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Monotherapy versus combination therapy of statin and renin–angiotensin system inhibitor in ST-segment elevation myocardial infarction

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Abstract

Background: *The beneficial effects of statin and renin–angiotensin system inhibitor (RASI) are well-known. In this retrospective cohort study, 2-year clinical outcomes were compared between monotherapy and combination therapy with statin and RASI in ST-segment elevation myocardial infarction (STEMI) patients after stent implantation.*

Methods: *A total of 17,414 STEMI patients were enrolled and divided into the three groups (group A: 2448 patients, statin alone; group B: 2431 patients, RASI alone; and group C: 12,535 patients, both statin and RASI). The principal clinical endpoint was the occurrence of major adverse cardiac events (MACEs) defined as all-cause death, recurrent myocardial infarction, and any repeat revascularization.*

Results: *After adjustment, the cumulative incidences of MACEs in group A (adjusted hazard ratio [aHR] 1.337; 95% confidence interval [CI] 1.064–1.679; p = 0.013) and in group B (aHR 1.375; 95% CI 1.149–1.646; p = 0.001) were significantly higher than in group C. The cumulative incidence of all-cause death in group A was significantly higher than that in group C (aHR 1.539; 95% CI 1.014––2.336; p = 0.043). The cumulative incidences of any repeat revascularization (aHR 1.317; 95% CI 1.031–1.681; p = 0.028), target lesion vascularization, and target vessel vascularization in group B were significantly higher than in group C.*

Conclusions: *A statin and RASI combination therapy significantly reduced the cumulative incidence of MACEs compared with a monotherapy of these drugs. Moreover, the combination therapy showed a reduced all-cause death rate compared with statin monotherapy, and a decreased repeat revascularization rate compared with RASI monotherapy.* (Cardiol J 2022; 29, 1: 93–104)

Key words: ST-segment elevation myocardial infarction, statin, renin–angiotensin system, long-term outcome

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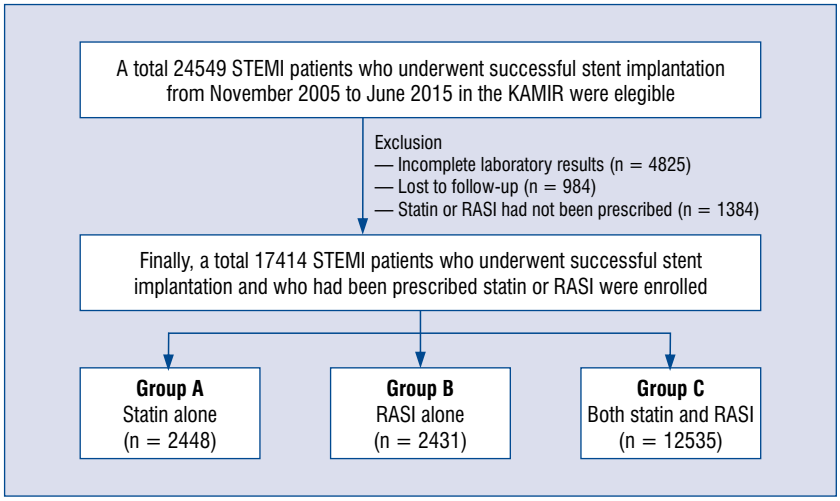

Figure 1. Flow chart; KAMIR — Korea Acute myocardial Infarction Registry; STEMI — ST-segment elevation myocardial infarction; RASI — renin–angiotensin system inhibitor.

Introduction

Through the inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, statin plays essential roles in primary and secondary prevention of adverse cardiovascular events [1–3]. The European guidelines recommend starting high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term in patients with ST-segment elevation myocardial infarction (STEMI) (Class 1A) [4]. Similarly, the American guidelines recommend the use of early high-intensity statin therapy and should be continued in all STEMI patients (Class 1B) [5]. Renin–angiotensin system inhibitors (RASI) are beneficial for reducing mortality in STEMI patients after percutaneous coronary intervention (PCI) [6], and RASI is recommended in the current guidelines as Class 1A [4, 5]. Even though the beneficial effects of statin and RASI are well-known, results focused on the comparative efficacy of combination therapy of statin and RASI, including an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and statin, or RASI monotherapy on the occurrence of major adverse cardiac events (MACEs) during a long-term follow-up period in patients with STEMI who underwent successful stent implantation are limited. In this study, we investigated the difference in clinical outcome parameters between this combination therapy and monotherapy in STEMI patients after successful stent implantation, during a 2-year clinical follow-up period.

