













ST-elevation versus non-ST-elevation myocardial infarction after combined use of statin with renin–angiotensin system inhibitor: Data from the Korea Acute Myocardial Infarction Registry

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Abstract

Background: Limited data are available comparing the combined effects of statins and renin–angiotensin system inhibitor (RASi) between patients with ST-segment elevation myocardial infarction (STEMI) and those with non-STEMI (NSTEMI). We compared the effects of statins combined with RASi in STEMI and NSTEMI patients after stent implantation during a 2-year follow-up period.

Methods: A total of 21,890 acute myocardial infarction (AMI) patients who underwent successful stent implantation and who received statins with RASi were enrolled. They were separated into the STEMI group ($n = 12,490$) and the NSTEMI group ($n = 9400$). The major clinical endpoint was the occurrence of major adverse cardiac events (MACEs) defined as all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization.

Results: Two propensity score-matched groups (5891 pairs, $n = 11,782$, C -statistic = 0.821) were generated. Even though the cumulative incidences of MACE, Re-MI, total repeat revascularization were similar between the two groups, the cumulative incidences of all-cause death (hazard ratio [HR] 1.407; 95% confidence interval [CI] 1.106–1.790; $p = 0.005$) and cardiac death (HR 1.311; 95% CI 0.983–1.749; $p = 0.046$) were significantly higher in the NSTEMI group.

Conclusions: In this study, statin with RASi combination therapy was more beneficial to the STEMI patients than to the NSTEMI patients in reducing all-cause death and cardiac death. (Cardiol J)

Key words: non-ST-segment elevation myocardial infarction, renin–angiotensin system, statin, ST-segment elevation myocardial infarction

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Introduction

Intensive statin therapy has produced greater reductions in the risks of cardiovascular death, non-fatal myocardial infarction (MI), ischemic stroke, and coronary revascularization than less intensive statin therapy in patients with acute coronary syndrome [1–3]. Moreover, statins are recommended for all acute MI (AMI) patients, regardless of cholesterol concentration at presentation [4–6]. More recently, Kim et al. [7] reported that statin therapy was more effective in reducing the cumulative risks of major adverse cardiac events (MACEs), all-cause death, and target vessel revascularization (TVR) in a ST-segment elevation myocardial infarction (STEMI) group than in a non-STEMI (NSTEMI) group in Korean patients with AMI after successful drug-eluting stent (DES) implantation. Current guidelines recommended that angiotensin-converting enzyme inhibitors (ACEIs) should be prescribed within the first 24 hours for all AMI patients with left ventricular (LV) systolic dysfunction, unless contraindicated. Furthermore, the patients who do not tolerate ACEIs should be given angiotensin receptor blockers (ARBs) [5, 6, 8, 9]. A previous report [10] showed that the mortality reduction capability of renin-angiotensin system inhibitors (RASIs) was more prominent in STEMI patients compared with NSTEMI patients. Hence, combination therapy with statins and RASIs may be an important treatment modality in patients with hypertension, hypercholesterolemia, diabetes, metabolic syndrome, or obesity, to reduce or prevent cardiovascular disease [11, 12]. Nevertheless, the data concerning long-term clinical outcomes of statin with RASI combination therapy in patients with STEMI and NSTEMI after stent implantation are limited. Therefore, we compared the effects of statins combined with RASI in STEMI and NSTEMI patients after successful percutaneous coronary intervention (PCI) over a 2-year follow-up period.

Methods

Study design and population

The study population of this non-randomized, multicenter, observational, retrospective cohort study was obtained from the Korea AMI Registry (KAMIR). KAMIR was designed to capture real-world treatment practices and the short- and long-term outcomes of AMI patients; to evaluate the current epidemiology and analyze the prognostic factors of AMI; and to improve the long-term prognosis of the individual patients.

Eligible patients were ≥ 18 years of age at the time of hospital admission [13]. A total of 45,863 AMI patients who underwent successful stent implantation from November 2005 to June 2015 were evaluated. This study protocol was approved by the ethics committee at each participating center, and informed consent was obtained from all individual participants prior to enrollment. These processes were conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. The exclusion criteria were as follows: (1) incomplete laboratory results ($n = 10,506$, 22.9%); (2) lost to follow-up ($n = 2562$, 5.6%); (3) statin and RASI had not been prescribed ($n = 2392$, 5.2%); (4) statin only prescribed ($n = 4409$, 9.6%); and (5) RASI only prescribed ($n = 4185$, 9.1%). Finally, a total of 21,890 AMI patients who underwent successful stent implantation and who had been prescribed both statin and RASI were enrolled. Among these, 12,490 (57.1%) were STEMI patients and the remaining 9400 (42.9%) were NSTEMI patients (Fig. 1). Any information concerning adverse events in these 21,890 participants with AMI including the time intervals and the types of events after the index PCI, which occurred during the follow-up period, was monitored at the outpatient clinic, by phone calls, or by reviewing the patients' charts at each participating center, and all participants completed a 2-year clinical follow-up [14].

PCI procedure and medical treatment

Diagnostic coronary angiography and PCI were performed after an administration of unfractionated heparin (50–100 IU/kg) according to standard technique [15]. Before PCI, all patients received loading doses of acetylsalicylic acid (ASA) 200–300 mg and clopidogrel 300–600 mg; alternatively, ticagrelor 180 mg or prasugrel 60 mg was administered. Moreover, dual antiplatelet therapy (DAPT), such as a daily dose of 100 mg ASA and 75 mg clopidogrel or ticagrelor 90 mg twice daily or prasugrel 5–10 mg/day, was recommended for more than 12 months after PCI. The choice of triple antiplatelet therapy (cilostazol 100 mg twice daily added to DAPT) was determined by the discretion of the individual operators [10]. The statins and their doses were as follows: 10–40 mg of atorvastatin, 5–10 mg of rosuvastatin, 2–4 mg of pitavastatin, 10–40 mg of simvastatin, 10–40 mg of pravastatin, 80 mg fluvastatin, and 50–100 mg lovastatin per day. The RASI used and their doses were as follows: 12.5–75 mg of captopril, 2.5–10 mg of ramipril, 2–8 mg of perindopril, 1.25–5 mg of cilazapril, 5–10 mg of imidapril, 7.5–15 mg of moexipril, 2.5–10 mg of

