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Impact of renin-angiotensin system inhibitors on long-term clinical outcomes in patients with acute myocardial infarction treated with successful percutaneous coronary intervention with drug-eluting stents: Comparison between STEMI and NSTEMI

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HIGHLIGHTS

- Current guidelines recommend renin-angiotensin system inhibitors (RASI) in AMI patients.
- The mortality reduction capability of RASI was more prominent in STEMI patients compared with NSTEMI patients.
- The impact of RASI on MACE, re-MI, total revascularization, TLR, TVR, non-TVR was similar between the two groups.

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Keywords:
Myocardial infarction
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Non-ST-Segment elevation myocardial infarction

ABSTRACT

Background and aims: We compared the clinical impact of renin-angiotensin system inhibitors (RASI) on long-term clinical outcomes between ST-segment elevation (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) after successful percutaneous coronary intervention (PCI) with drug eluting stents (DES) because of the paucity of published data.

Methods: A total of 24,960 acute myocardial infarction (AMI) patients who underwent PCI with DES and were prescribed the RASI were enrolled and divided into two groups, the STEMI group (n = 14,061) and the NSTEMI group (n = 10,899). The clinical endpoint was the occurrence of major adverse cardiac events (MACE) defined as all-cause death, cardiac death (CD), recurrent myocardial infarction (re-MI), total coronary revascularization (target lesion revascularization [TLR], target vessel revascularization [TVR], non-TVR) during 2 years.

Results: After propensity score-matched (PSM) analysis, two PSM groups (6762 pairs, n = 13,524, C-statistic = 0.682) were generated. All-cause death (hazard ratio [HR], 1.386; 95% confidence interval [CI], 1.114–1.725; $p = 0.003$) and CD (HR, 1.358; 95% CI, 1.041–1.770; $p = 0.024$) rates were significantly higher in NSTEMI patients. However, the incidence of MACE, re-MI, total revascularization, TLR, TVR, non-TVR was not significantly different between the two groups. In addition, old age (≥65years), decreased left ventricular ejection fraction (< 50%), hypertension, creatine kinase isoenzyme level, cardiogenic shock, cardiopulmonary resuscitation on admission, and PCI within 24 h were common significant independent risk factors of all-cause death and CD.

Conclusions: The mortality reduction capability of RASI was more prominent in the STEMI patients compared with the NSTEMI patients.

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1. Introduction

The current European and American guidelines [1,2] recommend the use of angiotensin converting enzyme inhibitors (ACEI) within the first 24 h of ST-segment elevation myocardial infarction (STEMI), especially in patients with heart failure (HF), left ventricular (LV) systolic dysfunction, diabetes, or an anterior infarction (Class IA). In case of non-STEMI (NSTEMI), ACEI are also recommended similar to STEMI (Class IA) [3,4]. Angiotensin receptor blockers (ARB) are an alternative to ACEI for those who are intolerant to ACEI regardless of the