Methods

Study design and population

The Korea Acute Myocardial Infarction Registry (KAMIR) is a nationwide, prospective, multicenter registry in South Korea, established in November 2005. The KAMIR provides the public and physicians in the "real-world" clinical practice with the demographic characteristic and treatment strategies of the acute myocardial infarction (MI) in Korea [7]. The present study is a non-randomized, multicenter, observational, retrospective cohort study. A total of 24,549 STEMI patients in KAMIR from November 2005 to June 2015 were evaluated. Among them, patients who had the following conditions were excluded: (1) incomplete laboratory results (n = 4825, 19.7%), (2) lost to follow-up (n = 984, 4.0%), (3) statin or RASI had not been prescribed (n = 1384, 5.6%). After exclusion, a total of 17,414 STEMI patients who underwent successful stent implantation and who had been prescribed statin or RASI were enrolled. The patients were classified into group A (2448, 14.1%), group B (2431, 13.9%), and group C (12,535, 72.0%), and received statin alone, RASI alone, or both statin and RASI, respectively, as treatment (Fig. 1). The beneficial roles of statin and RASI in STEMI [4, 5] are well-known. For these reasons, patients who had not been prescribed these drugs in this study were excluded. The data collection was done via a web-based case report form, at each participating center; well-trained coordinators participated in data collection. The study protocol was approved

by the ethics committee at each participating center and the Chonnam National University Hospital Institutional Review Board (IRB) ethics committee (CNUH-2011-172) according to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent prior to enrollment. All the 17,414 patients completed a 2-year clinical follow-up through face-to-face interviews, phone calls, or chart review.

PCI procedure and medical treatment

Diagnostic coronary angiography and PCI were performed through the femoral and the radial artery approach according to the standard technique [8]. Before PCI, all patients were given loading doses of 200 to 300 mg acetylsalicylic acid (ASA) and 300 to 600 mg clopidogrel, when available; alternatively, 180 mg ticagrelor or 60 mg prasugrel was given. The recommended total duration of dual antiplatelet therapy (DAPT, the combination of ASA [100 mg/day] with clopidogrel [75 mg/day] or ticagrelor [90 mg twice a day] or prasugrel [5–10 mg/ /day]) was more than 12 months to patients who had undergone PCI. Triple antiplatelet therapy (100 mg cilostazol, twice a day added on to DAPT) was left to the discretion of the individual operators. 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 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

ST-segment elevation myocardial infarction was defined as the patient who had experienced chest pain with ST-segment elevation ≥ 2 mm in ≥ 2 contiguous precordial lead, or 1 ≥ 1 mm in ≥ 2 limb leads, or new-onset left bundle branch block on the admission electrocardiogram [5]. The major clinical endpoint was the occurrence of MACEs, defined as all-cause death, recurrent myocardial infarction (Re-MI), any repeat coronary revascularization, including target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR during the follow-up period. All-cause death was classified as cardiac or non-cardiac. 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 (CK-MB) above the upper normal limits, or an increase in troponin-T/troponin-I levels above the 99th percentile of the upper normal limit during the follow-up period [5]. TLR was defined as revascularization of the target lesion due to restenosis, or re-occlusion within the stent or 5 mm in and adjacent of the distal or proximal segment. TVR was defined as revascularization of the target vessel or any segment of the coronary artery containing the target lesion. Non-TVR was defined as revascularization of any segment of the non-target coronary artery.

Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (IBM; Armonk, NY, USA). For continuous variables, differences among the three groups were evaluated using the analysis of variance or the Jonckheere-Terpstra test, and post-hoc analysis between two groups was carried out using the Hochberg test or Dunnett-T3 test; data are expressed as the means ± standard deviations. For discrete variables, the differences between two groups among the three groups were analyzed using the χ^2 test or the Fisher exact test, as appropriate; data are expressed as counts and percentages. Only meaningful confounding covariates ($p < 0.001$ or those having predictive values) during the multivariable Cox regression analysis, which are listed were included as follows: age, sex (men), left ventricular ejection fraction (LVEF), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiopulmonary resuscitation (CPR) on admission, primary PCI, hypertension, diabetes mellitus (DM), dyslipidemia, blood N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), ASA, clopidogrel, ticagrelor, prasugrel, beta-blockers (BBs), calcium channel blockers (CCBs), American College of Cardiology/ /American Heart Association (ACC/AHA) lesion type B2 and C, intravascular ultrasound (IVUS), bare-metal stents (BMS), sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), everolimus--eluting stents (EES), and biolimus-eluting stents (BES). Various clinical outcomes were estimated using the Kaplan-Meier curve analysis, and dif-

ferences between groups were compared with the log-rank test. A two-tailed p value of < 0.05 indicated statistical significance.

Results

Baseline clinical, laboratory, angiographic, and procedural characteristics

Table 1 shows the baseline, laboratory, angiographic, and procedural characteristics of this cohort study. The study population is composed of patients who had relatively well preserved LVEF (mean 51.2 ± 10.9%). The number of men among the enrolled patients was the highest in group C. The mean ages of the patients enrolled in group A were older than the other groups. The frequency of primary PCI was the highest in group C. In group A, the mean blood levels of CK-MB, troponin-I, NT-proBNP; the prescription rates of more recently developed antiplatelet agents (e.g., ticagrelor, prasugrel) and CCB as the discharge medications; the number of CPR on admission; ACC/AHA type C lesion, the use of IVUS and the deployment of zotarolimus-eluting stent (ZES) were the highest. Moreover, the mean diameter of deployed stents was the lowest in group A. In group B, the number of cardiogenic shocks; the mean value of blood glucose, Hemoglobin A1c, creatinine; the number of clopidogrel as the discharge medication, left anterior descending coronary artery (LAD) as an infarct-related artery, ACC/AHA type B1; and the deployments of BMS, SES, PES, and ≥ 3-vessel disease were the highest. The mean length of the deployed stents was the shortest in group B. In group C, the mean values of BMI, SBP, DBP, total cholesterol, triglyceride, LDL-C; the prescription rate of ASA and BB as the discharge medications; the number of hypertensive patients, LAD as the treated vessel, ACC/AHA type B2 lesion, and EES were the highest. The mean number of deployed stents was not significantly different among the three groups.

