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Impacts of renin–angiotensin system inhibitors on two-year clinical outcomes in diabetic and dyslipidemic acute myocardial infarction patients after a successful percutaneous coronary intervention using newer-generation drug-eluting stents

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Abstract

This study investigated the impacts of renin–angiotensin system inhibitors (RASIs) on 2-year clinical outcomes in diabetes and dyslipidemic acute myocardial infarction (AMI) patients after a successful percutaneous coronary intervention (PCI) using newer-generation drug-eluting stents (DESs).

A total of 16,997 AMI patients were enrolled, and divided into four groups based on the presence or absence of diabetes and dyslipidemia as follows: diabetes –/dyslipidemia –(group A, 11,132 patients), diabetes +/dyslipidemia – (group B, 3,860 patients), diabetes –/dyslipidemia + (group C, 1,328 patients), and diabetes +/dyslipidemia + (group D, 677 patients). The clinical endpoint was the occurrence of major adverse cardiac events (MACEs), the composite of total death, recurrent myocardial infarction (re-MI), and any repeat revascularization, including target lesion revascularization (TLR), target vessel revascularization (TVR), and non-target vessel revascularization (non-TVR).

After RASIs therapy, the cumulative incidences of MACEs (adjusted hazard ratio [aHR], 1.330; 95% confidence interval [CI], 1.022–1.732; $P = .034$), any repeat revascularization (aHR, 1.584; 95% CI, 1.092–2.298; $P = .015$), TLR, and TVR were significantly higher in group B than group C. However, the cumulative incidences of all-cause death, cardiac death, re-MI, and non-TVR were similar in groups B and C.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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In this study, under the newer-generation DESs era, repeat revascularization rate reduction benefit of RASIs therapy in diabetic AMI patients was lesser than that in dyslipidemic AMI patients. However, larger randomized controlled studies are needed to confirm these results in the future.

Abbreviations: AMI = acute myocardial infarction, CAG = coronary angiography, DES = drug-eluting stents, KAMIR = Korea Acute Myocardial Infarction Registry, MACEs = major adverse cardiac events, NSTEMI = non-ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

Keywords: diabetes, dyslipidemia, renin–angiotensin system

1. Introduction

Current guidelines recommend the use of angiotensin converting enzyme inhibitors (ACEIs) in patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI).[1–4] Additionally, angiotensin II type I (AT1) receptor blockers (ARBs) are ACEIs alternatives for STEMI and NSTEMI patients intolerant to ACEIs.[1–4] Renin–angiotensin system inhibitors (RASIs) have been proven to ameliorate cardiovascular events via improving endothelial function, cardiovascular remodeling, and atherosclerosis progression.[5,6] Additionally, possible mechanisms for the beneficial role of RASIs in diabetes progression prevention have been suggested,[7,8] and according to these studies, the main roles of RASIs in diabetes patients were associated with insulin sensitivity improvement or insulin secretion enhancement.[9,10] Recent meta-analysis reported that ACEIs and ARBs have comparable effects on major cardiovascular and renal outcomes (odds ratio, 1.10; 95% confidence interval [CI], 0.90–1.40).[11] Anigotensin II has been shown to indirectly induce differentiation of adipocyte precursors into mature fat cell.[12] Angiotensin II further increases lipogenesis and trigyceride content in the adipocytes by increasing fatty acid synthase and glycerol-3-phosphate dehydrogenase.[13] Some previous studies[14–16] have suggested that overexpressed AT1 receptors, as well as an increased affinity of such receptors for circulating and locally released angiotensin II, are present in hypercholesterolemia patients, and that ACEIs and ARBs inhibit the production of angiotensin II or their binding to AT1 receptors in these patients. However, published data that focuses on the comparative beneficial effects of RASIs in diabetes and dyslipidemia, especially in the acute myocardial infarction (AMI) milieu, is limited. Hence, this study, which aimed at investigating the impacts of RASIs on the 2-year clinical outcomes in diabetic and dyslipidemic AMI patients who had undergone a successful percutaneous coronary intervention (PCI) using newer-generation drug-eluting stents (DESs), was conducted.

2. Methods

2.1. Study population

The data used for this study was obtained from the Korea AMI Registry (KAMIR).[17] A total of 45,843 AMI patients who underwent successful PCI between November 2005 and June 2015 were eligible. Patients with the following characteristics were excluded: deployed bare-metal stents (n=2,099, 4.6%), deployed first-generation DESs (n=9,967, 21.7%), RASIs were not prescribed (n=4,346, 9.5%), incomplete laboratory results (n=10,050, 21.9%), and lost to follow-up (n=2,384, 5.2%). Finally, a total of 16,997 AMI patients who had undergone successful PCI with the use of newer-generation DESs, including zotarolimus-eluting stent, everolimus-eluting stent, and biolimus-eluting stent were enrolled. Among them, 11,132 (65.5%) were classified as group A (diabetes and dyslipidemia negative group), 3,860 (22.7%) as group B (diabetes only group, i.e., diabetes positive and dyslipidemia negative), 1,328 (7.8%) as group C (dyslipidemia only group, i.e., diabetes negative and dyslipidemia positive), and the remaining 677 (4.0%) as group D (diabetes and dyslipidemia positive) (Fig. 1). The KAMIR is a nationwide, prospective, observational on-line registry in South Korea, established in November 2005. All data collection was done using a web-based case report form at each participating center and details of the registry can be found at the KAMIR website (http://www.kamir.or.kr). This 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 the 16,997 included patients provided written informed consent prior to enrollment, and also completed a 2-year clinical follow-up by face-to-face interviews, phone calls, or chart review.

2.2. Percutaneous coronary intervention and medical treatments

In accordance with general guidelines,[18] coronary angiography and PCI were performed via the femoral or the radial artery, and before PCI, all the patients were administered loading doses of aspirin (200–300 mg) and clopidogrel (300–600 mg) when available, or alternatively ticagrelor (180 mg) or prasugrel (60 mg). The total duration of dual antiplatelet therapy (DAPT), which is a combination of aspirin (100 mg/day) with clopidogrel (75 mg/day), ticagrelor (90 mg twice a day), or prasugrel (5–10 mg/day), was recommended for more than 12 months to patients who had undergone PCI. The administration of triple antiplatelet therapy (TAPT; 100 mg of cilostazol administered twice a day in addition to DAPT), was at the discretion of the individual operators.