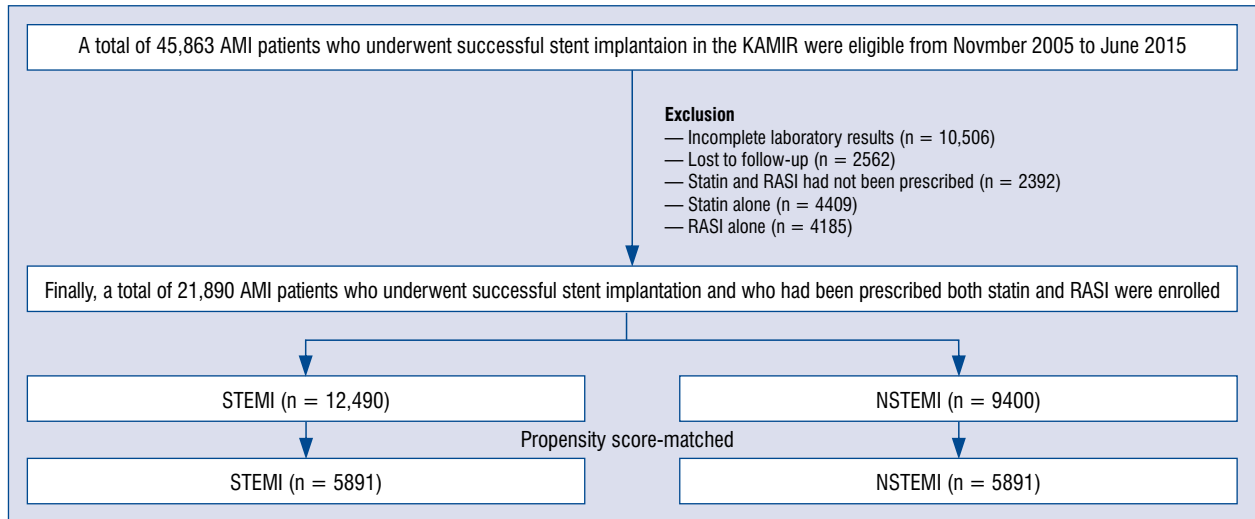


Figure 1. Flow chart; AMI — acute myocardial infarction; KAMIR — Korea Acute Myocardial Infarction Registry; NSTEMI — non-ST-segment elevation myocardial infarction; RASI — renin-angiotensin system inhibitor; STEMI — ST-segment elevation myocardial infarction.

enalapril, 5–10 mg of lisinopril, 10 mg of fosinopril, 3.75–7.5 mg of zofenopril, 25–100 mg of losartan, 150–300 mg of irbesartan, 40–160 mg of valsartan, 40–80 mg of telmisartan, 10–20 mg of olmesartan, 4–32 mg of candesartan, 600 mg of eprosartan, and 30–120 mg of fimasartan per day.

Study definitions and clinical outcomes

According to the current guidelines [6, 8], STEMI was defined as follows: ongoing chest pain and admission electrocardiogram showing 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 [8]. NSTEMI was defined as follows: absence of persistent ST-segment elevation with increased cardiac biomarkers and appropriate clinical context [6]. In the present study, early invasive treatment strategy was defined as performing PCI within 24 hours after admission [10]. The major clinical endpoint was the occurrence of MACEs, defined as all-cause death, recurrent myocardial infarction (Re-MI), and any coronary repeat revascularization during a 2-year follow-up period. Any coronary repeat revascularization comprised target lesion revascularization (TLR), TVR, and non-TVR. 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

(CK-MB) 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 [10]. The definitions of TLR, TVR, and non-TVR were previously published [10].

Statistical analyses

For continuous variables, differences between groups were evaluated with the unpaired t-test. Data are expressed as mean \pm standard deviation. For discrete variables, differences are expressed as counts and percentages, and were analyzed with χ^2 test or Fisher's exact test between the groups. Various clinical outcomes were estimated using the Kaplan-Meier method, and differences between the two groups were compared by the log-rank test. To adjust for potential confounders, propensity score-matched (PSM) analysis was performed. We tested all available variables that could be of potential relevance: baseline clinical, laboratory, angiographic, and procedural characteristics (Table 1). The C-statistic for PSM was 0.821. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 5891 matched pairs except for the serum levels of CK-MB and troponin-I. Many patients were excluded during this PSM analysis; to overcome this limitation, we performed multivariate analysis. Any variable with a p value of < 0.001 in univariate analysis and conventional risk factors of a poor outcome in the AMI population were considered as potential confounding factors and entered into the multivariate analysis (Table 2). Using Kaplan-Meier analysis, the differences