Clinical outcomes

Table 2 shows the cumulative incidences of major clinical outcomes during the 2-year follow-up period. After adjustment, the cumulative incidences of MACEs in group A (adjusted hazard ratio [aHR]: 1.337; 95% confidence interval [CI]: 1.064–1.679; p = 0.013) and in group B (aHR: 1.375; 95% CI: 1.149–1.646; p = 0.001) were significantly higher than those in group C (Table 3, Fig. 2A). The cumulative incidence of all-cause death in group A was significantly higher than that in group C (aHR: 1.539; 95% CI: 1.014–2.336; p = 0.043; Fig. 2B). The cumulative incidences of any repeat revascularization (aHR: 1.317; 95% CI: 1.031–1.681; p = 0.028; Fig. 2D), TLR (aHR: 1.754; 95% CI: 0.193–2.580; p = 0.004; Fig. 2E), and TVR (aHR: 1.539; 95% CI: 1.138–2.082; p = 0.005; Fig. 2F) in group B were significantly higher than those in group C. However, the cumulative incidences of cardiac, Re-MI, and non-TVR were similar among the three groups before and after adjustment. Table 4 shows the independent predictors for MACEs at 2 years. LVEF < 50% (aHR: 1.146; 95% CI: 1.019–1.289; p = 0.023), DM (aHR: 1.342; 95% CI: 1.187–1.518; p < 0.001), multivessel disease (aHR: 1.774; 95% CI: 1.570–2.005; p < 0.001), cardiogenic shock (aHR: 0.998; 95% CI: 0.996–1.000; p = 0.043), and CPR on admission (aHR: 2.240; 95% CI: 1.784–2.813; p < 0.001) were significant independent predictors for MACEs.

Discussion

The main findings of this study are as follows: First, the cumulative incidences of MACEs in group A and group B were significantly higher than those in group C. Second, the cumulative incidence of all-cause death in group A was significantly higher than that in group C. Third, the cumulative incidences of any repeat revascularization, TLR, and TVR in group B were significantly higher than those in group C. Finally, the cumulative incidences of cardiac, Re-MI, and non-TVR were similar among the three groups before and after adjustment.

Statins have both fundamental lipid-lowering capacity and additional pleiotropic actions [9]. In patients with STEMI, these pleiotropic activities include cardiovascular death, non-fatal MI, and coronary revascularization rate reduction capabilities [3, 10]. Even though the relative superiority on the long-term clinical outcome between ACEI and ARB in acute MI patients is still debatable [11–13], RASI is recommended in patients with STEMI after PCI [4, 5]. In this study, the cumulative incidence of MACEs, all-cause death, Re-MI, and any repeat revascularization (TLR, TVR, and non-TVR) between group A and group B were similar. It was assumed that the major causative factors for similar results between these two groups are related to a shared process, such as nitric oxide (NO) production [14]. The statins' pleiotropic action include the upregulation and activation of endothelial NO synthase [15], and the accumulated bradykinin after ACEI treatment lead to increased stimulations of the NO production [16]. The combination therapy of statin and RASI compensate unwanted effects