2.3. Study definitions and endpoints

In this study, the presence of dyslipidemia was defined as a positive dyslipidemia history, regardless of the presence or absence of the administration of lipid-lowering agents, or the administration of lipid-lowering agents, regardless of the presence or absence of a dyslipidemia history.[19] In addition, patients who neither had a history of dyslipidemia nor received lipid-lowering agents, but had laboratory results that were

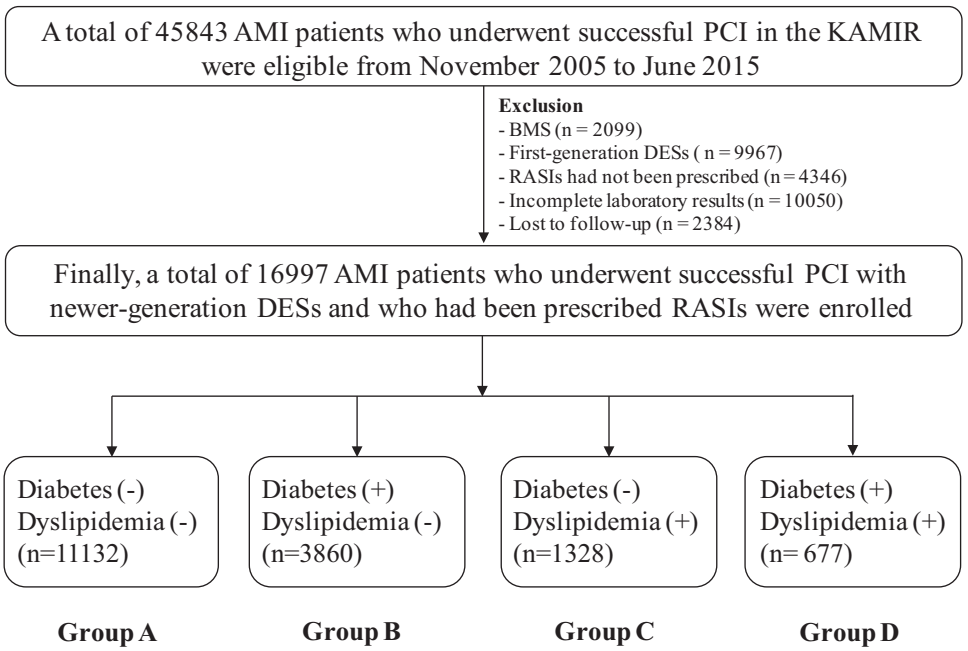

Figure 1. Flow chart.

compatible with the dyslipidemia diagnostic criteria, were considered dyslipidemic in this study. Given that the definition of dyslipidemia varies based on the guidelines used, as well as on ethnicity,[20–22] dyslipidemia was defined in accordance with the Asian guideline,[23] that is, patients whose 12 h fasting serum low-density lipoprotein cholesterol concentrations were ≥140 mg/dL, high-density lipoprotein–cholesterol concentrations were <40 mg/dL, and triglyceride (TG) concentrations were ≥150 mg/dL. Diabetes was defined by treatment with glucose-lowering medication, ≥6.5% glycosylated hemoglobin, fasting serum glucose ≥126 mg/dL, or non-fasting serum glucose ≥200 mg/dL.[24] If the admission electrocardiogram of patients who had ongoing chest pain showed ST-segment elevations 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 to V3 and/or ≥1 mm (0.1 mV) in other contiguous chest leads or limb leads, or new onset left bundle branch block, then the patients were considered to be suffering from ST-segment elevation myocardial infarction (STEMI).[2] If they showed absence of persistent ST-segment elevation with increased cardiac biomarkers, and the clinical context was appropriate, the patients were considered as NSTEMI.[4] The major clinical endpoint was the occurrence of major adverse cardiac events (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 (CD) or non-cardiac death. Re-MI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal MI imaging findings, 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, during the follow-up period.[2] TLR was defined as the revascularization of the target lesion due to restenosis or re-occlusion within the stent or 5 mm in and adjacent to the distal or proximal segment. TVR was defined as the revascularization of the target vessel or any segment of the coronary artery containing the target lesion. Non-TVR was defined as the revascularization of any segment of the non-target coronary artery.

2.4. Statistical analysis

All statistical analyses were performed using SPSS software v20 (IBM; Armonk, NY). Differences in the continuous variables of the four groups were evaluated using analysis of variance (ANOVA) or the Jonckheere–Terpstra test, and a post hoc analysis was performed using the Hochberg test or Dunnett-T3 test; data are presented as means ± standard deviation (SD). For discrete variables, differences between two of the four groups were analyzed using the χ^2 test or Fisher's exact test, as deemed appropriate, and data are presented as counts and percentages. During the multivariable Cox proportional hazards regression analysis, the confounding baseline covariates were selected if they were significantly different ($P < .001$) among the four groups, or had predictive values, which are listed as follows: age, gender (men), left ventricular ejection fraction (LVEF), body mass index, diastolic blood pressure, STEMI, NSTEMI, hypertension, previous myocardial infarction, previous PCI, previous coronary artery bypass graft, previous cerebrovascular accident, previous heart failure, current smoker, peak CK-MB, serum glucose, hemoglobin A1c, N-terminal pro-brain natriuretic peptide, serum creatinine, total cholesterol, triglyceride, low-density lipoprotein–cholesterol, high-density lipoprotein–cholesterol, cilostazole, calcium channel blocker, lipid lowering agent, left anterior descending coronary artery—infarct-related artery, right coronary artery-treated vessel, 1-vessel disease, 3-vessel disease, multi-vessel disease, stent diameter, stent length, and number of stents. Various clinical outcomes were estimated using the Kaplan–Meier curve analysis, and group differences were compared using the log-rank test. Two-tailed $P < .05$ was considered statistically significant.

Table 1

Baseline clinical, laboratory, angiographic, and procedural characteristics.