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

Variables	Patients		*p* value	Propensity score-matched patients		*p* value
	STEMI (n = 6762)	NSTEMI(n = 10899)		STEMI (n = 6762)	NSTEMI(n = 6762)	
Age (years)	60.9 ± 12.5	64.0 ± 11.9	< 0.001	63.3 ± 12.4	63.1 ± 12.1	0.446
Men, n (%)	10821 (77.0)	7684 (70.5)	< 0.001	4952 (73.2)	4958 (73.3)	0.907
LVEF (%)	51.5 ± 10.6	54.5 ± 10.9	< 0.001	53.4 ± 10.7	53.3 ± 10.9	0.403
< 50%, n (%)	5681 (40.4)	3013 (27.6)	< 0.001	2188 (32.4)	2139 (31.6)	0.366
BMI (kg/m^2)	24.1 ± 3.1	24.2 ± 3.1	0.169	24.1 ± 3.1	24.2 ± 3.0	0.441
SBP (mmHg)	128.9 ± 27.6	135.3 ± 26.1	< 0.001	132.6 ± 27.9	131.9 ± 25.1	0.104
DBP (mmHg)	79.0 ± 16.7	81.1 ± 15.1	< 0.001	80.2 ± 16.4	79.9 ± 15.1	0.172
Killip class III, n (%)	657 (4.7)	154 (1.4)	< 0.001	160 (2.4)	133 (2.0)	0.111
Cardiogenic shock, n (%)	721 (5.1)	183 (1.7)	< 0.001	154 (2.3)	132 (2.0)	0.189
CPR on admission, n (%)	452 (3.2)	153 (1.4)	< 0.001	135 (2.0)	114 (1.7)	0.179
Hypertension, n (%)	6486 (46.1)	5915 (54.3)	< 0.001	3425 (50.7)	3360 (49.7)	0.264
Diabetes mellitus, n (%)	3412 (24.3)	3327 (30.5)	< 0.001	1932 (28.6)	1887 (27.9)	0.390
Dyslipidemia, n (%)	1439 (10.2)	1418 (13.0)	< 0.001	751 (11.1)	769 (11.4)	0.624
Previous MI, n (%)	479 (3.4)	587 (5.4)	< 0.001	304 (4.5)	271 (4.0)	0.160
Previous PCI, n (%)	754 (5.4)	972 (8.9)	< 0.001	493 (7.3)	450 (6.7)	0.147
Previous CABG, n (%)	41 (0.3)	93 (0.9)	< 0.001	30 (0.4)	34 (0.5)	0.616
Previous HF, n (%)	116 (1.8)	178 (1.6)	< 0.001	67 (1.0)	76 (1.1)	0.449
Previous CVA, n (%)	718 (5.1)	784 (7.2)	< 0.001	428 (6.3)	406 (6.0)	0.432
Current smokers, n (%)	6750 (48.0)	4106 (37.7)	< 0.001	2828 (41.8)	2864 (42.4)	0.531
CK-MB (mg/dL)	172.2 ± 254.6	63.7 ± 140.2	< 0.001	90.9 ± 245.3	81.8 ± 171.5	0.012
Troponin-I (ng/mL)	57.4 ± 109.5	22.9 ± 43.1	< 0.001	32.8 ± 111.8	28.7 ± 52.0	0.005
NT-ProBNP (pg/mL)	1579.7 ± 4199.5	2207.4 ± 4720.2	< 0.001	1818.1 ± 3712.7	1864.0 ± 3545.3	0.468
hs-CRP (mg/dL)	9.8 ± 51.0	11.0 ± 50.4	0.076	10.5 ± 57.6	10.6 ± 46.0	0.880
Serum creatinine (mg/L)	1.06 ± 1.00	1.14 ± 1.35	< 0.001	1.09 ± 1.16	1.07 ± 1.05	0.216
Total cholesterol (mg/dL)	184.5 ± 43.8	182.7 ± 44.8	0.002	183.9 ± 44.5	183.7 ± 44.9	0.783
Triglyceride (mg/L)	134.5 ± 109.2	135.4 ± 106.3	0.497	135.3 ± 114.6	134.1 ± 109.6	0.523
HDL cholesterol (mg/L)	44.3 ± 18.3	43.6 ± 14.8	< 0.001	44.1 ± 19.9	44.0 ± 16.3	0.732
LDL cholesterol (mg/L)	116.7 ± 38.8	115.7 ± 39.3	0.030	116.6 ± 41.0	116.1 ± 39.8	0.487
Discharge medications						
Aspirin, n (%)	13963 (99.3)	10810 (99.2)	0.277	6707 (99.2)	6713 (99.3)	0.555
Clopidogrel, n (%)	12660 (90.0)	9737 (89.3)	0.072	6091 (90.1)	6102 (90.2)	0.751
Ticagrelor, n (%)	776 (5.5)	659 (6.0)	0.076	367 (5.4)	359 (5.3)	0.760
Prasugrel, n (%)	458 (3.3)	361 (3.3)	0.809	212 (3.1)	214 (3.2)	0.922
Cilostazole, n (%)	3517 (25.0)	2652 (24.3)	0.217	1644 (24.3)	1704 (25.2)	0.232
Beta-blockers, n (%)	12120 (88.6)	9288 (85.2)	0.028	5797 (85.7)	5766 (85.3)	0.449
CCB, n (%)	670 (4.8)	1010 (9.3)	< 0.001	449 (6.6)	448 (6.6)	0.972
Lipid lowering agents	11827 (84.1)	9298 (85.3)	0.009	5760 (85.2)	5728 (84.7)	0.442
Angiographic & procedural characteristics						
PCI within 24 h	13293 (94.5)	8591 (78.8)	< 0.001	5159 (76.3)	5105 (75.5)	0.278
Infarct-related artery						
Left main, n (%)	152 (1.1)	266 (2.4)	< 0.001	108 (1.6)	103 (1.5)	0.729
Left anterior descending, n (%)	7432 (52.9)	4617 (42.4)	< 0.001	3316 (49.0)	3298 (48.8)	0.757
Left circumflex, n (%)	1315 (9.4)	2990 (27.4)	< 0.001	1065 (15.7)	1029 (15.2)	0.392
Right coronary artery, n (%)	5149 (36.6)	3004 (27.6)	< 0.001	2268 (33.5)	2316 (34.3)	0.383
Treated vessel						
Left main, n (%)	242 (1.7)	417 (3.8)	< 0.001	172 (2.5)	175 (2.6)	0.870
Left anterior descending, n (%)	8371 (59.5)	5958 (54.7)	< 0.001	3934 (58.2)	3900 (57.7)	0.554
Left circumflex, n (%)	2263 (16.1)	4259 (29.1)	< 0.001	1707 (25.2)	1642 (24.3)	0.195
Right coronary artery, n (%)	5794 (30.0)	3941 (36.2)	< 0.001	2678 (39.6)	2747 (40.6)	0.226
ACC/AHA lesion type						
Type B1, n (%)	2064 (14.7)	1711 (15.7)	0.026	1074 (15.9)	1067 (15.8)	0.869
Type B2, n (%)	4299 (30.6)	4010 (36.8)	< 0.001	2273 (33.6)	2240 (33.1)	0.547
Type C, n (%)	6618 (47.1)	4400 (40.4)	< 0.001	2904 (42.9)	2937 (43.4)	0.567
Extent of coronary artery disease						
1-vessel, n (%)	7402 (52.6)	4819 (44.2)	< 0.001	3269 (48.3)	3306 (48.9)	0.524
2-vessel, n (%)	4082 (29.0)	3589 (32.9)	< 0.001	2101 (31.1)	2065 (30.5)	0.503
≥3-vessel, n (%)	2518 (17.9)	2426 (22.3)	< 0.001	1364 (20.2)	1363 (20.2)	0.983
Multi-vessel disease, n (%)	6600 (46.9)	6015 (55.2)	< 0.001	3465 (51.2)	3428 (50.7)	0.630
Drug-eluting stents						
SES, n (%)	2394 (17.0)	1563 (14.3)	< 0.001	1063 (15.7)	1089 (16.1)	0.541
PES, n (%)	2070 (14.7)	1427 (13.1)	< 0.001	932 (13.8)	977 (14.4)	0.266
ZES, n (%)	3058 (21.7)	2188 (20.1)	0.001	1370 (20.3)	1359 (20.1)	0.814
EES, n (%)	3934 (28.0)	3460 (31.7)	< 0.001	2033 (30.1)	2013 (29.8)	0.707
BES, n (%)	1089 (7.1)	1100 (10.1)	< 0.001	609 (9.0)	574 (8.5)	0.287
Others, n (%)	1627 (11.6)	1312 (12.0)	0.256	828 (12.2)	812 (12.0)	0.673