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

Variables	Total (n = 17,414)	Group A Statin alone (n = 2448)	Group B RASI alone (n = 2431)	Group C Statin and RASI (n = 12535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
Men	13337 (76.6%)	1821 (74.4%)	1842 (75.8%)	9674 (77.2%)	0.264	0.003	0.132	0.007
Age [years]	62.2 ± 12.7	63.1 ± 12.8	62.8 ± 12.9	61.9 ± 12.6	0.439	< 0.001	0.001	< 0.001
LVEF [%]	51.2 ± 10.9	50.5 ± 11.1	51.5 ± 10.8	51.2 ± 10.9	0.381	< 0.001	< 0.001	< 0.001
BMI [kg/m^2]	24.1 ± 3.2	23.8 ± 3.2	23.9 ± 3.3	24.2 ± 3.2	< 0.001	< 0.001	< 0.001	< 0.001
SBP [mmHg]	12.7 ± 27.7	122.7 ± 26.1	125.6 ± 28.5	129.0 ± 27.8	< 0.001	< 0.001	< 0.001	< 0.001
DBP [mmHg]	78.5 ± 16.8	76.0 ± 16.4	77.3 ± 16.9	79.2 ± 16.8	0.009	< 0.001	< 0.001	< 0.001
Cardiogenic shock	972 (5.6%)	162 (6.6%)	163 (6.7%)	647 (5.2%)	0.903	0.004	0.002	0.001
CPR on admission	561 (3.2%)	135 (5.5%)	67 (2.8%)	359 (2.9%)	< 0.001	< 0.001	0.770	< 0.001
Primary PCI	16121 (92.6%)	2256 (92.2%)	2188 (90.0%)	16677 (93.2%)	0.008	0.077	< 0.001	< 0.001
Hypertension	7974 (45.8%)	987 (40.3%)	1129 (46.4%)	5858 (46.7%)	< 0.001	< 0.001	0.792	< 0.001
Diabetes mellitus	4179 (24.0%)	583 (23.8%)	639 (26.3%)	2957 (23.6%)	0.046	0.810	0.004	0.017
Dyslipidemia	1832 (10.5%)	281 (11.5%)	172 (7.1%)	1379 (11.0%)	< 0.001	0.491	< 0.001	< 0.001
Previous MI	472 (2.7%)	79 (3.2%)	60 (2.5%)	333 (2.7%)	0.111	0.114	0.595	0.206
Previous PCI	726 (4.2%)	117 (4.8%)	93 (3.8%)	516 (4.1%)	0.101	0.136	0.506	0.214
Previous CABG	54 (0.3%)	13 (0.5%)	3 (0.1%)	38 (0.3%)	0.013	0.077	0.121	0.036
Previous CVA	887 (5.1%)	113 (4.6%)	130 (5.3%)	644 (5.1%)	0.240	0.281	0.669	0.465
Previous heart failure	121 (0.7%)	21 (0.9%)	30 (1.2%)	70 (0.6%)	0.208	0.081	< 0.001	0.001
Current smokers	8381 (48.1%)	1146 (46.8%)	1160 (47.7%)	6075 (48.5%)	0.527	0.135	0.500	0.297
CK-MB [mg/dL]	175.6 ± 238.9	190.0 ± 2736	184.1 ± 3100	171.2 ± 214.5	0.482	0.001	0.051	0.001
Troponin-I [ng/mL]	64.3 ± 260.2	76.7 ± 619.7	58.3 ± 88.7	63.1 ± 140.3	0.192	0.333	0.046	0.010
Serum glucose [mg/dL]	172.1 ± 74.3	173.1 ± 76.4	176.5 ± 77.1	171.0 ± 73.3	0.128	0.207	0.001	0.013
Hemoglobin A1c (ng/dL)	6.6 ± 2.0	6.6 ± 2.2	6.8 ± 2.9	6.5 ± 1.8	0.178	0.293	0.022	0.020
NT-proBNP [pg/mL]	1515.8 ± 5292.7	2325.2 ± 7028.4	1789.9 ± 4633.6	1324.0 ± 3638.3	0.109	0.002	< 0.001	< 0.001
Hs-CRP [mg/dL]	10.8 ± 60.9	9.8 ± 46.7	11.4 ± 80.4	10.9 ± 58.7	0.467	0.385	0.804	0.523
Serum creatinine [mg/L]	1.06 ± 1.15	1.09 ± 1.54	1.12 ± 1.06	1.05 ± 1.07	0.424	0.281	0.006	< 0.001
Total cholesterol [mg/dL]	185.0 ± 44.2	183.5 ± 44.6	176.8 ± 44.4	186.8 ± 43.8	< 0.001	0.001	< 0.001	< 0.001
Triglyceride [mg/L]	133.8 ± 111.7	128.7 ± 100.9	126.0 ± 102.9	136.3 ± 115.2	0.361	0.001	< 0.001	< 0.001
HDL cholesterol [mg/L]	44.1 ± 18.5	43.5 ± 16.2	44.0 ± 14.0	44.3 ± 19.6	0.242	0.041	0.446	0.008
LDL cholesterol [mg/L]	117.4 ± 40.0	116.0 ± 38.2	110.0 ± 38.9	119.1 ± 40.4	< 0.001	< 0.001	< 0.001	< 0.001