Variables	Total (n = 16,997)	Group A diabetes (−)/dyslipidemia (−) (n = 11,132)	Group B diabetes (+)/dyslipidemia (−) (n = 3,860)	Group C diabetes (−)/dyslipidemia (+) (n = 1,328)	Group D diabetes (+)/dyslipidemia (+) (n = 677)	*P*
Men, n (%)	12,693 (74.7)	8597 (77.2)	2602 (67.4)	1018 (76.7)	476 (70.3)	<.001
Age (years)	62.9 ± 12.4	62.3 ± 12.8	65.7 ± 11.0	60.0 ± 11.9	63.3 ± 11.2	<.001
LVEF (%)	52.7 ± 10.9	53.0 ± 10.6	51.3 ± 11.6	53.9 ± 10.4	52.4 ± 11.2	<.001
<50%, n (%)	6233 (36.7)	3998 (35.9)	1579 (40.9)	415 (31.3)	241 (35.6)	<.001
BMI (kg/m^2)	24.2 ± 3.2	24.1 ± 3.2	24.2 ± 3.1	24.9 ± 3.3	24.8 ± 3.0	<.001
Systolic blood pressure (mm Hg)	132.0 ± 27.5	131.8 ± 27.3	131.4 ± 28.0	133.7 ± 30.0	135.0 ± 28.1	.002
Diastolic blood pressure (mm Hg)	80.1 ± 16.3	80.5 ± 16.5	78.5 ± 15.8	81.2 ± 16.2	79.4 ± 16.2	<.001
Cardiogenic shock, n (%)	627 (3.7)	384 (3.4)	167 (4.3)	51 (3.8)	25 (3.7)	.098
STEMI, n (%)	9479 (55.8)	6495 (58.3)	1950 (50.5)	725 (54.6)	309 (45.6)	<.001
Primary PCI, n (%)	9084 (95.8)	6244 (96.1)	1863 (95.5)	686 (94.6)	291 (94.2)	.082
NSTEMI, n (%)	7518 (44.2)	4637 (41.7)	1910 (49.5)	603 (45.4)	368 (54.8)	<.001
CPR on admission, n (%)	490 (2.9)	322 (2.9)	111 (2.9)	37 (2.8)	20 (3.0)	.996
Hypertension, n (%)	8471 (49.8)	4673 (42.0)	2547 (66.0)	772 (58.1)	479 (70.8)	<.001
Previous MI, n (%)	635 (3.7)	281 (2.5)	212 (5.5)	83 (6.3)	59 (8.7)	<.001
Previous PCI, n (%)	1027 (6.0)	465 (4.2)	311 (8.1)	141 (10.6)	110 (16.2)	<.001
Previous CABG, n (%)	74 (0.4)	25 (0.2)	35 (0.9)	8 (0.6)	6 (0.9)	<.001
Previous CVA, n (%)	995 (5.9)	532 (4.8)	314 (8.1)	82 (6.2)	67 (9.9)	<.001
Previous heart failure, n (%)	174 (1.0)	77 (0.7)	62 (1.6)	19 (1.4)	16 (2.4)	<.001
Current smokers, n (%)	7389 (43.5)	5216 (46.9)	1336 (34.6)	583 (43.9)	254 (37.5)	<.001
Peak CK-MB (mg/dL)	122.9 ± 197.8	134.9 ± 202.6	95.2 ± 199.0	122.8 ± 176.6	83.2 ± 110.1	<.001
Peak troponin-I (ng/mL)	43.4 ± 117.0	44.2 ± 104.0	42.5 ± 139.8	44.7 ± 159.1	32.4 ± 56.9	.140
Serum glucose (mg/dL)	166.6 ± 76.1	146.1 ± 52.9	227.0 ± 99.6	142.3 ± 48.7	210.0 ± 87.1	<.001
Hemoglobin A1c (ng/dL)	6.58 ± 2.12	6.0 ± 1.92	7.76 ± 2.23	5.95 ± 0.92	7.67 ± 1.58	<.001
NT-ProBNP (pg/mL)	1689.4 ± 4497.8	1295.8 ± 3581.4	2937.2 ± 6366.5	899.6 ± 2766.2	2348.3 ± 5817.4	<.001
High-sensitivity CRP (mg/dL)	8.85 ± 49.4	8.84 ± 51.0	9.37 ± 45.6	6.69 ± 45.1	10.6 ± 52.2	.020
Serum creatinine (mg/L)	1.07 ± 1.02	1.00 ± 0.93	1.22 ± 1.22	1.02 ± 1.01	1.20 ± 1.12	<.001
Total cholesterol (mg/dL)	184.2 ± 45.2	187.2 ± 42.5	174.2 ± 47.5	194.2 ± 50.4	171.4 ± 51.7	<.001
Triglyceride (mg/L)	137.4 ± 113.3	133.1 ± 111.2	140.3 ± 118.4	155.0 ± 111.8	156.1 ± 115.2	<.001
HDL cholesterol (mg/L)	43.5 ± 15.1	44.1 ± 15.8	41.6 ± 13.3	44.1 ± 14.8	41.4 ± 11.2	<.001
LDL cholesterol (mg/L)	116.2 ± 40.5	119.3 ± 41.0	107.0 ± 36.4	123.2 ± 42.9	101.4 ± 38.2	<.001
Discharge medications, n (%)						
Aspirin, n (%)	16',900 (99.4)	11,063 (99.4)	3838 (99.4)	1324 (99.7)	675 (99.7)	.380
Clopidogrel, n (%)	14,689 (86.4)	9587 (86.1)	3358 (87.0)	1138 (85.7)	606 (89.5)	.045
Ticagrelor, n (%)	1354 (8.0)	910 (8.2)	290 (7.5)	114 (8.6)	40 (5.9)	.096
Prasugrel, n (%)	789 (4.6)	538 (4.8)	159 (4.1)	68 (5.1)	24 (3.5)	.120
Cilostazole, n (%)	3292 (19.4)	2048 (18.4)	846 (21.9)	255 (19.2)	143 (21.1)	<.001
BB, n (%)	14,972 (88.1)	9801 (88.0)	3383 (87.6)	1181 (88.9)	607 (89.7)	.355
CCB, n (%)	986 (5.8)	537 (4.8)	273 (7.1)	95 (7.2)	81 (12.0)	<.001
Lipid lowering agents, n (%)	14,908 (87.7)	9787 (87.9)	3310 (85.8)	1215 (91.5)	596 (88.0)	<.001
Diabetes management						
Diet, n (%)			379 (9.8)		57 (8.4)	
Oral agent, n (%)			3147 (81.5)		561 (82.9)	
Insulin, n (%)			267 (6.9)		52 (7.7)	
Untreated, n (%)			67 (0.2)		7 (0.1)	
Infarct-related artery (IRA)						
Left main, n (%)	297 (1.7)	181 (1.6)	77 (2.0)	21 (1.6)	18 (2.7)	.121
Left anterior descending, n (%)	8161 (48.0)	5472 (49.2)	1783 (46.2)	616 (46.4)	290 (42.8)	<.001
Left circumflex, n (%)	2849 (16.8)	1857 (16.7)	632 (16.4)	234 (17.6)	126 (18.6)	.418
Right coronary artery, n (%)	5690 (33.5)	3622 (32.5)	1368 (35.4)	457 (34.4)	243 (35.9)	.004
Treated vessel						
Left main, n (%)	471 (2.8)	285 (2.6)	125 (3.2)	38 (2.9)	23 (3.4)	.112
Left anterior descending, n (%)	9277 (57.5)	6394 (57.4)	2267 (58.7)	743 (55.9)	373 (55.1)	.150
Left circumflex, n (%)	4416 (26.0)	2798 (25.1)	1060 (27.5)	372 (28.0)	186 (27.5)	.007
Right coronary artery, n (%)	6780 (39.9)	4283 (38.5)	1665 (43.1)	544 (41.0)	288 (42.5)	<.001
ACC/AHA lesion type						
Type B1, n (%)	2420 (14.2)	1642 (14.8)	499 (12.9)	184 (13.9)	95 (14.0)	.046
Type B2, n (%)	5704 (33.6)	3738 (33.6)	1353 (35.1)	408 (30.7)	205 (30.3)	.008
Type C, n (%)	7350 (43.2)	4737 (42.6)	1697 (44.0)	616 (46.4)	300 (44.3)	.035
Type B2/C, n (%)	13,054 (76.8)	8475 (76.2)	3050 (79.0)	1024 (77.1)	505 (74.6)	.002

(*continued*)

Table 1

(continued).

Variables	Total (n = 16,997)	Group A diabetes (−)/dyslipidemia (−) (n = 11,132)	Group B diabetes (+)/dyslipidemia (−) (n = 3,860)	Group C diabetes (−)/dyslipidemia (+) (n = 1,328)	Group D diabetes (+)/dyslipidemia (+) (n = 677)	P
Extent of coronary artery disease						
1-vessel, n (%)	8488 (49.9)	5912 (53.1)	1623 (42.0)	674 (50.8)	279 (41.2)	<.001
2-vessel, n (%)	5260 (30.9)	3364 (30.2)	1280 (33.2)	410 (30.9)	206 (30.4)	.008
≥3-vessel, n (%)	3249 (19.1)	1856 (16.7)	957 (24.8)	244 (18.4)	192 (28.4)	<.001
MVD, n (%)	8509 (50.1)	5220 (46.9)	2237 (58.0)	654 (49.2)	398 (58.8)	<.001
IVUS, n (%)	3254 (19.1)	2132 (19.2)	684 (17.7)	286 (21.5)	152 (22.5)	.002
OCT, n (%)	103 (0.6)	70 (0.6)	18 (0.5)	8 (0.6)	7 (1.0)	.333
FFR, n (%)	182 (1.1)	130 (1.2)	40 (1.0)	8 (0.6)	4 (0.6)	.154
Types of stent						
ZES, n (%)	5654 (33.3)	3688 (33.1)	1251 (32.4)	495 (37.3)	220 (32.5)	.011
EES, n (%)	7696 (45.3)	4947 (44.4)	1829 (47.4)	600 (45.2)	320 (47.3)	.011
BES, n (%)	2208 (13.0)	1518 (13.6)	466 (12.1)	138 (10.4)	86 (12.7)	.002
Stent diameter (mm)	3.15 ± 0.43	3.17 ± 0.43	3.10 ± 0.42	3.15 ± 0.42	3.09 ± 0.44	<.001
Stent length (mm)	26.6 ± 11.1	26.3 ± 10.8	27.5 ± 12.0	26.7 ± 10.6	26.9 ± 10.7	<.001
Number of stent	1.47 ± 0.78	1.43 ± 0.75	1.56 ± 0.83	1.51 ± 0.83	1.52 ± 0.82	<.001

Values are means ± SD or numbers and percentages. The *P* value for continuous data was obtained from the analysis of variance or the Jonckheere–Terpstra test, and post hoc analysis was done using the Hochberg test or Dunnett-T3 test. The *P* value for categorical data was obtained from the chi-square or the Fisher's exact test.