(*continued on next page*)

Table 1 (*continued*)

Variables	Patients		*p* value	Propensity score-matched patients		*p* value
	STEMI (n = 6762)	NSTEMI(n = 10899)		STEMI (n = 6762)	NSTEMI(n = 6762)	
Stent diameter (mm)	3.19 ± 0.39	3.10 ± 0.39	< 0.001	3.13 ± 0.39	3.14 ± 0.40	0.130
Stent length (mm)	26.2 ± 8.6	26.7 ± 10.7	< 0.001	26.4 ± 9.2	26.3 ± 9.7	0.581
Number of stent	1.38 ± 0.71	1.56 ± 0.89	< 0.001	1.47 ± 0.79	1.47 ± 0.81	0.722

Values are mean ± SD or n (%). *p* value for continuous data from analysis of the unpaired *t*-test. *p* value for categorical data from chi-square test.
BB, beta-blockers; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass graft; CVA, cerebrovascular accidents; HF, heart failure; CK-MB, creatine kinase myocardial band; NT-ProBNP, N-terminal pro-brain natriuretic peptide; hs-CRP, high sensitivity-C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CCB, calcium channel blockers; ACC/AHA, American College of Cardiology/American Heart Association; SES, sirolimus-eluting stents, PES, paclitaxel-eluting stents; ZES, zotarolimus-eluting stents; EES, everolimus-eluting stents; BES, biolimus-eluting stents.