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

Variables	Total (n = 17,414)	Group A Statin alone (n = 2448)	Group B RASI alone (n = 2431)	Group C Statin and RASI (n = 12535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
Discharge medications:								
ASA	17278 (99.2%)	2405 (98.2%)	2400 (98.7%)	12437 (99.5%)	0.169	< 0.001	< 0.001	< 0.001
Clopidogrel	15711 (90.2%)	2130 (87.0%)	2346 (96.5%)	11235 (89.6%)	< 0.001	< 0.001	< 0.001	< 0.001
Ticagrelor	931 (5.3%)	170 (6.9%)	26 (1.1%)	735 (5.9%)	< 0.001	0.040	< 0.001	< 0.001
Prasugrel	576 (3.3%)	112 (4.6%)	22 (0.9%)	442 (3.5%)	< 0.001	0.012	< 0.001	< 0.001
Cilostazole	4267 (24.5%)	584 (23.9%)	604 (24.8%)	3079 (24.6%)	0.421	0.457	0.767	0.693
BB	14594 (83.8%)	1657 (67.7%)	2064 (84.9%)	10873 (86.7%)	< 0.001	< 0.001	0.015	< 0.001
CCB	827 (4.7%)	161 (6.6%)	117 (4.8%)	549 (4.4%)	0.008	< 0.001	0.343	< 0.001
Infarct-related artery:								
LM	149 (0.9%)	23 (0.9%)	14 (0.6%)	112 (0.9%)	0.143	0.825	0.117	0.265
LAD	9035 (51.9%)	1207 (49.3%)	1279 (52.6%)	6549 (52.2%)	0.021	0.008	0.741	0.021
LCx	1621 (9.3%)	242 (9.9%)	237 (9.7%)	1142 (9.1%)	0.873	0.226	0.319	0.349
RCA	6598 (37.9%)	976 (39.9%)	898 (36.9%)	4724 (37.7%)	0.035	0.042	0.486	0.073
Treated vessel:								
LM	258 (1.5%)	32 (1.3%)	29 (1.2%)	197 (1.6%)	0.719	0.329	0.161	0.273
LAD	10229 (58.7%)	1371 (56.0%)	1416 (58.2%)	7442 (59.4%)	0.113	0.002	0.303	0.007
LCx	2829 (16.2%)	399 (16.3%)	392 (16.1%)	2038 (16.3%)	0.869	0.960	0.870	0.984
RCA	7417 (42.6%)	1078 (44.0%)	1014 (41.7%)	5325 (42.5%)	0.101	0.155	0.482	0.232
ACC/AHA lesion type:								
Type B1	2508 (14.4%)	358 (14.6%)	405 (16.7%)	1745 (13.9%)	0.050	0.360	< 0.001	0.002
Type B2	5060 (29.1%)	615 (25.1%)	684 (28.1%)	3761 (30.0%)	0.017	< 0.001	0.065	< 0.001
Type C	8193 (47.0%)	1232 (50.3%)	1032 (42.5%)	5929 (47.3%)	< 0.001	0.006	< 0.001	< 0.001
Extent of CAD:								
1-vessel	9078 (52.1%)	1287 (52.6%)	1220 (50.2%)	6571 (52.4%)	0.095	0.890	0.043	0.116
2-vessel	5201(29.9%)	753 (30.8%)	737 (30.3%)	3711 (29.6%)	0.737	0.253	0.482	0.455
≥ 3-vessel	3135 (18.0%)	408 (16.7%)	474 (19.5%)	2253 (18.0%)	0.010	0.122	0.075	0.036
IVUS	2397 (13.8%)	371 (15.2%)	278 (11.4%)	1748 (13.9%)	< 0.001	0.116	0.001	< 0.001
OCT	29 (0.2%)	2 (0.1%)	2 (0.1%)	25 (0.2%)	0.994	0.298	0.213	0.233
FFR	104 (0.6%)	16 (0.7%)	2 (0.1%)	86 (0.7%)	0.001	0.858	< 0.001	0.002

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

Variables	Total (n = 17,414)	Group A Statin alone (n = 2448)	Group B RASI alone (n = 2431)	Group C Statin and RASI (n = 12535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
Types of stent:								
BMS	1127 (6.5%)	105 (4.3%)	185 (7.6%)	837 (6.7%)	< 0.001	< 0.001	0.095	< 0.001
SES	2865 (16.5%)	376 (15.4%)	558 (23.0%)	1931 (15.4%)	< 0.001	0.955	< 0.001	< 0.001
PES	2446 (14.0%)	313 (12.8%)	466 (19.2%)	1667 (13.3%)	< 0.001	0.493	< 0.001	< 0.001
ZES	3869 (22.2%)	585 (23.9%)	486 (20.0%)	2798 (22.3%)	0.001	0.088	0.011	0.004
EES	4754 (27.3%)	693 (28.3%)	480 (19.7%)	3581 (28.6%)	< 0.001	0.795	< 0.001	< 0.001
BES	1343 (7.7%)	203 (8.3%)	100 (4.1%)	1040 (8.3%)	< 0.001	0.994	< 0.001	< 0.001
Stent diameter [mm]	3.20 ± 0.42	3.18 ± 0.44	3.20 ± 0.42	3.20 ± 0.42	0.044	0.008	0.956	0.007
Stent length [mm]	25.9 ± 9.0	26.1 ± 9.4	24.8 ± 7.0	26.1 ± 9.2	< 0.001	0.973	< 0.001	0.011
Number of stent	1.40 ± 0.72	1.40 ± 0.71	1.38 ± 0.70	1.41 ± 0.73	0.511	0.430	0.100	0.222

Values are means ± standard deviation or numbers and percentages. The p value for continuous data was obtained from the analysis of variance or the Jonckheere-Terpstra test. The p value for categorical data was obtained from the chi-square or the Fisher's exact test. Group A — statin alone; Group B — RASI alone; Group C — both statin and RASI; 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 grafting; CVA — cerebrovascular accidents; CK-MB — creatinine 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; BB — beta-blockers; CCB — calcium channel blockers; LM — left main coronary artery; LAD — left anterior descending coronary artery; LCx — left circumflex coronary artery; RCA — right coronary artery; ACC/AHA — American College of Cardiology/American Heart Association; CAD — coronary artery disease; IVUS — intravascular ultrasound; OCT — optical coherence tomography; FFR — fractional flow reserve; BMS — bare-metal stents; SES — sirolimus-eluting stents; PES — paclitaxel-eluting stents; ZES — zotarolimus-eluting stents; EES — everolimus-eluting stents; BES — biolimus-eluting stents

Table 2. Cumulative clinical events at 2 years.