ACC/AHA = American College of Cardiology/American Heart Association, BB = beta-blockers, BES = biolimus-eluting stents, BMI = body mass index, CABG = coronary artery bypass graft, CCB = calcium channel blockers, CK-MB = creatine kinase myocardial band, CRP = C-reactive protein, CVA = cerebrovascular accident, EES = everolimus-eluting stents, FFR = fractional flow reserve, HDL = high-density lipoprotein, IVUS = intravascular ultrasound, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MI = myocardial infarction, MVD = multivessel disease, NSTEMI = non-STEMI, NT-ProBNP = N-terminal pro-brain natriuretic peptide, OCT = optical coherence tomography, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, ZES = zotarolimus-eluting stents.

3. Results

3.1. Baseline clinical, angiographic and procedural characteristics

Table 1 shows the baseline, laboratory, angiographic, and procedural characteristics of the study population, which had a mean age of 62.9 ± 12.4 years, and a mean left ventricular ejection fraction (LVEF) value of 52.7 ± 10.9%. The number of men among the enrolled patients was highest in group A (77.2%). The observed number of patients showing cardiovascular risk factors such as hypertension, ≥3-vessel disease, and previous MI, PCI, cerebrovascular accident, and heart failure, were highest in group D. Blood glucose, hemoglobin A1c, N-terminal pro-brain natriuretic peptide, and creatinine levels were highest in group B. In group C, blood total cholesterol and low-density lipoprotein–cholesterol levels, as well as the prescription rate of lipid lowering agents were the highest. However, the number of STEMI cases, current smokers, and the mean serum peak CK-MB value were highest in group A. The left main coronary artery and right coronary artery were the most frequent infarct-related artery in group D, while left anterior descending coronary artery was the most frequent infarct-related artery in group A. The numbers of American College of Cardiology/American Heart Association (ACC/AHA) type B2 and ACC/AHA type B2/C lesions were highest in group B, while the number of ACC/AHA type C lesions was highest in group C. During the PCI, the use of intravascular ultrasound was most frequent in group D. The diameter of the deployed stent was largest in group A, while its total length was longest in group B.

3.2. Clinical outcomes

The cumulative frequencies of MACEs, all-cause death, CD, any repeat revascularization, TLR, and TVR over the 2-year follow-up period are summarized in Table 2. Before adjustment, the cumulative incidences of MACEs, CD, any repeat revascularization, TLR, and TVR were highest in group D, while the cumulative incidence of all-cause death was highest in group B. However, the cumulative incidence of non-TVR in the different

Table 2

Cumulative clinical events at 2 years.

Variables	Total (n = 1,6997)	Group A diabetes (−)/dyslipidemia (−) (n = 11,132)	Group B diabetes (+)/dyslipidemia (−) (n = 3,860)	Group C diabetes (−)/dyslipidemia (+) (n = 1,328)	Group D diabetes (+)/dyslipidemia (+) (n = 677)	P
MACEs	1118 (6.6)	633 (5.7)	342 (8.9)	78 (5.9)	65 (9.6)	<.001
All-cause death, n (%)	399 (2.3)	213 (1.9)	140 (3.6)	26 (2.0)	20 (3.0)	<.001
Cardiac death	278 (1.6)	153 (1.4)	85 (2.2)	23 (1.7)	17 (2.5)	.001
Re-MI, n (%)	262 (1.5)	146 (1.3)	79 (2.0)	17 (1.3)	20 (3.0)	<.001
Any repeat revascularization	569 (3.3)	326 (2.9)	170 (4.4)	40 (3.0)	33 (4.9)	<.001
TLR	157 (0.9)	83 (0.7)	55 (1.4)	7 (0.5)	12 (1.8)	<.001
TVR	340 (2.0)	188 (1.7)	106 (2.7)	23 (1.7)	23 (3.4)	<.001
Non-TVR	239 (1.4)	145 (1.3)	66 (1.7)	18 (1.4)	10 (1.5)	.323

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.