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

Variables	Total study population			Propensity score-matched patients		
	STEMI (n = 12,490)	NSTEMI (n = 9400)	P	STEMI (n = 5891)	NSTEMI (n = 5891)	P
Age [years]	61.9 ± 12.6	64.2 ± 12.0	< 0.001	63.3 ± 12.5	63.3 ± 12.2	0.654
Men	9638 (77.2%)	6622 (70.4%)	< 0.001	4361 (74.0%)	4350 (73.8%)	0.817
LVEF [%]	51.5 ± 10.8	54.6 ± 11.1	< 0.001	53.5 ± 10.9	53.8 ± 11.0	0.136
BMI [kg/m ²]	24.2 ± 3.1	24.2 ± 3.1	0.448	24.1 ± 3.0	24.2 ± 3.0	0.525
SBP [mmHg]	129.1 ± 27.8	135.1 ± 26.3	< 0.001	132.6 ± 26.8	132.8 ± 26.1	0.587
DBP [mmHg]	79.2 ± 16.8	81.1 ± 15.3	< 0.001	80.2 ± 15.8	80.4 ± 15.5	0.624
Cardiogenic shock	645 (5.2%)	154 (1.6%)	< 0.001	129 (2.2%)	137 (2.3%)	0.620
CPR on admission	358 (2.9%)	133 (1.4%)	< 0.001	119 (2.0%)	105 (1.8%)	0.345
Hypertension	5831 (46.7%)	5117 (54.4%)	< 0.001	3010 (51.1%)	3004 (51.0%)	0.912
Diabetes mellitus	2944 (23.6%)	2762 (29.4%)	< 0.001	1568 (26.6%)	1582 (26.9%)	0.771
Dyslipidemia	1383 (11.1%)	1246 (13.3%)	< 0.001	723 (12.3%)	692 (11.7%)	0.380
Previous MI	334 (2.7%)	458 (4.9%)	< 0.001	226 (3.8%)	213 (3.6%)	0.527
Previous PCI	514 (4.1%)	701 (7.5%)	< 0.001	332 (5.6%)	332 (5.6%)	1.000
Previous CABG	38 (0.3%)	63 (0.7%)	< 0.001	27 (0.5%)	29 (0.5%)	0.789
Previous HF	71 (0.6%)	131 (1.4%)	< 0.001	46 (0.8%)	41 (0.7%)	0.591
Previous CVA	637 (5.1%)	670 (7.1%)	< 0.001	353 (6.0%)	362 (6.1%)	0.728
Current smokers	6067 (48.6%)	3620 (38.5%)	< 0.001	2549 (43.3%)	2546 (43.2%)	0.956
CK-MB [mg/dL]	171.3 ± 216.0	65.3 ± 168.6	< 0.001	101.4 ± 214.8	82.0 ± 207.2	< 0.001
Troponin-I [ng/mL]	59.6 ± 126.9	23.1 ± 43.5	< 0.001	37.8 ± 155.3	28.6 ± 52.4	< 0.001
NT-proBNP [pg/mL]	1497.5 ± 2832.4	2101.7 ± 4751.4	< 0.001	1748.2 ± 3636.7	1761.3 ± 3162.3	0.836
hs-CRP [mg/dL]	10.9 ± 51.0	11.9 ± 55.9	0.207	11.5 ± 52.0	11.1 ± 45.3	0.616
Serum creatinine [mg/L]	1.05 ± 1.00	1.09 ± 1.16	0.007	1.06 ± 1.00	1.07 ± 1.07	0.667
Blood glucose [mg/dL]	170.8 ± 72.3	158.5 ± 76.2	< 0.001	162.4 ± 65.1	161.2 ± 79.5	0.348
Total cholesterol [mg/dL]	186.8 ± 43.4	185.0 ± 45.6	0.004	185.9 ± 43.6	185.7 ± 45.9	0.818
Triglyceride [mg/L]	136.4 ± 113.3	136.3 ± 108.3	0.943	136.4 ± 112.8	137.2 ± 113.6	0.702
HDL cholesterol [mg/L]	44.2 ± 19.3	43.5 ± 15.4	0.001	43.8 ± 19.4	43.6 ± 16.3	0.638
LDL cholesterol [mg/L]	119.0 ± 38.8	117.7 ± 39.4	0.016	117.9 ± 38.8	117.8 ± 39.9	0.874
Discharge medications:						
ASA	12430 (99.5%)	9341 (99.4%)	0.142	5859 (99.5%)	5856 (99.4%)	0.713
Clopidogrel	11212 (89.8%)	8340 (88.7%)	0.013	5263 (89.3%)	5247 (89.1%)	0.635
Ticagrelor	727 (5.8%)	625 (6.6%)	0.012	366 (6.2%)	365 (6.2%)	0.970
Prasugrel	438 (3.5%)	344 (3.7%)	0.547	208 (3.5%)	223 (3.8%)	0.462
Cilostazol	3077 (24.6%)	2202 (23.4%)	0.038	1366 (23.2%)	1386 (23.5%)	0.663
Beta-blockers	10824 (86.7%)	8082 (86.0%)	0.145	5094 (86.5%)	5114 (86.8%)	0.588
CCB	549 (4.4%)	824 (8.8%)	< 0.001	354 (6.0%)	350 (5.9%)	0.876
Angiographic and procedural characteristics						
PCI within 24 hours	11668 (93.4)	7444 (79.2)	< 0.001	5203 (88.3)	5213 (88.5)	0.774
Infarct-related artery:						
Left main	112 (0.9%)	188 (2.0%)	< 0.001	73 (1.2%)	75 (1.3%)	0.869
Left anterior descending	6535 (52.3%)	3988 (42.4%)	< 0.001	2885 (49.0%)	2869 (48.7%)	0.768
Left circumflex	1138 (9.1%)	2603 (27.7%)	< 0.001	932 (15.8%)	932 (15.8%)	1.000
Right coronary artery	4705 (37.7%)	2621 (27.9%)	< 0.001	2001 (34.0%)	2015 (34.2%)	0.786
Treated vessel:						
Left main	196 (1.6%)	332 (3.5%)	< 0.001	133 (2.3%)	129 (2.2%)	0.803
Left anterior descending	7414 (59.4%)	5202 (55.3%)	< 0.001	3436 (58.3%)	3444 (58.5%)	0.881
Left circumflex	2027 (16.2%)	3733 (39.7%)	< 0.001	1535 (26.1%)	1504 (25.5%)	0.514
Right coronary artery	5301 (42.4%)	3486 (37.1%)	< 0.001	2415 (41.0%)	2414 (41.0%)	0.985

Table 1 (cont.). Baseline clinical, laboratory, angiographic, and procedural characteristics.

Variables	Total study population			Propensity score-matched patients		
	STEMI (n = 12,490)	NSTEMI (n = 9400)	P	STEMI (n = 5891)	NSTEMI (n = 5891)	P
Treated vessel:						
Left main	196 (1.6%)	332 (3.5%)	< 0.001	133 (2.3%)	129 (2.2%)	0.803
Left anterior descending	7414 (59.4%)	5202 (55.3%)	< 0.001	3436 (58.3%)	3444 (58.5%)	0.881
Left circumflex	2027 (16.2%)	3733 (39.7%)	< 0.001	1535 (26.1%)	1504 (25.5%)	0.514
Right coronary artery	5301 (42.4%)	3486 (37.1%)	< 0.001	2415 (41.0%)	2414 (41.0%)	0.985
ACC/AHA lesion type:						
Type B1	1745 (14.0%)	1448 (15.4%)	0.003	875 (14.9%)	908 (15.4%)	0.396
Type B2	3706 (29.7%)	3418 (36.4%)	< 0.001	1969 (33.4%)	1984 (33.7%)	0.770
Type C	5911 (47.3%)	3752 (39.9%)	< 0.001	2543 (43.2%)	2488 (42.2%)	0.306
Extent of coronary artery disease:						
1-vessel	6534 (52.3%)	4040 (43.2%)	< 0.001	2809 (47.7%)	2774 (47.1%)	0.518
2-vessel	3701 (29.6%)	3212 (34.2%)	< 0.001	1882 (31.9%)	1895 (32.2%)	0.797
≥ 3-vessel	2255 (18.1%)	2148 (22.9%)	< 0.001	1200 (20.4%)	1222 (20.7%)	0.616
Multi-vessel disease	5956 (47.7%)	5360 (57.0%)	< 0.001	3082 (52.3%)	3117 (52.9%)	0.518
Drug-eluting stents:						
BMS	834 (6.7%)	534 (5.7%)	0.003	344 (5.8%)	358 (6.1%)	0.586
SES	1941 (15.5%)	1207 (12.8%)	< 0.001	782 (13.3%)	815 (13.8%)	0.374
PES	1667 (13.3%)	1123 (11.9%)	0.002	747 (12.7%)	716 (12.2%)	0.386
ZES	2780 (22.3%)	2006 (21.3%)	0.104	1254 (21.3%)	1273 (21.6%)	0.670
EES	3548 (28.4%)	3168 (33.7%)	< 0.001	1939 (32.9%)	1885 (32.0%)	0.288
BES	1012 (8.1%)	1002 (10.7%)	< 0.001	543 (9.2%)	541 (9.2%)	0.949
Stent diameter [mm]	3.20 ± 0.42	3.10 ± 0.42	< 0.001	3.14 ± 0.41	3.14 ± 0.42	0.572
Stent length [mm]	26.1 ± 9.1	26.7 ± 11.2	< 0.001	26.5 ± 9.9	26.5 ± 10.4	0.965
Number of stents	1.41 ± 0.72	1.60 ± 0.88	< 0.001	1.51 ± 0.80	1.52 ± 0.79	0.811