Variables	Total (n = 17,414)	Group A (n = 2448)	Group B (n = 2431)	Group C (n = 12,535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
MACEs	1262 (7.2%)	193 (7.9%)	214 (8.8%)	855 (6.8%)	0.246	0.059	0.001	0.001
All-cause death:	358 (2.1%)	67 (2.7%)	59 (2.4%)	232 (1.9%)	0.528	0.004	0.060	0.007
Cardiac death	248 (1.4%)	44 (1.8%)	39 (1.6%)	165 (1.3%)	0.602	0.063	0.262	0.133
Re-MI:	257 (1.5%)	44 (1.8%)	32 (1.3%)	181 (1.4%)	0.175	0.188	0.627	0.324
Any repeat revascularization:	737 (4.2%)	94 (3.8%)	136 (5.6%)	507 (4.0%)	0.004	0.637	0.001	0.001
TLR	246 (1.4%)	34 (1.4%)	52 (2.1%)	160 (1.3%)	0.046	0.653	0.001	0.004
TVR	426 (2.4%)	50 (2.0%)	82 (3.4%)	294 (2.3%)	0.004	0.360	0.003	0.004
Non-TVR	323 (1.9%)	44 (1.8%)	57 (2.3%)	222 (1.8%)	0.179	0.928	0.056	0.155

Values are means ± standard deviation or numbers and percentages. The p values for categorical data were obtained from chi-square or Fisher's exact test. Group A — statin alone; Group B — RASI alone; Group C — both statin and RASI; MACEs — major adverse cardiac events; Re-MI — recurrent myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization

Table 3. Hazard ratio for 2-year major clinical outcomes by Cox-proportional hazard ratio analysis.

	Hazard ratio (95% confidence interval), P		
	Group A vs. B	Group A vs. C	Group B vs. C
MACE:			
Unadjusted	1.057 (0.870–1.285), 0.574	1.187 (1.016–1.388), 0.031	1.256 (1.081–1.459), 0.003
Adjusted*	1.093 (0.822–1.454), 0.540	1.337 (1.064–1.679), 0.013	1.375 (1.149–1.646), 0.001
All-cause death:			
Unadjusted	1.185 (0.835–1.681), 0.343	1.506 (1.148–1.977), 0.003	1.275 (0.958–1.696), 0.096
Adjusted*	1.386 (0.803–2.390), 0.241	1.539 (1.014–2.336), 0.043	1.172 (0.767–1.793), 0.463
Cardiac death:			
Unadjusted	1.164 (0.756–1.792), 0.490	1.386 (0.994–1.933), 0.054	1.192 (0.841–1.690), 0.323
Adjusted*	1.125 (0.528–2.394), 0.768	1.090 (0.609–1.951), 0.772	1.244 (0.726–2.131), 0.426
Re-MI:			
Unadjusted	1.434 (0.910–2.262), 0.121	1.276 (0.918–1.774), 0.147	1.135 (0.779–1.652), 0.510
Adjusted	1.048 (0.528–2.081), 0.894	1.041 (0.637–1.699), 0.873	1.180 (0.725–1.921), 0.499
Any repeat revascularization:			
Unadjusted	1.377 (1.059–1.791), 0.017	1.024 (0.822–1.276), 0.831	1.345 (1.113–1.625), 0.002
Adjusted*	1.038 (0.712–1.513), 0.847	1.263 (0.926–1.722), 0.141	1.317 (1.031–1.681), 0.028
TLR:			
Unadjusted	1.450 (0.941–2.234), 0.092	1.119 (0.773–1.620), 0.119	1.624 (0.188–2.221), 0.002
Adjusted*	1.111 (0.618–1.998), 0.724	1.648 (0.999–2.717), 0.050	1.754 (0.193–2.580), 0.004
TVR:			
Unadjusted	1.555 (1.094–2.210), 0.014	1.116 (0.827–1.506), 0.474	1.391 (1.089–1.777), 0.008
Adjusted*	1.184 (0.736–1.905), 0.487	1.286 (0.857–1.930), 0.224	1.539 (1.138–2.082), 0.005
Non-TVR:			
Unadjusted	1.230 (0.830–1.823), 0.302	1.004 (0.755–1.442), 0.796	1.284 (0.960–1.718), 0.092
Adjusted*	1.067 (0.578–1.968), 0.836	1.166 (0.721–1.886), 0.531	1.074 (0.717–1.610), 0.729