	Hazard ratio (95% CI) unadjusted	*P*	Event rates at 2 years* (%)	Log-rank	Hazard ratio (95% CI) adjusted†	*P*
MACEs						
Group A vs			6.1			
Group B	1.579 (1.385–1.801)	<.001	9.6	<0.001	1.355 (1.176–1.562)	<.001
Group C	1.032 (0.816–1.306)	.790	6.3	0.790	1.034 (0.806–1.325)	.795
Group D	1.730 (1.340–2.233)	<.001	10.4	<0.001	1.499 (1.142–1.969)	.004
Group B vs group C	1.531 (1.197–1.958)	.001		0.001	1.330 (1.022–1.732)	.034
Group B vs group D	1.096 (0.841–1.429)	.496		0.496	1.104 (0.838–1.455)	.483
Group C vs group D	1.675 (1.205–2.328)	.002		0.002	1.429 (1.003–2.035)	.048
All-cause death						
Group A vs			2.0			
Group B	1.907 (1.540–2.360)	<.001	3.9	<0.001	1.476 (1.169–1.864)	.001
Group C	1.024 (0.682–1.539)	.908	2.0	0.908	1.198 (0.772–1.859)	.421
Group D	1.555 (0.984–2.460)	.059	3.1	0.057	1.481 (0.905–2.423)	.118
Group B vs group C	1.862 (1.225–2.830)	.004		0.003	1.248 (0.792–1.968)	.340
Group B vs group D	1.224 (0.766–1.956)	.397		0.396	1.137 (0.698–1.853)	.607
Group C vs group D	1.515 (0.846–2.714)	.162		0.158	1.194 (0.628–2.270)	.588
Cardiac death						
Group A vs			1.4			
Group B	1.610 (1.235–2.098)	<.001	2.4	<0.001	1.185 (0.889–1.578)	.247
Group C	1.261 (0.814–1.955)	.299	1.8	0.298	1.330 (0.825–2.144)	.242
Group D	1.838 (1.114–3.034)	.017	2.7	0.015	1.692 (0.997–2.871)	.051
Group B vs group C	1.276 (0.805–2.023)	.299		0.298	1.130 (0.681–1.875)	.637
Group B vs group D	1.143 (0.679–1.924)	.615		0.614	1.201 (0.703–2.051)	.502
Group C vs group D	1.455 (0.777–2.724)	.241		0.237	1.280 (0.648–2.528)	.478
Re-MI						
Group A vs			1.4			
Group B	1.574 (1.197–2.069)	.001	2.3	0.001	1.277 (0.954–1.710)	.100
Group C	1.024 (0.620–1.692)	.927	1.4	0.927	1.091 (0.654–1.820)	.739
Group D	2.295 (1.438–3.662)	<.001	3.3	<0.001	1.685 (1.017–2.792)	.043
Group B vs group C	1.614 (0.956–2.726)	.073		0.071	1.367 (0.796–2.349)	.257
Group B vs group D	1.459 (0.893–2.382)	.132		0.129	1.373 (0.822–2.293)	.226
Group C vs group D	2.350 (1.231–4.486)	.010		0.008	1.739 (0.878–3.445)	.112
Any repeat revascularization						
Group A vs			3.2			
Group B	1.529 (1.270–1.840)	<.001	4.9	<0.001	1.434 (1.176–1.749)	<.001
Group C	1.027 (0.740–1.426)	.874	3.4	0.874	1.091 (0.768–1.549)	.627
Group D	1.699 (1.188–2.430)	.004	5.4	0.003	1.457 (0.999–2.125)	.051
Group B vs group C	1.490 (1.056–2.102)	.023		0.022	1.584 (1.092–2.298)	.015
Group B vs group D	1.111 (0.765–1.614)	.579		0.579	1.021 (0.695–1.501)	.915
Group C vs group D	1.656 (1.044–2.625)	.032		0.030	1.555 (0.946–2.555)	.082
TLR						
Group A vs.			0.8			
Group B	1.933 (1.375–2.717)	<.001	1.6	<0.001	1.855 (1.282–2.685)	.001
Group C	1.416 (0.655–3.062)	.377	0.6	0.374	1.355 (0.618–2.969)	.448
Group D	2.415 (1.319–4.425)	.004	2.0	0.003	2.019 (1.057–3.856)	.033
Group B vs group C	2.739 (1.247–6.015)	.012		0.009	1.593 (1.072–2.341)	.043
Group B vs group D	1.248 (0.669–2.331)	.486		0.485	1.197 (0.632–2.269)	.581
Group C vs group D	3.421 (1.347–8.690)	.010		0.006	1.635 (0.995–2.978)	.039
TVR						
Group A vs.			1.9			
Group B	1.648 (1.299–2.091)	< .001	3.1	<0.001	1.556 (1.205–2.010)	.001
Group C	1.025 (0.665–1.580)	.911	1.9	0.911	1.099 (0.694–1.742)	.686
Group D	2.050 (1.330–3.161)	.001	3.8	0.001	1.651 (1.038–2.628)	.038
Group B vs group C	1.610 (1.026–2.528)	.038		0.037	1.670 (1.029–2.711)	.034
Group B vs group D	1.242 (0.792–1.950)	.345		0.344	1.118 (0.699–1.787)	.642
Group C vs group D	1.999 (1.122–3.563)	.119		0.117	1.780 (0.955–3.317)	.069
Non-TVR						
Group A vs.			1.4			
Group B	1.328 (0.992–1.776)	.056	1.9	0.056	1.235 (0.907–1.683)	.180
Group C	1.040 (0.637–1.698)	.875	1.5	0.875	1.084 (0.642–1.832)	.762
Group D	1.147 (0.604–2.177)	.675	1.6	0.675	1.072 (0.556–2.068)	.835
Group B vs group C	1.275 (0.757–2.147)	.361		0.360	1.369 (0.777–2.411)	.277
Group B vs group D	1.154 (0.593–2.244)	.673		0.672	1.181 (0.601–2.322)	.630
Group C vs group D	1.105 (0.510–2.395)	.799		0.799	1.126 (0.494–2.566)	.778

BMI = body mass index, CABG = coronary artery bypass graft, CCB = calcium channel blocker, CI = confidence interval, CK-MB = creatine kinase myocardial band, CVA = cerebrovascular accidents, DBP = diastolic blood pressure, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, HF = heart failure, IRA = infarct-related artery, LAD = left anterior descending coronary artery, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, MACEs = major adverse cardiac event, MI = myocardial infarction, NSTEMI = non-STEMI, NT-ProBNP = N-terminal pro-brain natriuretic peptide, PCI = percutaneous coronary intervention, RCA = right coronary artery, Re-MI = recurrent myocardial infarction, STEMI = ST-segment elevation myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

* Event rates at 2 years were calculated by Kaplan–Meyer analysis.

† Adjusted model includes age, gender (men), LVEF, BMI, DBP, STEMI, NSTEMI, hypertension, previous MI, previous PCI, previous CABG, previous CVA, previous HF, current smoker, peak CK-MB, serum glucose, HbA1c, NT-ProBNP, serum creatinine, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, cilostazole, CCB, lipid lowering agent, LAD-IRA, RCA-treated vessel, 1-vessel disease, ≥ 3-vessel disease, stent diameter, stent length, number of stent.