Values are mean ± standard deviation or number (%). The p values for continuous data were obtained from analysis of the unpaired t-test. The p values for categorical data were obtained from chi-square test. STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; CPR — cardiopulmonary resuscitation; PCI — percutaneous coronary intervention; MI — myocardial infarction; CABG — coronary artery bypass graft; CVA — cerebrovascular accident; HF — heart failure; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; hs-CRP — high-sensitivity-C-reactive protein; HDL — high-density lipoprotein; LDL — low-density lipoprotein; ASA — acetylsalicylic acid; CCB — calcium channel blockers; ACC/AHA — American College of Cardiology/American Heart Association; BMS — bare-metal stent; SES — sirolimus-eluting stent; PES — paclitaxel-eluting stent; ZES — zotarolimus-eluting stent; EES — everolimus-eluting stent; BES — biolimus-eluting stent

between the groups were compared using the log-rank test. For all analyses, a two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software, version 20 (IBM; Armonk, NY, USA) [7].

Results

Baseline clinical, laboratory, angiographic, and procedural characteristics

In the total study population, the mean age of the NSTEMI group was greater than that of the STEMI group (64.2 ± 12.0 years vs. 61.9 ± 12.6 years, $p < 0.001$, Table 1). The following val-

ues were higher in the STEMI group than in the NSTEMI group: number of men; value of cardiogenic shock, cardiopulmonary resuscitation (CPR), and current smokers; levels of CK-MB, troponin I, blood glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol; prescription rates of clopidogrel and cilostazol; numbers of PCI within 24 hours, left anterior descending artery (LAD, infarct-related artery [IRA] and treated vessel) and right coronary artery (RCA, IRA and treated vessel); and numbers of American College of Cardiology/American Heart Association (ACC/AHA) type C and 1-vessel disease. By contrast, the NSTEMI

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

Outcomes	Cumulative events at 2-year (%)				
	STEMI	NSTEMI	Log-rank	Hazard ratio (95% CI)	P
Total study population					
MACEs	851 (7.2)	728 (8.3)	0.003	1.159 (1.050–1.280)	0.003
All-cause death	228 (1.9)	255 (2.9)	< 0.001	1.512 (1.265–1.808)	< 0.001
Cardiac death	164 (1.4)	170 (1.9)	0.002	1.398 (1.128–1.733)	0.002
Re-MI	181 (1.5)	149 (1.7)	0.319	1.117 (0.899–1.387)	0.319
Total repeat revascularization:	507 (4.3)	399 (4.7)	0.310	1.070 (0.939–1.220)	0.310
TLR	160 (1.4)	122 (1.4)	0.774	1.035 (0.818–1.310)	0.774
TVR	294 (2.5)	244 (2.8)	0.153	1.132 (0.955–1.341)	0.154
Non-TVR	222 (1.9)	162 (1.9)	0.933	0.991 (0.810–1.214)	0.933
Propensity score-matched patients					
MACEs	414 (7.4)	452 (8.2)	0.132	1.108 (0.969–1.266)	0.132
All-cause death	114 (2.0)	158 (2.9)	0.005	1.407 (1.106–1.790)	0.005
Cardiac death	82 (1.4)	106 (1.9)	0.046	1.311 (0.983–1.749)	0.046
Re-MI	94 (1.7)	90 (1.7)	0.847	0.972 (0.728–1.298)	0.847
Total repeat revascularization:	241 (4.4)	252 (4.7)	0.485	1.065 (0.893–1.271)	0.485
TLR	85 (1.5)	71 (1.3)	0.308	0.849 (0.619–1.163)	0.308
TVR	150 (2.7)	150 (2.8)	0.871	1.019 (0.813–1.278)	0.871
Non-TVR	98 (1.8)	107 (2.0)	0.444	1.113 (0.846–1.464)	0.444
Multivariate analysis*					
MACEs	851 (7.2)	728 (8.3)	0.003	1.081 (0.965–1.210)	0.178
All-cause death	228 (1.9)	255 (2.9)	< 0.001	1.528 (1.264–1.852)	0.001
Cardiac death	164 (1.4)	170 (1.9)	0.002	1.406 (1.146–1.802)	0.020
Re-MI	181 (1.5)	149 (1.7)	0.319	1.021 (0.798–1.308)	0.866
Total repeat revascularization:	507 (4.3)	399 (4.7)	0.310	0.975 (0.839–1.134)	0.746
TLR	160 (1.4)	122 (1.4)	0.774	0.857 (0.653–1.124)	0.264
TVR	294 (2.5)	244 (2.8)	0.153	0.979 (0.805–1.190)	0.830
Non-TVR	222 (1.9)	162 (1.9)	0.933	0.963 (0.764–1.213)	0.748