*Adjusted model was included age, gender (men), LVEF, BMI, SBP, DBP, CPR on admission, primary PCI, hypertension, DM, dyslipidemia, N-proBNP, serum creatinine, total cholesterol, triglyceride, LDL-cholesterol, ASA, clopidogrel, ticagrelor, prasugrel, BB, CCB, ACC/AHA lesion type B2 and C, IVUS, BMS, SES, PES, EES, BES. Abbreviations — see Table 1

of statin and has additive or synergistic effects on endothelial dysfunction, inflammation, and lipid profiles [17–19]. Furthermore, the statin plus RASI combination reduced cardiovascular events more than statin alone and to a greater extent than RASI therapy alone [18, 20]. As expected, additional beneficial effects of the statin and RASI combination therapy were observed in reducing MACEs compared to that achieved with monotherapy alone in this study. Previous studies have shown that both the statin and the RASI could reduce the death rate and revascularization rate in STEMI patients [21–23]. Additionally, the relative superiority between these two abilities, according to the drugs, was suspected in this study. Figure 2B shows the Kaplan-Meier curve of all-cause death among the three groups. The cumulative incidence of all-cause death in group A was continuously higher than that in group C during the 2-year follow-up period. However, the cumulative incidence of all-cause death between group B and group C was statistically insignificant. In contrast, the cumulative incidence of total revascularization in group B was continuously higher than that in group C (Fig. 2D). The cumulative incidence between group A and group C was insignificantly different. The Kaplan-Meier curve of TLR (Fig. 2E) and TVR (Fig. 2F) also showed similar patterns among the three groups. Regarding the results of this study, it was cautiously supposed that the possibility that RASI was more likely related with mortality reduction rather than revascularization reduction, and statin was more likely related with repeat revascularization reduction rather than mortality reduction in these STEMI patients after successful stent implantation. In this study, independent predictors for MACEs at 2 years were decreased LVEF (< 50%), DM, multivessel disease, cardiogenic shock, and CPR on admission (Table 4). Therefore, in these situations, the combination therapy of statin and RASI might be helpful in reducing MACEs.

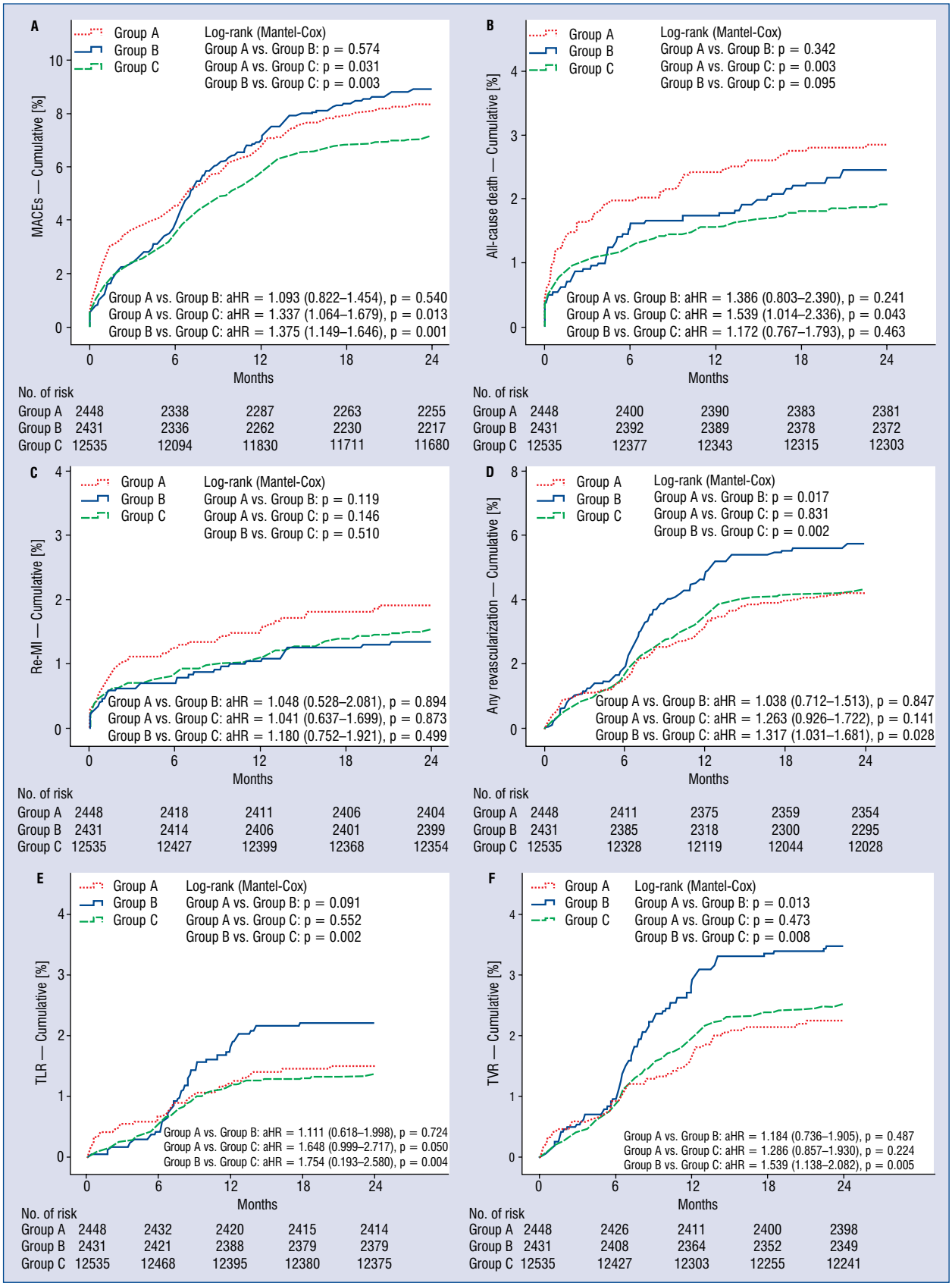

Figure 2. Kaplan-Meier curved analysis for major adverse cardiac events (MACEs; **A**), all-cause death (**B**), recurrent myocardial infarction (Re-MI; **C**), any repeat revascularization (**D**), target lesion revascularization (TLR; **E**), and target vessel revascularization (TVR; **F**) during a 2-year follow-up perioad d; aHR — adjusted hazard ratio.