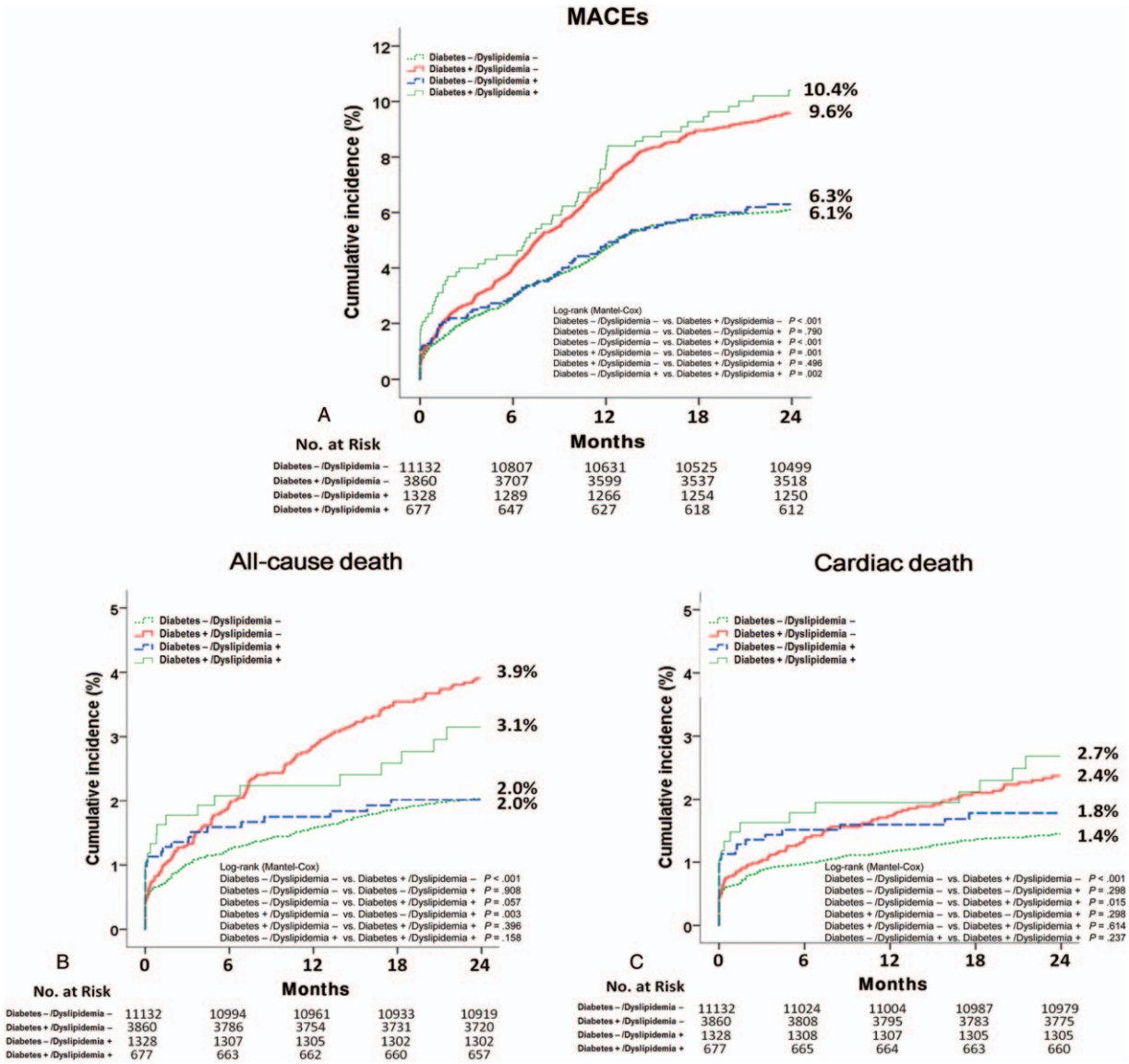

Figure 2. Kaplan–Meier curved analysis for MACEs (A), all-cause death (B), cardiac death (C), re-MI (D), any repeat revascularization (E), TLR (F), and TVR (G).

groups was similar before and after adjustment. Furthermore, after adjustment, group B (9.6% vs 6.1%, Log-rank $P < .001$; adjusted hazard ratio [aHR], 1.355; 95% CI, 1.176–1.562; $P < .001$, Table 3 and Fig. 2) and D (10.4% vs 6.1%, Log-rank $P < .001$; aHR, 1.499; 95% CI, 1.142–1.969; $P = .004$) showed higher cumulative incidences of MACEs compared with group A. Additionally, the cumulative incidences of all-cause death (aHR, 1.476; 95% CI, 1.169–1.846; $P = .001$), any repeat revascularization (aHR, 1.434; 95% CI, 1.176–1.749; $P < .001$), TLR (aHR, 1.855; 95% CI, 1.282–2.685; $P = .001$), and TVR (aHR, 1.556; 95% CI, 1.205–2.010; $P = .001$) in group B were significantly higher than those in group A (Table 3 and Fig. 2). Furthermore, the cumulative incidences of Re-MI (aHR, 1.685; 95% CI, 1.107–2.792; $P = .043$), TLR (aHR, 2.019; 95% CI, 1.057–3.856; $P = .033$), and TVR (aHR, 1.651; 95% CI, 1.038–2.628; $P = .038$) in group D were significantly higher than those in group A (Table 3). Comparing the MACEs cumulative incidences of group B and C showed that it was significantly higher in group B than in group C (aHR, 1.330; 95% CI, 1.022–1.732; $P = .034$). After adjustment, even though the cumulative incidences of all-cause death, CD, and re-MI were similar for group B and C, the cumulative incidences of any repeat revascularization (aHR, 1.584; 95% CI, 1.092–2.298; $P = .015$), TLR (aHR, 1.593; 95% CI, 1.072–2.341; $P = .043$), and TVR (aHR, 1.670; 95% CI, 1.029–2.711; $P = .034$) were significantly higher in group B compared with group C. Figure 3 shows subgroup analysis for MACEs for groups B and C at 2 years. Regarding men, decreased LVEF (<50%), NSTEMI, regardless of presence or absence of hypertension, and the use of lipid lowering agents, RASIs showed more beneficial effect on reducing MACEs in the group C compared with the group B. Additionally, old age (≥65 years), decreased LVEF (<50%), hypertension, STEMI, cardiopulmonary resuscitation on admission, serum creatinine, multi-vessel disease, and the use of intravascular ultrasound were independent MACEs predictors (Table 4).

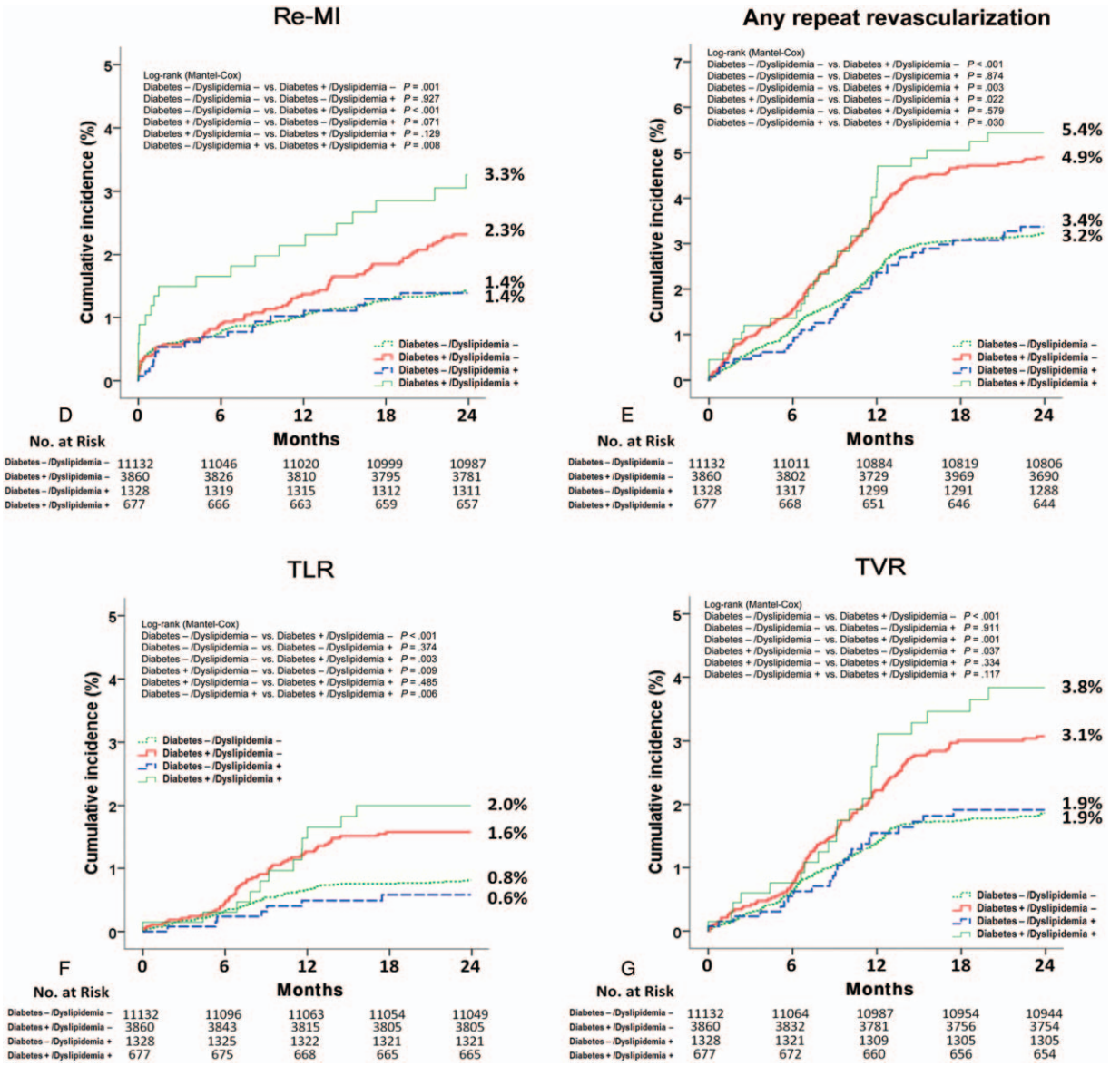

Figure 2. (Continued).