*Adjusted by age, men, LVEF, SBP, DBP, cardiogenic shock, CPR on admission, hypertension, diabetes, dyslipidemia, previous history of MI, PCI, CABG, HF, and CVA, current smoker, serum level of CK-MB, troponin I, NT-proBNP, blood glucose, CCB, PCI within 24 hours, IRA, treated vessel, ACC/AHA type B2, and C lesion, the extent of coronary artery disease, types of stents (SES, EES, and BES), stent diameter, stent length, and number of stents. STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; CI — confidence interval; MACE — major adverse cardiac events; Re-MI — re-myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization; Non-TVR — non-TVR; LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; DBP — diastolic blood pressure; CPR — cardiopulmonary resuscitation; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; HF — heart failure; CVA — cerebrovascular accidents; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; CCB — calcium channel blockers; IRA — infarct-related artery; ACC/AHA — American College of Cardiology/American Heart Association; SES — sirolimus-eluting stent; EES — everolimus-eluting stents; BES — biolimus-eluting stents

group showed higher values than the STEMI group for the following: left ventricular ejection fraction (LVEF, $54.6 \pm 11.1\%$ vs. $51.5 \pm 10.8\%$, $p < 0.001$); systolic blood pressure; diastolic blood pressure; number of patients with hypertension, diabetes, dyslipidemia, previous history of MI, PCI, coronary artery bypass graft, heart failure (HF), and cerebrovascular accident; levels of serum N-terminal pro-B-type natriuretic peptide and se-

rum creatinine; prescription rates of ticagrelor and calcium channel blockers; the number of left main coronary artery (LM, IRA and treated vessel), left circumflex artery (LCx, IRA and treated vessel); and the frequency of multi-vessel disease (MVD). Bare-metal stents (BMS) and first-generation DESs were more frequently deployed in the STEMI group, and the everolimus-eluting stents and biolimus-eluting stents were more frequently de-

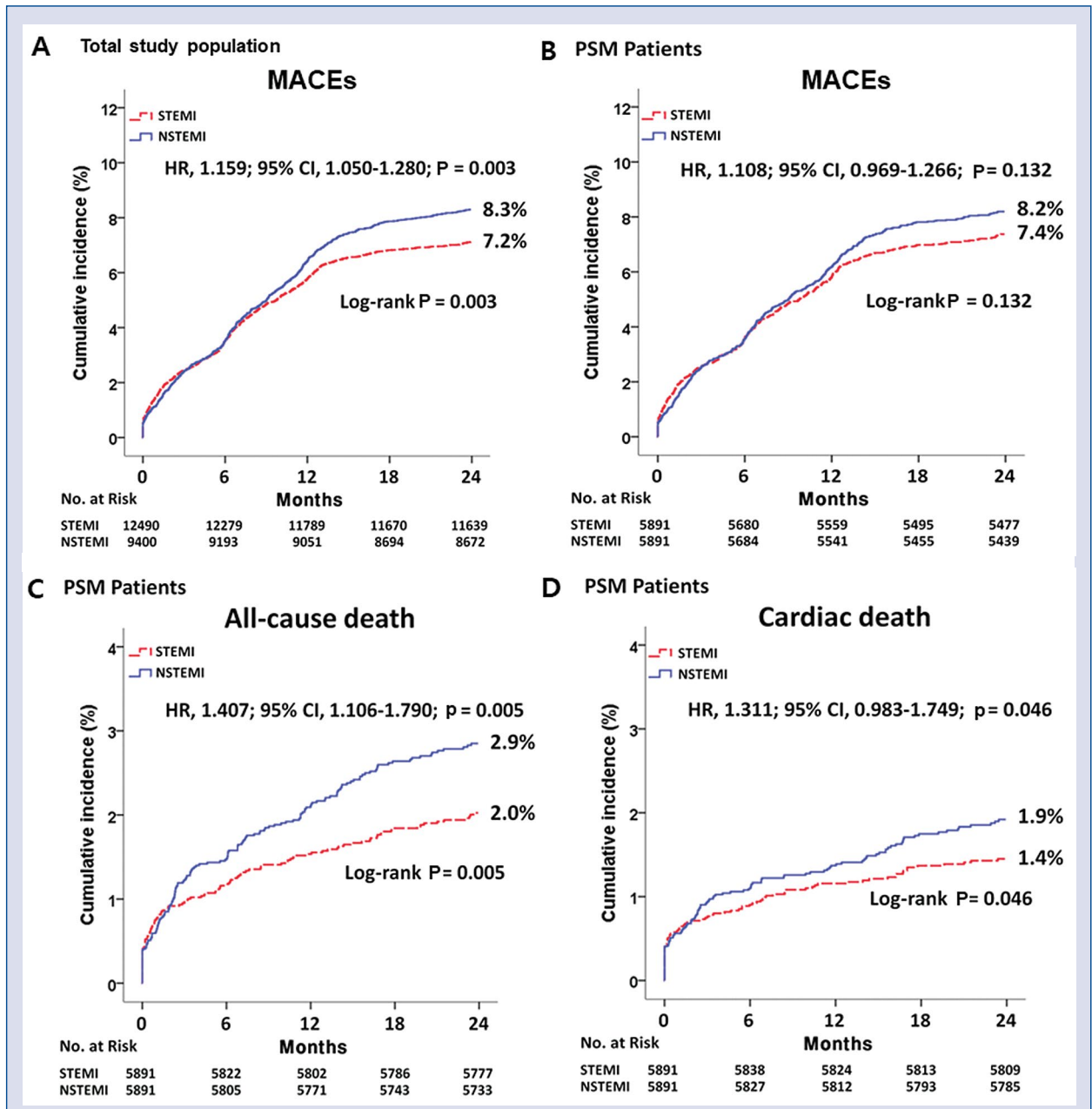


Figure 2. Kaplan-Meier analysis for major adverse cardiac events (MACEs) (A, B), all-cause death (C), and cardiac death (D); PSM — propensity score-matched; HR — hazard ratio; CI — confidence interval; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction.

ployed in the NSTEMI group. After PSM analysis, baseline differences between the two groups were well balanced. However, the blood levels of CK-MB and troponin I levels were not well balanced.