Table 4. Multivariate Cox-proportional regression analysis for independent predictor of MACEs.

Variables	Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P
Groups				
A vs. B	1.057 (0.870–1.285)	0.574	1.063 (0.870–1.298)	0.550
A vs. C	1.187 (1.016–1.388)	0.031	1.208 (1.037–1.408)	0.019
B vs. C	1.256 (1.081–1.459)	0.003	1.217 (1.044–1.418)	0.012
Age, ≥ 65 years	1.042 (1.013–1.071)	0.004	1.034 (0.990–1.081)	0.129
Gender, men	1.208 (1.066–1.367)	0.003	1.038 (0.899–1.199)	0.281
LVEF, < 50%	1.248 (1.118–1.394)	< 0.001	1.146 (1.019–1.289)	0.023
Hypertension	1.211 (1.084–1.352)	0.001	1.082 (0.961–1.217)	0.192
Diabetes mellitus	1.481 (1.315–1.667)	< 0.001	1.342 (1.187–1.518)	< 0.001
Dyslipidemia	1.066 (0.894–1.271)	0.478	1.027 (0.857–1.232)	0.772
Previous MI	1.373 (1.020–1.849)	0.037	1.206 (0.890–1.633)	0.227
Multi-vessel disease	1.897 (1.691–2.129)	< 0.001	1.774 (1.570–2.005)	< 0.001
Current smokers	1.145 (1.025–1.279)	0.017	1.043 (0.869–1.251)	0.842
Cardiogenic shock	1.301 (1.049–1.614)	0.017	1.135 (0.908–1.419)	0.043
CPR on admission	2.385 (1.941–2.972)	< 0.001	2.240 (1.784–2.813)	< 0.001
ACC/AHA type B2/C	1.027 (0.902–1.168)	0.689	1.028 (0.900–1.174)	0.701
Stent diameter, < 3.0 mm	1.242 (1.093–1.412)	0.001	1.116 (0.978–1.273)	0.103
Stent length, ≥ 28 mm	1.149 (1.027–1.285)	0.015	1.048 (0.934–1.176)	0.421
LAD — IRA	1.002 (0.898–1.119)	0.967	1.072 (0.881–1.305)	0.541
LAD — treated vessel	1.158 (1.034–1.298)	0.011	1.190 (0.978–1.447)	0.083
IVUS	1.117 (0.956–1.307)	0.164	1.083 (0.923–1.271)	0.329

HR — hazard ratio; CI — confidence interval; IRA — infarct-related artery; other abbreviations — see Table 1

Unlike previous studies [18, 24], the present study population was composed of solely STEMI patients. While some previous studies [25, 26] were conducted before the widespread use of statin and dual antiplatelet agents, diverse kinds of statins and newly developed antiplatelet agents were used in this study. More than 50 high-volume University or community hospitals with facilities for primary PCI and onsite cardiac surgery in South Korea participated in this study. Therefore, this comparative study might provide meaningful information to interventional cardiologists regarding the importance of a statin and RASI combination therapy rather than a monotherapy of each drug, and some different clinical outcome characteristics of the statin monotherapy and RASI monotherapy compared with a combination therapy in STEMI patients, after successful stent implantation during a 2-year follow-up period.

Limitations of the study

This study had several limitations. First, there may be some under-reporting and/or missed data due to limitations of registry data. Second, this study was based on medications at discharge, and this registry data did not include a full detailed data concerning the starting times of statin and RASI therapy, change of prescription doses, long-term adherence, and discontinuation during the follow-up period; these factors might, therefore, act as substantial bias in this study. Third, the achievement of target blood cholesterol level (i.e., LDL-C) was a critical prognostic parameter after statin therapy during the follow-up period. However, the follow-up results could not presented for these lipid profiles due to a limitation of the registry data, which might act as a bias. Fourth, because this study reflectsa multicenter "real-world" clinical practice, diverse kinds and doses of statins and RASI were prescribed; all of which could not be adjusted during statistical analysis, and might be another limitation of this study. Fifth, the selection of either monotherapy or combination therapy of statin and RASI after PCI was left to physician preferences; which might act as selection bias. Sixth, a multivariate analysis was done to strengthen the present results; variables

not included in this registry may have affected the study outcomes.

Conclusions

In conclusion, a statin and RASI combination therapy significantly reduced the cumulative incidence of MACEs compared with a monotherapy of these drugs. Moreover, this combination therapy showed a reduced all-cause death rate compared with statin monotherapy, and a decreased repeat revascularization rate compared with RASI monotherapy.

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