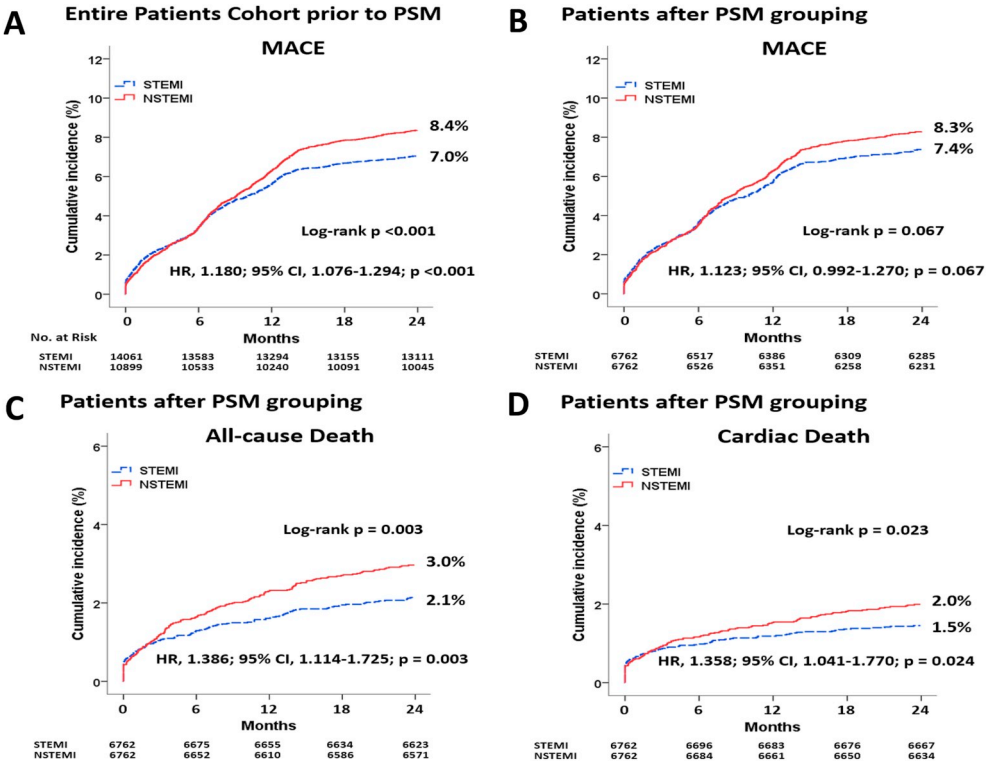

Fig. 1. Kaplan-Meier curve analysis for MACE, all-cause death, and cardiac death during 2 years.

conditions of STEMI or NSTEMI (Class IA or Class IB) [1–4]. Furthermore, current guidelines emphasize the importance of secondary prevention of acute myocardial infarction (AMI) to reduce recurrent ischemic events and prolong patient survival [1,3]. Although numerous studies demonstrated the beneficial role of ACEI or ARB in AMI patients [5–8], there are very limited data concerning the impact of renin-angiotensin system inhibitors (RASI) treatment on long-term clinical outcomes between STEMI and NSTEMI, after percutaneous coronary intervention (PCI) with drug-eluting stents (DES). Therefore, we conducted the study to compare the relative beneficial role of RASI on 2-year major clinical outcomes between STEMI and NSTEMI in patients who underwent successful PCI with DES.

2. Materials and methods

2.1. Study design and population

This study evaluated the 2-year comparative effectiveness of RASI between STEMI and NSTEMI in patients with AMI from the Korean Acute Myocardial Infarction registry (KAMIR). KAMIR is a nationwide, prospective, observational on-line registry in South Korea; details of this registry can be found at the KAMIR website (http://www.kamir.or.kr). The study was a non-randomized, multicenter, observational, retrospective study. The study protocol was approved by the ethics committee at each participating center and informed consents were obtained from all individual participants included in the study prior to enrollment. These processes were conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. A total of 53,281 AMI patients between January 2005 and June 2015 in the KAMIR were investigated. Patients with the following conditions were excluded [1]: uncertainty of diagnosis (n = 475, 0.9%) [2], PCI not done or failed (n = 3329, 6.2%) [3], coronary artery bypass grafts (CABG) done (n = 135, 0.3%) [4], bare-metal stent (BMS) deployed (n = 2441, 4.6%) [5], follow-up loss (n = 3729, 7.0%) [6], not participated (n = 1229, 2.3%) [7], incomplete laboratory results (n = 6756, 12.7%) [8], RASI contraindicated or not prescribed (n = 10477, 19.7%). Finally, a total 24,960 acute myocardial infarction (AMI) patients who underwent PCI with DES and were prescribed the RASI were enrolled and they were divided into two groups; the STEMI group (n = 14061, 56.3%) and the NSTEMI group (n = 10899, 43.7%) (Supplemental Data

Table 2
Clinical outcomes by Kaplan-Meier analysis and Cox-proportional hazard ratio analysis up to 2 years. Cumulative events at 2-year (%).

Outcomes	STEMI	NSTEMI	Log-rank	Hazard ratio (95% CI)	*p* value
Patients					
MACE	950 (7.0)	854 (8.4)	< 0.001	1.180 (1.076–1.294)	< 0.001
All-cause death	265 (2.0)	297 (2.9)	< 0.001	1.468 (1.244–1.732)	< 0.001
Cardiac death	186 (1.4)	196 (1.9)	0.002	1.377 (1.127–1.683)	0.002
Re-MI	197 (1.4)	179 (1.8)	0.085	1.194 (0.975–1.462)	0.086
Total revascularization	559 (4.2)	460 (4.5)	0.208	1.082 (0.957–1.225)	0.208
TLR	171 (1.3)	118 (1.2)	0.408	0.906 (0.716–1.145)	0.409
TVR	306 (2.3)	267 (2.7)	0.093	1.151 (0.977–1.356)	0.093
Non-TVR	262 (2.0)	199 (2.0)	0.976	0.997 (0.829–1.199)	0.976
Propensity score matched patients					
MACE	477 (7.4)	531 (8.3)	0.067	1.123 (0.992–1.270)	0.067
All-cause death	139 (2.1)	191 (3.0)	0.003	1.386 (1.114–1.725)	0.003
Cardiac death	95 (1.5)	128 (2.0)	0.023	1.358 (1.041–1.770)	0.024
Re-MI	102 (1.6)	108 (1.7)	0.631	1.068 (0.815–1.401)	0.631
Total revascularization	285 (4.5)	281 (4.5)	0.956	0.995 (0.844–1.174)	0.956
TLR	92 (1.4)	74 (1.2)	0.179	0.811 (0.597–1.101)	0.180
TVR	166 (2.6)	158 (2.5)	0.729	0.962 (0.774–1.196)	0.729
Non-TVR	122 (1.9)	126 (2.0)	0.739	1.043 (0.813–1.338)	0.739
Multivariate analysis[a]					
MACE	950 (7.0)	854 (8.4)	< 0.001	1.107 (0.998–1.227)	0.054
All-cause death	265 (2.0)	297 (2.9)	< 0.001	1.359 (1.129–1.637)	0.001
Cardiac death	186 (1.4)	196 (1.9)	0.002	1.294 (1.032–1.621)	0.025
Re-MI	197 (1.4)	179 (1.8)	0.085	1.013 (0.807–1.273)	0.909
Total revascularization	559 (4.2)	460 (4.5)	0.208	0.997 (0.868–1.144)	0.962
TLR	171 (1.3)	118 (1.2)	0.408	0.771 (0.592–1.005)	0.054
TVR	306 (2.3)	267 (2.7)	0.093	0.983 (0.817–1.183)	0.857
Non-TVR	262 (2.0)	199 (2.0)	0.976	0.987 (0.804–1.212)	0.902