Clinical outcomes

In the total study population, the cumulative incidence of MACEs (hazard ratio [HR] 1.159; 95% confidence interval [CI] 1.050–1.280; p = 0.003, Fig. 2A), all-cause death (HR 1.512;

95% CI 1.265–1.808; p < 0.001), and CD (HR 1.398; 95% CI 1.128–1.733; p = 0.002) were higher in the NSTEMI group than in the STEMI group. After PSM analysis, the cumulative incidence of MACEs was not significantly different between the groups (Fig. 2B). However, the cumulative incidences of all-cause death (HR 1.407; 95% CI 1.106–1.790; p = 0.005, Fig. 2C) and CD (HR 1.311; 95% CI 0.983–1.749; p = 0.046, Fig. 2D) were significantly higher in the NSTEMI group

than in the STEMI group. Before and after PSM analysis, the cumulative incidences of Re-MI, any repeat revascularization, TLR, TVR, and non-TVR were not statistically different between the groups. Figure 3 shows subgroup analysis for MACEs at 2 years. In cases of male sex (HR 1.13; 95% CI 1.00–1.27; $p = 0.047$), low LVEF ($< 50\%$, HR 1.47; 95% CI 1.26–1.71; $p < 0.001$), cardiogenic shock (HR 1.17; 95% CI 1.06–1.29; $p = 0.002$), and PCI within 24 hours (HR 1.15; 95% CI 1.03–1.28; $p = 0.012$) statins combined with RASI showed greater reduction in MACEs for patients with STEMI than for those with NSTEMI. Advanced age (≥ 65 years), low LVEF ($< 50\%$), diabetes, CPR on admission, N-terminal pro-B-type natriuretic peptide, serum creatinine, total cholesterol, triglyceride, LDL-cholesterol, PCI within 24 hours, BMS, and MVD were meaningful independent risk factors for both all-cause death and CD in PSM patients (Table 3).

Discussion

According to current guidelines [5, 6, 8, 9], more than 80% of the patients with AMI received statin therapy in Korea [16]. Similarly, more than 50% of these patients received RASI therapy to reduce cardiovascular mortality [17]. However, the comparative studies regarding long-term clinical outcomes of statin with RASI combination therapy between STEMI and NSTEMI after stent implantation have not been reported. We believe this may be the first report focusing on this issue. Moreover, the present study confirms that statin combined with RASI was more effective in patients with STEMI rather than in patients with NSTEMI with respect to all-cause death and CD rates over a 2-year follow-up.

The key findings of this study are as follows: First, after PSM analysis, the cumulative incidences of all-cause death and CD were significantly higher in patients with NSTEMI than in those with STEMI after combined statin and RASI therapy. Second, the cumulative incidences of MACEs, Re-MI, and any repeat revascularization including TLR, TVR, and non-TVR were not significantly different between the two groups after PSM analysis. Third, advanced age (≥ 65 years), male sex, low LVEF ($< 50\%$), diabetes, CPR on admission, PCI within 24 hours, BMS, and MVD were independent risk factors for both all-cause death and CD in PSM patients.

Statins both reduce LDL-cholesterol and decrease the occurrences of cardiovascular death,

non-fatal MI, and repeat coronary revascularization by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity, as well as other not fully understood processes [3, 18, 19]. The beneficial effects of statins are evident in both STEMI and NSTEMI patients [5, 6, 8, 9]. However, data comparing the long-term prognosis of STEMI and NSTEMI patients, especially those focused on the usage of statins, are limited. In the era of DES, Kim et al. [7] demonstrated that MACEs and mortality reduction capacity of statin therapy was prominent compared with statin non-use, and statins were more effective in patients with STEMI compared with NSTEMI. Regardless of STEMI or NSTEMI, RASI provides mortality reduction benefit by diminishing the rate of progressive LV dilation and remodeling, especially in patients with LV dysfunction [5, 6]. Even though Kim et al. [10] reported greater reduction in mortality following RASI in STEMI patients than in NSTEMI patients after successful PCI, long-term clinical outcome data comparing the status of STEMI and NSTEMI patients post successful stent implantation after combined statin and RASI therapy are also limited. Koh et al. [20] suggested that combined statins and RASI may improve endothelial function, insulin resistance, and atherosclerosis. In our study, the cumulative incidences of all-cause death (HR 1.407; 95% CI 1.106–1.790; $p = 0.005$) and CD (HR 1.311; 95% CI 0.983–1.749; $p = 0.046$) were also significantly higher in the NSTEMI group than in the STEMI group. Taken together, these results suggest that RASI monotherapy or statins combined with RASI was more beneficial for STEMI patients than for NSTEMI patients in terms of reduced mortality. Statins decrease the production of oxygen-derived free radicals by reducing LDL-cholesterol, increasing nitric oxide (NO) synthesis, promoting antioxidant effects, and inhibiting upregulation of angiotensin II type 1 (AT1) receptor expression. RASI inhibits binding of angiotensin II to the AT1 receptor and induces decreased production of oxygen-derived free radicals. Accumulated bradykinins after ACEI treatment lead to increased stimulation of NO production [20]. NO production may be a shared process for both statins and RASI. Kim et al. [10] showed that RASI after PSM was more effective in reducing all-cause death (HR 1.386; 95% CI 1.114–1.725; $p = 0.003$) and CD (HR 1.358; 95% CI 1.041–1.7770; $p = 0.024$) in patients with STEMI compared with NSTEMI after PSM. However, we found that statins combined with RASI did not show greater relative risk reduction of all-cause

Table 3. Multivariate Cox-proportional regression analysis for predictors of all-cause death and cardiac death in propensity score-matched patients.