4. Discussion

The main findings of this study include:

1. post RASIs therapy, the cumulative incidences of MACEs, any repeat revascularization, TLR, and TVR were significantly higher in group B than group C;
2. the cumulative incidences of all-cause death, CD, re-MI, and non-TVR were similar in group B and C;
3. the cumulative incidences of MACEs, all-cause death, any repeat revascularization, TLR, and TVR in group B were significantly higher than those in group A;
4. the cumulative incidences of MACEs, re-MI, TLR, and TVR in group D were significantly higher than those in group A; and
5. old age (≥65 years), decreased LVEF (<50%), hypertension, STEMI, cardiopulmonary resuscitation on admission, serum creatinine, multi-vessel disease, and intravascular ultrasound use were independent MACEs predictors.

Kawasaki et al[25] demonstrated that ARBs improve diastolic dysfunction in diabetic patients, at least via the attenuation of myocardial fibrosis. Although dyslipidemia is a major determinant of long-term clinical outcomes in AMI patients, many recent studies have focused on high-dose statin therapy, rather than the important role of RASI.[26,27] The SMILE (Survival of Myocardial Infarction Long-term Evaluation) trial[28] and its post hoc analysis[29] demonstrated that compared with the placebo and normocholesterolemic group, the early treatment with zofenopril was more effective in reducing morbidity and mortality in AMI and hypercholesterolemia patients (relative risk reduction = 43%, $P = .034$). Despite these previous studies that have proven the beneficial effects of RASIs in diabetes and dyslipidemia, there exist limited comparative data on the long-term major clinical outcomes of RASI therapy in diabetic and dyslipidemic AMI patients. Thus, the main objective of this study was to compare diabetes and dyslipidemia. Characteristically, our results dem-

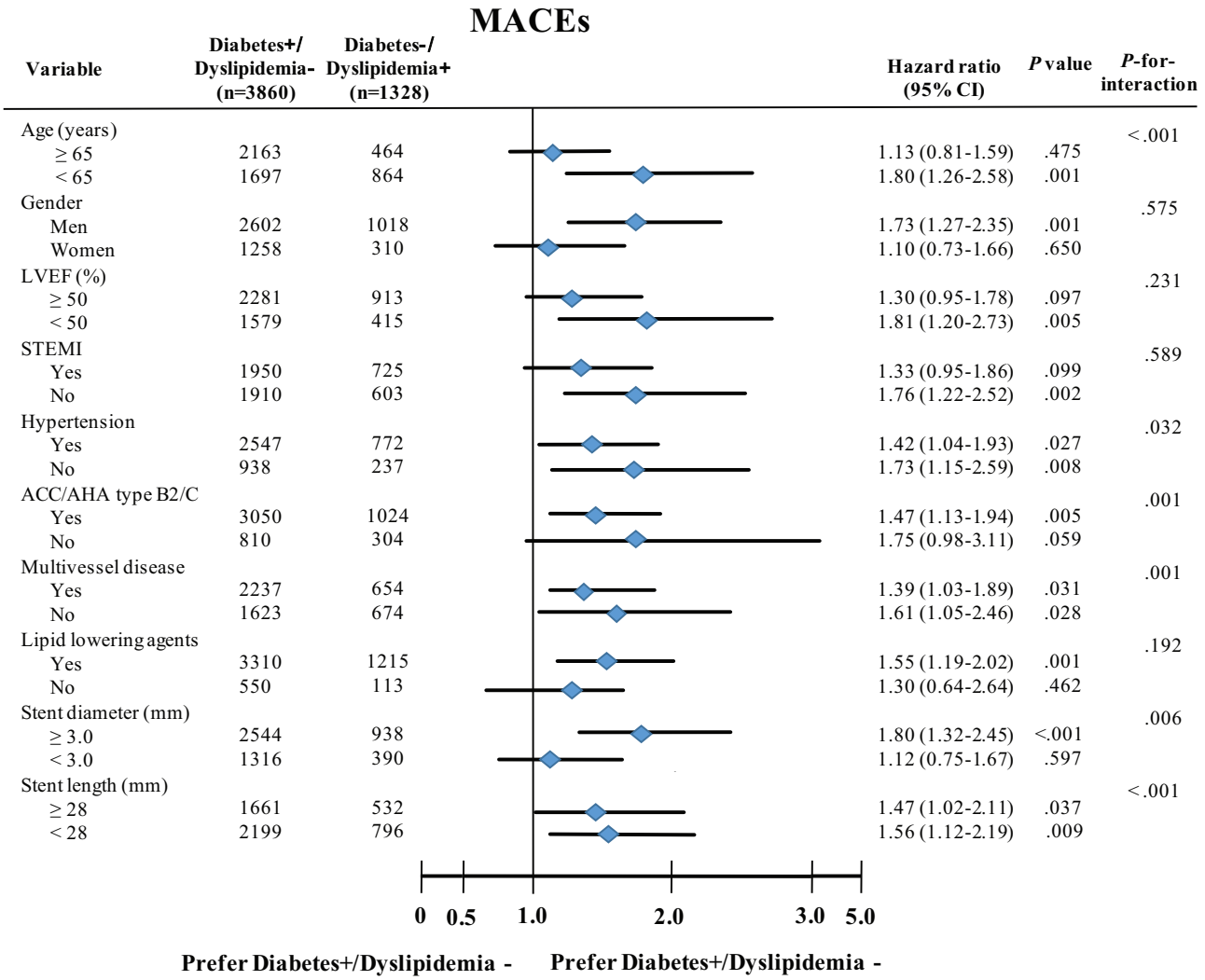

Figure 3. Subgroup analysis for MACEs between the group B and the group C at 2 years.

onstrated that the cumulative incidences of MACEs (aHR, 1.330; 95% CI, 1.022–1.732; $P=.034$), any repeat revascularization (aHR, 1.584; 95% CI, 1.092–2.298; $P=.015$), TLR (aHR, 1.593; 95% CI, 1.072–2.341; $P=.043$), and TVR (aHR, 1.670; 95% CI, 1.029–2.711; $P=.034$) were significantly higher in group B compared with group C in AMI patients who underwent successful PCI with newer-generation DESs after RASIs therapy. In Tables 2 and 3, the higher cumulative incidence of MACEs in groups B (aHR, 1.355; 95% CI, 1.176–1.562; $P<.001$) and D (aHR, 1.499; 95% CI, 1.142–1.969; $P=.004$) in comparison with group A was expected. The potential mortality reduction capability of RASIs in AMI patients had been reported in previous studies,[6,30,31] and in the present study, RASIs therapy-reduced mortality rates were similar in groups B and C (all-cause death [aHR, 1.248; 95% CI, 0.792–1.968; $P=.340$] and CD [aHR, 1.130; 95% CI, 0.681–1.875; $P=.637$]) indicating that the results of this study are compatible with those of previous studies.[6,30,31] Compared with non-diabetic patients, diabetes appeared to increase the risk of TLR, TVR, and MACEs after PCI, conferred a poorer clinical outcome, and was associated with plaque growth and vascular instability.[32–34] The characteristics of lesions in diabetic patients are known to be longer, and present in smaller vessels compared with non-diabetic patients.[35] In the present study, the number of multi-vessel disease cases (58.0% vs 49.2%, $P<.001$) and the total length of the deployed stents (27.5 ± 12.0 mm vs 26.7 ± 10.6 mm, $P=.018$) were significantly higher in group B than group C. Thus, these baseline lesion characteristics may have contributed to the higher cumulative incidences of any repeat revascularization, TLR, and TVR observed in group B as compared to group C, after multivariable analysis. Additionally, in this study, we tried to get the results to reflect current "real-world" practice, which involves the use of newer-generation DESs. Hence, patients who received bare-metal stents or first-generation DESs were excluded. Diabetes patients treated with first-generation DESs reportedly showed higher rates of repeat revascularization compared with non-diabetes patients (TLR [6.8% vs 4.6%, $P=.0002$] and TVR [9.4% vs 6.2%, $P<.0001$]).[32] In the newer-generation DESs era, the rate of recurrence of any repeat revascularization was also significantly higher in diabetes patients (20.2% vs 12.7%, $P=.007$).[36] Although the precise mechanisms of the observed restenosis are not fully understood, some suggested mechanisms include abnormal vascular wall response to the implanted stent and smooth muscle cell proliferation.[37] In addition, Mizia-Stec