[a] Adjusted by age, men, LVEF, SBP, DBP, Killip class III, 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, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, beta-blockers, CCB, lipid lowering agents, PCI within 24 h, infarct-related artery (LM, LAD, LCx, and RCA), treated vessel (LM, LAD, LCx, and RCA), ACC/AHA type B1, B2, and C lesion, the extent of coronary artery disease (1-vessel, 2-vessel, ≥ 3-vessel, and MVD), types of DES (SES, PES, ZES, EES, and BES), stent diameter, stent length, number of stents.

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; CI, confidence interval; MACE, major adverse cardiac events; Re-MI, re-myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; Non-TVR, non-target vessel revascularization. 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-brain natriuretic peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; 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; MVD, multi-vessel disease; DES, drug-eluting stents; SES, sirolimus-eluting stent, PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stents; EES, everolimus-eluting stents; BES, biolimus-eluting stents.

1). In this study, all 24,960 patients completed a 2-year clinical follow-up by face-to-face interviews, phone calls, or chart review.

2.2. PCI procedures and medical treatment

Diagnostic coronary angiography and PCI were performed according to general guidelines [9] through either the femoral or the radial artery after administration of unfractionated heparin (50–100 IU/kg). Patient activated clotting time (ACT) was maintained > 250 s during the procedure. Before PCI, all patients were given loading doses of 200–300 mg aspirin and 300–600 mg clopidogrel. If the patients had typical angina and/or signs of ischemia and ≥50% diameter restenosis or ≥70% diameter restenosis in a coronary artery by visual estimation, revascularization was considered indicated. After discharge, the patients were recommended to stay on the same medications they received during hospitalization, including all kinds of antiplatelet agents (aspirin, clopidogrel, ticagrelor, and prasugrel), beta-blockers (BB), ACEI, ARB and lipid lowering agents. The total duration of dual antiplatelet therapy (DAPT, the combination of aspirin [100 mg/day] and clopidogrel [75 mg/day]) was recommended for more than 12 months to patients who had undergone PCI. Triple antiplatelet therapy (TAPT, 100 mg cilostazol twice a day added on to DAPT) was left to the discretion of the individual operators.

2.3. Study definitions and clinical follow-up

STEMI was defined as the patient who has 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, and elevation of cardiac enzyme at least more than 3 times the upper limit of normal range [10]. If the patients showed absence of persistent ST-segment elevation, with increased cardiac biomarkers, and clinical context was appropriate, the patients were considered as NSTEMI [4,11]. In case of NSTEMI, an early invasive treatment strategy was defined as performing PCI within 24 h after admission. The major clinical endpoint was the occurrence of major adverse cardiac events (MACE) defined as all-cause death, cardiac death (CD), recurrent myocardial infarction (re-MI), total coronary revascularization including target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR during the 2-year follow-up period. All-cause death was classified as cardiac (CD) or non-cardiac death. Re-MI was defined as recurrent symptoms with new ST-segment elevation or re-elevation of cardiac markers to at least twice the upper normal limit after index PCI. TLR was defined as a 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 a revascularization of the target vessel or any segment of the coronary artery containing the target lesion. Non-TVR was defined as a revascularization of any segment of the non-target coronary artery.