Variables	All-cause death		Cardiac death	
	HR (95% CI)	P	HR (95% CI)	P
STEMI vs. NSTEMI	2.822 (2.102–3.789)	< 0.001	2.643 (1.858–3.759)	< 0.001
Age ≥ 65 years	2.617 (1.945–3.521)	< 0.001	2.491 (1.748–3.551)	< 0.001
Male	1.009 (0.774–1.315)	0.949	1.057 (0.770–1.450)	0.733
LVEF < 50%	1.961 (1.531–2.510)	< 0.001	1.887 (1.403–2.540)	< 0.001
Systolic blood pressure	0.991 (0.982–0.999)	0.024	0.992 (0.983–1.002)	0.121
Diastolic blood pressure	1.012 (0.999–1.026)	0.072	1.010 (0.994–1.027)	0.204
Hypertension	1.186 (0.916–1.535)	0.196	1.236 (0.905–1.689)	0.183
Diabetes mellitus	1.522 (1.184–1.956)	0.001	1.453 (1.074–1.967)	0.015
Dyslipidemia	1.140 (0.758–1.715)	0.528	1.086 (0.693–1.702)	0.720
Cardiogenic shock	1.074 (0.517–2.233)	0.847	1.372 (0.524–3.591)	0.519
CPR on admission	3.289 (2.034–5.318)	< 0.001	4.001 (2.322–6.895)	< 0.001
CK-MB	1.000 (0.999–1.001)	0.814	1.000 (0.999–1.001)	0.969
Troponin-I	1.000 (1.000–1.001)	0.407	1.000 (1.000–1.001)	0.497
NT-proBNP	1.001 (1.000–1.002)	< 0.001	1.002 (1.001–1.003)	< 0.001
hs-CRP	1.001 (0.999–1.003)	0.256	1.000 (0.998–1.003)	0.766
Serum creatinine	1.128 (1.074–1.186)	< 0.001	1.124 (1.057–1.195)	< 0.001
Total cholesterol	0.994 (0.991–0.997)	< 0.001	0.992 (0.989–0.996)	< 0.001
Triglyceride	0.996 (0.994–0.998)	< 0.001	0.996 (0.994–0.999)	0.001
HDL-cholesterol	0.993 (0.982–1.003)	0.173	0.994 (0.981–1.006)	0.308
LDL-cholesterol	0.994 (0.991–0.998)	0.001	0.993 (0.989–0.997)	0.001
Beta-blocker	1.562 (1.038–2.353)	0.033	1.600 (0.978–2.617)	0.061
PCI within 24 hours	1.483 (1.167–1.885)	0.001	1.395 (1.046–1.860)	0.024
LAD (IRA)	1.122 (0.752–1.676)	0.572	1.020 (0.633–1.643)	0.934
LAD (treated)	1.120 (0.744–1.686)	0.586	1.065 (0.659–1.721)	0.796
ACC/AHA type B2/C lesion	1.124 (0.824–1.533)	0.461	1.007 (0.703–1.442)	0.970
BMS	3.104 (1.905–5.056)	< 0.001	2.481 (1.360–4.527)	0.003
SES	1.940 (1.048–3.591)	0.035	2.041 (0.974–4.275)	0.059
PES	1.343 (0.755–2.389)	0.316	1.142 (0.591–2.210)	0.692
ZES	1.128 (0.702–1.813)	0.618	1.084 (0.616–1.909)	0.780
EES	1.150 (0.725–1.824)	0.552	1.112 (0.642–1.924)	0.706
BES	1.066 (0.606–1.874)	0.825	1.196 (0.598–2.390)	0.613
MVD	1.301 (1.003–1.687)	0.048	1.343 (0.981–1.840)	0.042
Stent diameter	0.856 (0.630–1.162)	0.317	0.714 (0.490–1.040)	0.079
Stent length	0.999 (0.987–1.012)	0.883	0.998 (0.983–1.013)	0.791

HR — hazard ratio; CI — confidence interval; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; LVEF — left ventricular ejection fraction; CPR — cardiopulmonary resuscitation; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; hs-CRP — high sensitivity-C-reactive protein; HDL — high-density lipoprotein; LDL — low-density lipoprotein; PCI — percutaneous coronary intervention; LAD — left anterior descending coronary artery; IRA — infarct-related artery; ACC/AHA — American College of Cardiology/American Heart Association; BMS — bare-metal stent; SES — sirolimus-eluting stent; PES — paclitaxel-eluting stent; ZES — zotarolimus-eluting stent; EES — everolimus-eluting stent; BES — biolimus-eluting stent; MVD — multivessel disease

death (40.7% vs. 38.6%) or CD (31.1% vs. 35.8%) compared with the results of Kim et al. [10]. We speculated that one of the major causative factors for the similar relative risk reduction potency for all-cause death and CD in these two studies (Kim

et al. [10] and the present study) is related, at least in part, with this shared NO production process [19]. This has included suggestion that this similar NO mediated protective mechanism may be attenuated their effects on endothelium each

other. However, this supposition supports the need for further study to confirm these findings. Other possible factor for these results was the presence of BMS. BMS was not included in the Kim et al. [10] study. However, the proportion of BMS in the total study population was low, and BMS was an independent significant predictor for both all-cause death and cardiac death in PSM patients (Table 3). Nevertheless, with regard to the beneficial effect of statin monotherapy by reducing MACEs, all-cause death, and TVR in patients with STEMI [7], statin and RASI combination therapy showed an additional beneficial effect on reducing the cumulative incidence of CD (HR 1.311; 95% CI 0.983–1.749; $p = 0.046$) in this study.

On PSM analysis, many patients (10,108/21,890, 46.2%) were excluded and the serum CK-MB and troponin-I levels were not well-matched. To overcome these limitations, we performed standard multivariate analysis. Nevertheless, the results of multivariate analysis were similar to the results of the PSM analysis. After multivariate analysis, the cumulative incidences of all-cause death (HR 1.528; 95% CI 1.264–1.852; $p = 0.001$) and CD (HR 1.406; 95% CI 1.146–1.802; $p = 0.020$) were significantly higher in NSTEMI patients than in STEMI patients. The cumulative incidences of MACEs, Re-MI, and any repeat revascularization were similar between the two groups (Table 2).

The condition of the STEMI group was worse than that of the NSTEMI group with respect to baseline characteristics. The values of cardiogenic shock (5.2% vs. 1.6%, $p < 0.001$) and CPR on admission (2.9% vs. 1.4%, $p < 0.001$); the number of current smokers (48.6% vs. 38.5%, $p < 0.001$), LAD (IRA, treated vessel), RCA (IRA, treated vessel), and ACC/AHA type C; and the levels of CK-MB, troponin I were significantly higher in the STEMI group. However, the cumulative incidences of all-cause death and CD were significantly lower in the STEMI group than in the NSTEMI group. These results were associated with the beneficial effects of RASI and were compatible with those of the OPTIMAAL study [21]. In the OPTIMAAL study, the clinical benefit of RASI was larger in the high-risk patient subgroup, including anterior MI, decreased LVEF ($\leq 40\%$), HF, prior MI, and tachycardia. On subgroup analysis, for patients who had decreased LVEF and who were in cardiogenic shock, statin combined with RASI reduced MACEs in patients with STEMI more than in those with NSTEMI (Fig. 3).