Table 4

Independent predictors for MACE at 2 years.

Variables	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (≥65 years)	1.523 (1.353–1.713)	<.001	1.257 (1.103–1.431)	.001
Men	1.297 (1.141–1.473)	<.001	1.094 (0.952–1.257)	.207
LVEF (≤50%)	1.344 (1.194–1.513)	<.001	1.291 (1.141–1.462)	<.001
Hypertension	1.347 (1.197–1.516)	<.001	1.194 (1.054–1.353)	.005
STEMI	1.222 (1.087–1.374)	.001	1.175 (1.037–1.332)	.012
Cardiogenic shock	1.367 (1.043–1.793)	.024	1.206 (0.910–1.599)	.193
CPR on admission	2.302 (1.798–2.947)	<.001	2.207 (1.711–2.846)	<.001
Serum creatinine	1.089 (1.054–1.125)	<.001	1.081 (1.044–1.121)	<.001
ACC/AHA type B2/C lesion	1.172 (1.016–1.352)	.029	1.077 (0.928–1.249)	.329
MVD	1.796 (1.589–2.030)	<.001	1.609 (1.406–1.843)	<.001
Clopidogrel	1.078 (0.889–1.306)	.445	1.053 (0.865–1.283)	.607
Cilostazole	0.944 (0.814–1.094)	.442	0.913 (0.785–1.063)	.242
LAD (IRA)	0.994 (0.884–1.118)	.921	1.073 (0.925–1.245)	.352
RCA (treated vessel)	1.116 (0.991–1.256)	.070	1.058 (0.906–1.236)	.477
IVUS	1.319 (1.148–1.516)	<.001	1.296 (1.123–1.494)	<.001
Stent diameter (≥3mm)	1.149 (1.013–1.304)	.031	1.073 (0.941–1.224)	.291
Stent length (≥28mm)	1.276 (1.134–1.436)	<.001	1.132 (1.000–1.280)	.050
Number of stent	1.186 (1.110–1.268)	<.001	1.009 (0.932–1.091)	.829

ACC/AHA =American College of Cardiology/American Heart Association, CPR = cardiopulmonary resuscitation, HR = hazard ratio, IRA = infarct-related artery, IVUS = intravascular ultrasound, LAD = left anterior descending coronary artery, LVEF = left ventricular ejection fraction, MACE = major adverse cardiac events, MVD = multivessel disease, RCA = right coronary artery, STEMI = ST-segment elevation myocardial infarction.

et al[38] suggested that in-stent coronary restenosis is associated with impaired endothelial-dependent vasodilation rather than the stent type used. Endothelial dysfunction is an important cardiovascular risk factor, given that it is a critical factor in the genesis of vascular disease.[39] Dyslipidemia is another well-known factor, crucial for endothelial damage, and an important predictor of atherosclerosis development.[40] The causes of restenosis are complex, and include endothelial dysfunction, thrombosis, proliferation of smooth muscle cells, vascular remodeling, inflammatory reaction, and the release of various cytokines.[41] Unfortunately, due to the complexity of these causative factors involved in restenosis in diabetes and dyslipidemia, the main cause of the different revascularization rates in diabetes and dyslipidemia could not be narrowed down to any one specific factor, in the present study.

Despite these limitations, the results of this study may provide meaningful information that can help interventional cardiologists better understand the important roles of RASIs with respect to MACEs, any repeat revascularization, TLR, and TVR in diabetes mellitus and dyslipidemia in AMI patients who have undergone a successful PCI using newer-generation DESs.

The KAMIR is a nationwide, prospective, observational on-line registry in South Korea since November 2005. More than 50 high-volume University or community hospitals with facilities for primary PCI and onsite cardiac surgery participated in this study. Therefore, we believe the study population of this study is sufficiently large to provide meaningful results. Furthermore, the results of this comparative study may persuade interventional cardiologists of the different clinical impacts of RASIs between diabetes and dyslipidemia with respect to long-term follow-up in AMI patients after successful PCI with newer-generation DESs.

This study had some limitations. First, dyslipidemia was defined according to the Asian guidelines, including the guidelines of the Japan Atherosclerosis Society,[23] whereas this criterion may differ based on ethnicity or region. Second, there was the possibility of sample selection bias, given that the total numbers of diabetes and dyslipidemia patients in this study were relatively lower compared with those in a previous trial.[42] This selection bias may be related to the fact that many patients were excluded using the exclusion criteria, which included the deployment of first-generation DESs (n = 9,967, 21.7%) and incomplete laboratory results (n = 10,050, 21.9%). Additionally, in this registry cohort, the cumulative incidence of all-cause death was higher in group B than group D (3.6% vs 3.0%, $P = .381$, Table 2). Even though this difference was not statistically significant but numerically different (aHR, 1.137; 95% CI, 0.698–1.853; $P = .396$, Table 3), it is hard to explain the exact cause. It also may be associated with sample selection bias. Third, there may be some under-reporting and/or missed data because the study was a non-randomized study. Fourth, the study was based on medications at discharge, and this registry data did not include detailed or full data on the prescription doses, long-term adherence, discontinuation, and drug-related adverse events. Therefore, this might have been an important source of bias in this study. Fifth, the achievement of the target blood cholesterol level (i.e., low-density lipoprotein–cholesterol) was a very important prognostic parameter in diabetes or dyslipidemia patients during the follow-up period. However, in this KAMIR, the follow-up data was not provided. Therefore, this might have introduced a bias. Sixth, during the follow-up period, the patients enrolled in groups B or C could have been transferred to group D. However, this information could not be verified because of the limitations of the registry data; thus, this could also act as a bias. Seven, to strengthen the results of this study, multivariable analyses were performed; however, the variables that were not included in the data registry might have affected the study outcome. Last, rise in blood pressure is closely linked to an increase in measures of obesity, which, in turn, associated with an increase insulin resistance and worsening of an atherogenic lipid profile.[43] Therefore, arterial hypertension could influence our results. However, in this study, we were more focused on the comparative clinical outcomes between diabetes and dyslipide-

mia rather than arterial hypertension. This may be important limitation in this study.

To conclude, in this study, under the newer-generation DESs era, repeat revascularization rate reduction benefit of RASIs therapy in diabetic AMI patients was lesser than that in dyslipidemic AMI patients. However, larger randomized controlled studies are needed to confirm these results in the future.

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