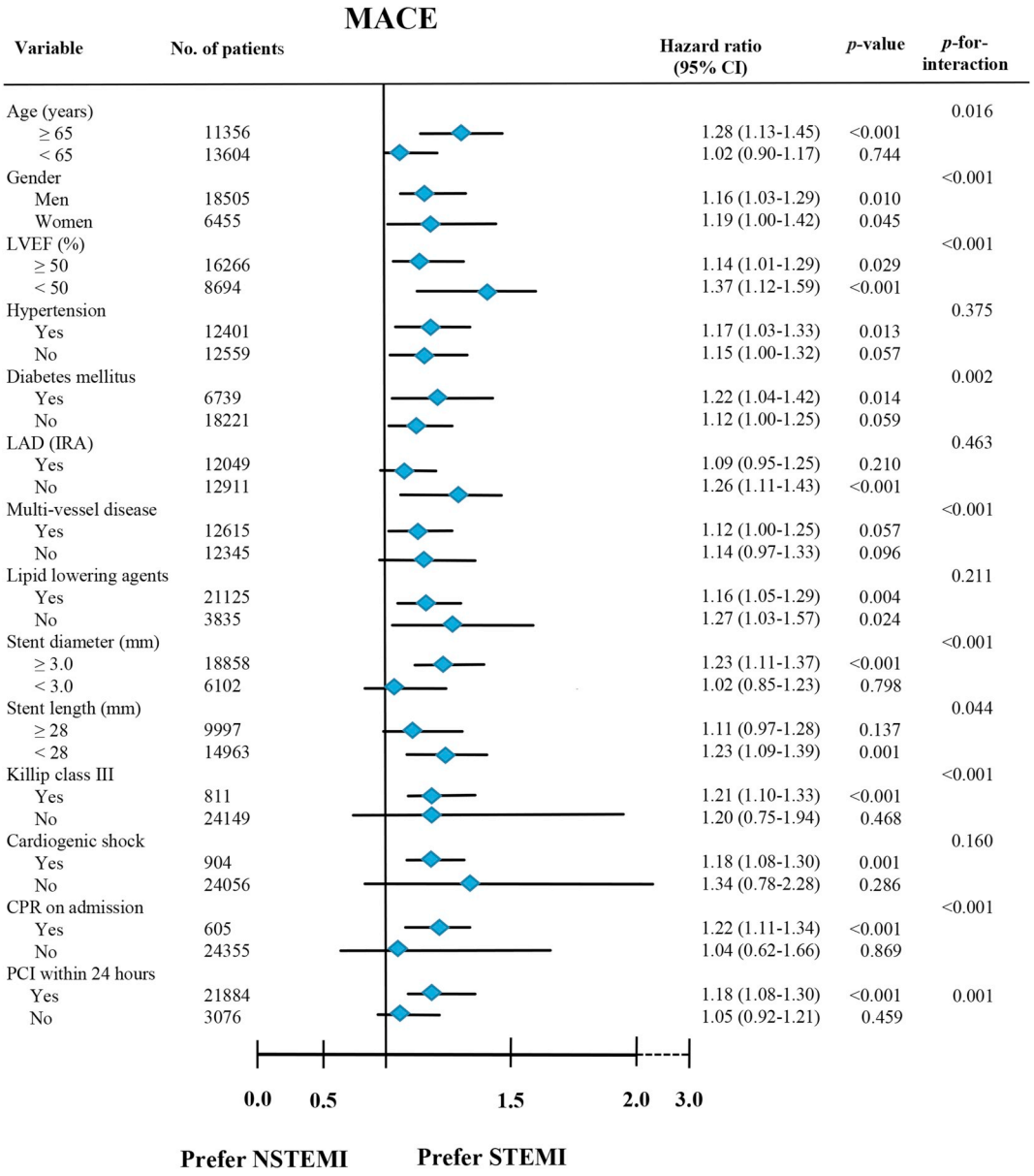

Fig. 2. Subgroup analysis for MACE.

2.4. Laboratory measurements

Serum creatine kinase isoenzyme (CK-MB) level was measured by immune-inhibition method using Stat Fax 3300 Biochemistry analyser (Awareness Technology Inc., Florida, USA) and serum troponin-I level was measured by chemiluminescence immunoassay on Abbott Architec c4000 analyser (Abbott Laboratories, Illinois, USA). In addition, N-terminal pro-brain natriuretic peptide (NT-ProBNP) concentration was measured using the Elecsys proBNP immunoassay (Roche Diagnostic, Mannheim, Germany).

2.5. Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (SPSS Inc., Chicago, IL, USA). For continuous variables, differences between groups were evaluated with the unpaired *t*-test. Data are expressed as mean ± standard deviations. For discrete variables, differences are expressed as counts and percentages, and were analyzed with χ^2 test between the groups. To adjust for potential confounders, propensity score-matched (PSM) analysis was performed using a logistic regression model. We tested all available variables that could be of potential relevance, such as all baseline clinical, angiographic and procedural factors. The logistic model by which the propensity scores were estimated showed good predictive value (C-statistic = 0.682). Patients in the STEMI group were one-to-one matched to those in the NSTEMI group according to propensity scores, with the nearest available pair matching method. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 6762 well-matched pairs except for the serum levels of CK-MB and troponin-I. To overcome these unadjusted variables, we performed a multivariate analysis where we included all possible variables such as, age, men, left ventricular ejection fraction (LVEF), systolic blood pressure (SBP), diastolic blood pressure (DBP), Killip class III, cardiogenic shock, cardiopulmonary resuscitation (CPR) on admission, hypertension, diabetes, dyslipidemia, previous history of myocardial infarction (MI), PCI, CABG, HF, and cerebrovascular accidents (CVA), current smoker, serum level of CK-MB, Troponin I, NT-ProBNP, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density (LDL) cholesterol, beta-blockers, calcium channel blockers (CCB), lipid lowering agents, PCI within 24 h, infarct-related artery (IRA, left main [LM], left anterior

Table 3
Independent predictors for all-cause death and cardiac death at 2 years in PSM patients.