Another considerable factor for determining the cumulative incidences of all-cause death and CD was the treatment strategy. In the present study, 93.5% (11,627/12,490) of the STEMI patients had undergone primary PCI, and about 79.2% (7444/9400) of the NSTEMI patients had received early invasive treatment. The higher incidence of primary PCI may be associated with favorable all-cause death rates and CD in STEMI patients. Currently, the reasons for the higher incidence of death in NSTEMI during long-term follow-up remain poorly understood [22, 23]. In patients with NSTEMI, studies recommended that a selective invasive strategy may be preferable in selected patients to improve long-term outcomes [24, 25].

KAMIR is a nationwide, prospective, observational, on-line registry in South Korea that has been compiling data since November 2005. More than 50 high-volume university and community hospitals with facilities for primary PCI and onsite cardiac surgery have participated [13]. Therefore, we believe the population of this study is sufficiently large to provide reasonably accurate results. Furthermore, the results of this comparative study may persuade interventional cardiologists of the benefits of statins combined with RASI with respect to reducing all-cause death and CD in STEMI patients compared with those in NSTEMI patients after PCI.

Limitations of the study

Our study had several limitations. First, there may be some under-reporting and/or missed data because of the non-randomized retrospective nature of the study. Second, our study was based on medications at discharge, and the registry data did not include full detailed data concerning the starting time of statin or RASI therapy, changes in prescription doses, long-term adherence, or discontinuation during the follow-up period; therefore, these factors may contribute bias. Third, we could not provide serial follow-up results compared with initial laboratory results because of limitations related to the registry data; this too may introduce bias. Fourth, we reported 2-year clinical outcomes between the two groups in this study; nevertheless, a 2-year follow-up period is relatively short for the determination of long-term major clinical outcomes. Finally, the long inclusion period could also have influenced the patient's profile and may have biased the results, because RASI, AT1, and statins in recent years have been modernized in late generations with, generally, better bioprofile.

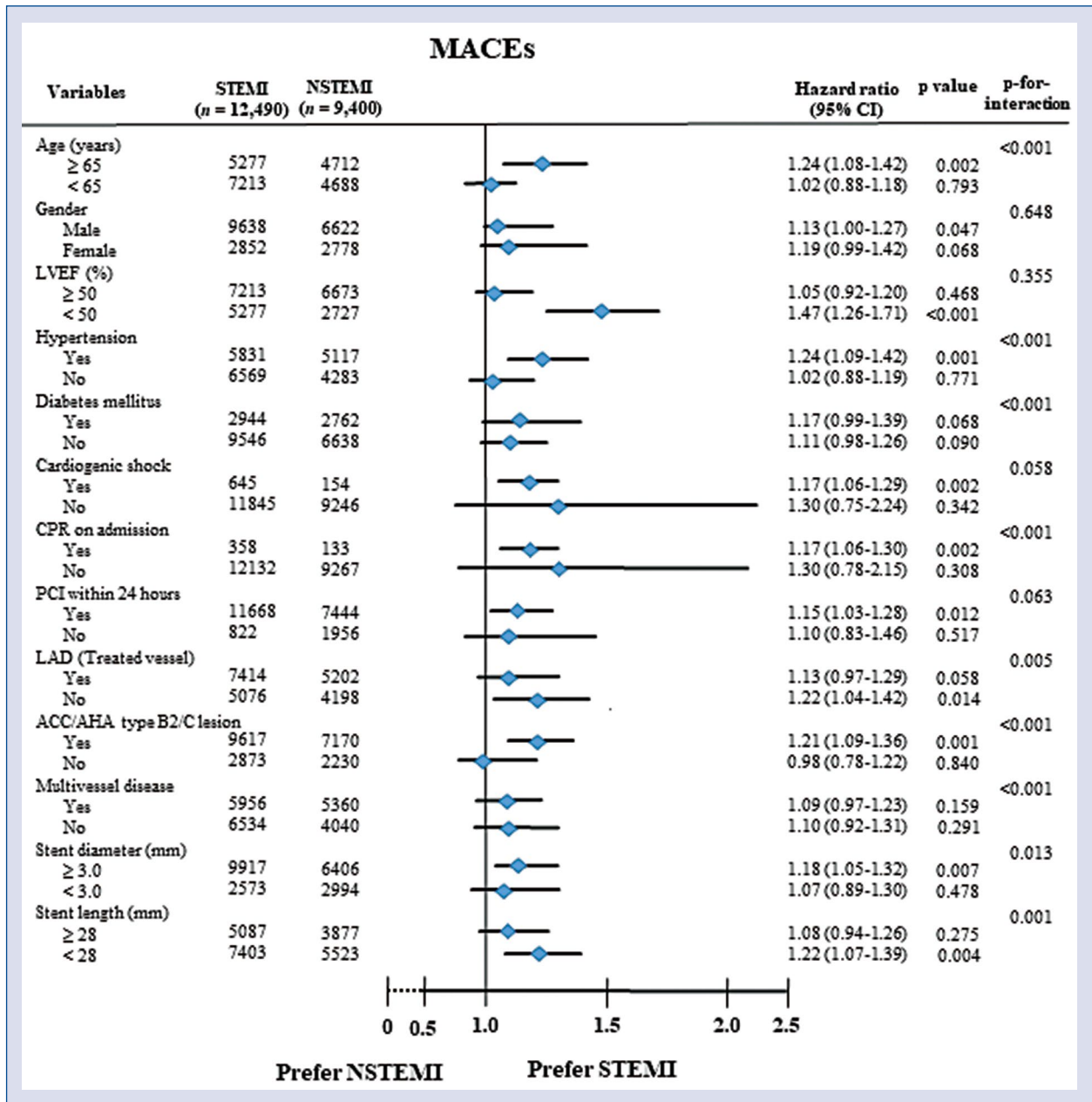


Figure 3. Subgroup analysis for major adverse cardiac events (MACEs); CI — confidence interval; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction; LVEF — left ventricular ejection fraction; CPR — cardiopulmonary resuscitation; PCI — percutaneous coronary intervention; LAD — left anterior descending artery; ACE/AHA — American College of Cardiology/American Heart Association.

Conclusions

In conclusion, despite the fact that the cumulative incidences of MACEs, Re-MI, and any repeat revascularization including TLR, TVR, and non-TVR were not statistically significantly different between the two groups, with respect to all-cause death and CD rates during a 2-year follow-up period, combined use of statin with RASI was more effective in patients

with STEMI than in those with NSTEMI. However, further studies are warranted to elucidate this focus.

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