
[36] P.M. Ridker, C.P. Cannon, D. Morrow, et al., Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE IT-TIMI 22) investigators. C-reactive protein levels and outcomes after statin therapy, N. Engl. J. Med. 352 (2005) 20–28.
[37] G.C. Fonarow, R.S. Wright, F.A. Spencer, et al., National Registry of Myocardial Infarction 4 Investigators. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality, Am. J. Cardiol. 96 (2005) 611–616.
[38] V.G. Athyros, A.I. Kakafika, K. Tziomalos, et al., Pleiotropic effects of statins–clinical evidence, Curr. Pharmaceut. Des. 15 (2009) 479–489.
[39] B.S. Wiggins, J.J. Saseen, R.L. Page 2ndet al., American heart association clinical pharmacology committee of the council on clinical Cardiology; council on hypertension; council on quality of care and outcomes research; and council on functional genomics and translational biology. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American heart association, Circulation 134 (2016) e468–e495.
[40] G.W. Stone, A.J. Lansky, S.J. Pocock, et al., HORIZONS-AMI Trial Investigators. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction, N. Engl. J. Med. 360 (2009) 1946–1959.