Univariate		All-cause death multivariate		p value	Univariate	Cardiac death multivariate		p value
Variables	HR (95% CI)	p value	HR (95% CI)		HR (95% CI)	p value	HR (95% CI)	
Age ≥65 years	3.221 (2.542–4.111)	< 0.001	2.630 (2.021–3.422)	< 0.001	3.037 (2.265–4.070)	< 0.001	2.575 (1.878–3.531)	< 0.001
Gender (men)	1.544 (1.233–1.933)	< 0.001	0.956 (0.753–1.213)	0.710	1.333 (1.008–1.763)	0.044	0.814 (0.606–1.094)	0.173
LVEF < 50%	0.407 (0.328–0.506)	< 0.001	0.492 (0.393–0.616)	< 0.001	0.422 (0.325–0.549)	< 0.001	0.485 (0.363–0.638)	< 0.001
Systolic blood pressure	0.995 (0.991–1.000)	0.029	0.989 (0.982–0.996)	0.002	0.996 (0.991–1.001)	0.107	0.992 (0.984–1.001)	0.066
Diastolic blood pressure	0.996 (0.989–1.003)	0.262	1.017 (1.005–1.029	0.005	0.995 (0.986–1.003)	0.210	1.011 (0.996–1.026)	0.144
Hypertension	0.535 (0.426–0.671)	< 0.001	0.693 (0.547–0.879)	0.002	0.538 (0.409–0.709)	< 0.001	0.680 (0.510–0.907)	0.009
Diabetes mellitus	0.559 (0.449–0.696)	< 0.001	0.727 (0.579–0.912)	0.006	0.590 (0.451–0.772)	< 0.001	0.787 (0.597–1.039)	0.091
Dyslipidemia	1.031 (0.729–1.457)	0.863	0.927 (0.654–1.314)	0.669	0.880 (0.592–1.307)	0.525	0.798 (0.535–1.190)	0.268
Killip class III	0.430 (0.276–0.669)	< 0.001	0.707 (0.406–1.232)	0.221	2.288 (1.332–3.931)	< 0.001	0.694 (0.352–1.367)	0.291
Cardiogenic shock	0.247 (0.171–0.358)	< 0.001	0.301 (0.199–0.455)	< 0.001	0.261 (0.165–0.413)	0.003	0.271 (0.165–0.444)	< 0.001
CPR on admission	0.206 (0.142–0.300)	< 0.001	0.479 (0.307–0.748)	< 0.001	4.992 (3.184–7.824)	< 0.001	0.528 (0.305–0.916)	0.023
CK-MB	0.998 (0.997–1.000)	0.013	0.999 (0.997–1.000)	0.021	0.998 (0.996–1.000)	0.016	0.998 (0.996–1.000)	0.019
Troponin I	1.000 (0.998–1.001)	0.825	1.000 (0.999–1.001)	0.954	1.000 (0.997–1.002)	0.719	1.000 (0.998–1.002)	0.987
Beta blocker	1.122 (0.836–1.505)	0.444	1.013 (0.753–1.362)	0.933	0.877 (0.594–1.295)	0.510	0.783 (0.529–1.160)	0.223
Lipid lowering agent	1.439 (1.103–1.876)	0.007	1.375 (1.053–1.797)	0.020	1.382 (0.996–1.917)	0.053	1.335 (0.960–1.856)	0.086
PCI within 24 h	0.247 (0.171–0.358)	< 0.001	0.439 (0.285–0.677)	< 0.001	0.261 (0.165–0.413)	< 0.001	0.481 (0.283–0.819)	0.007
LAD (IRA)	0.879 (0.708–1.091)	0.241	1.129 (0.789–1.616)	0.506	0.983 (0.756–1.278)	0.898	1.191 (0.766–1.851)	0.437
LAD (treated)	0.784 (0.627–0.982)	0.034	0.837 (0.582–1.205)	0.339	0.895 (0.684–1.171)	0.419	0.933 (0.600–1.453)	0.760
ACC/AHA type B2/C lesion	0.746 (0.567–0.981)	0.036	0.793 (0.599–1.049)	0.104	0.780 (0.561–1.085)	0.140	0.835 (0.597–1.169)	0.293
MVD	0.626 (0.500–0.784)	< 0.001	0.822 (0.648–1.043)	0.107	0.624 (0.475–0.819)	0.001	0.816 (0.611–1.089)	0.168
Stent diameter	0.703 (0.529–0.934)	0.015	0.869 (0.648–1.165)	0.346	0.631 (0.445–0.894)	0.010	0.735 (0.513–1.053)	0.094
Stent length	1.007 (0.996–1.018)	0.235	0.999 (0.987–1.010)	0.803	1.008 (0.995–1.021)	0.240	1.000 (0.986–1.013)	0.948

HR, hazard ratio; LVEF, left ventricular ejection fraction; BMI, body mass index; CPR, cardiopulmonary resuscitation; CK-MB, creatine kinase myocardial band; ACC/AHA, American College of Cardiology/American Heart Association.
College of Cardiology/American Heart Association.

descending [LAD], left circumflex [LCx], and right coronary artery [RCA]), treated vessel (LM, LAD, LCx, and RCA), American College of Cardiology/American Heart Association (ACC/AHA) type B1, B2, and C lesion, the extent of coronary artery disease (1-vessel, 2-vessel, ≥ 3-vessel, and multi-vessel disease [MVD]), types of DES (sirolimus-eluting stent [SES], paclitaxel-eluting stent [PES], zotarolimus-eluting stents [ZES], everolimus-eluting stents [EES], and biolimus-eluting stents [BES]), stent diameter, stent length, number of stents. Cox-proportional hazard models were used to assess the adjusted hazard ratio (HR) comparing the two groups in the PSM population. For all analyses, a two sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline clinical, laboratory, angiographic and procedural characteristics

Prior to PSM, the mean age of the NSTEMI group was higher than the STEMI group (64.0 ± 11.9 *vs.* 60.9 ± 12.5, $p < 0.001$, Table 1). The number of patients who had decreased LVEF (< 50%) was higher in the STEMI group than NSTEMI group (40.4% *vs.* 27.6%, $p < 0.001$). Therefore, the baseline mean value of LVEF was higher in the NSTEMI group (STEMI, 51.5 ± 10.6% *vs.* NSTEMI, 54.5 ± 10.9, $p < 0.001$). Before PSM, the number of men, Killip class III, cardiogenic shock, CPR on admission, previous history of HF, current smokers and the levels of CK-MB, troponin I, total cholesterol, HDL-cholesterol, LDL-cholesterol and the prescription rate of BB, the number of PCI within 24 h, LAD (IRA, treated vessel) and RCA (IRA), and the number of ACC/AHA type C, 1-vessel disease were higher in the STEMI. By contrast, the NSTEMI group showed higher level of LVEF, SBP, DBP, serum NT-ProBNP, serum creatinine and hypertension, DM, dyslipidemia, previous history of MI, PCI, CABG, and CVA than the STEMI group. In addition, CCB and lipid lowering agents were much more frequently prescribed and LM and LCx were more common IRA, and more frequently treated in the NSTEMI group. ACC/AHA type B1, B2 and 2-vessel, 3-vessel, and MVD were also higher in the NSTEMI group. The SES, PES and ZES were more frequently deployed in the STEMI group and the EES and BES were more frequently deployed in the NSTEMI group. The number of deployed stents (1.56 ± 0.89 *vs.* 1.38 ± 0.71, $p < 0.01$) and the length of deployed stent (26.7 ± 10.7 mm *vs.* 26.2 ± 8.6, $p < 0.001$) were higher in the NSTMI group. The diameter of deployed stents was larger in the STEMI group (3.19 ± 0.39 mm *vs.* 3.10 ± 0.39 mm) However, these baseline differences between the two groups were well balanced after PSM except for CK-MB and troponin I level.

3.2. Clinical outcomes

In all patients, the cumulative incidence of MACE (7.0% *vs.* 8.4%, Log-rank $p < 0001$, HR, 1.180; 95% confidence interval [CI], 1.079–1.294; $p < 0.001$, Fig. 1A), all-cause death (2.0% *vs.* 2.9%, Log-rank $p < 0.001$, HR, 1.468; 95% CI, 1.244–1.732; $p < 0.001$), CD (1.4% *vs.* 1.9%, Log-rank $p = 0.002$, HR, 1.377; 95% CI, 1.127–1.683; $p = 0.002$) was higher in the NSTEMI group than the STEMI group. After PSM analysis, the cumulative incidence of all-cause death (2.1% *vs.* 3.0%, Log-rank $p = 0.003$, HR, 1.386; 95% CI, 1.114–1.725; $p = 0.003$, Fig. 1C) and CD (1.5% *vs.* 2.0%, $p = 0.023$, HR, 1.358; 95% CI, 1.041–1.770; $p = 0.024$, Fig. 1D) was also significantly higher in the NSTEMI group than the STEMI group. However, the cumulative incidences of MACE (Fig. 1B), re-MI, total revascularization (TLR, TVR, and non-TVR) were not significantly different between the two groups. After multivariate analysis, the NSTEMI group also showed statistically increased incidence of all-cause death (HR, 1.359; 95% CI, 1.129–1.637; $p = 0.001$) and cardiac death (HR, 1.294; 95% CI, 1.032–1.621; $p = 0.025$) compared with the STEMI group (Table 2). Fig. 2 shows subgroup analysis for MACE at 2 years. In case of hypertension (HR, 1.17; 95% CI, 1.03–1.33; $p = 0.013$), non-LAD (IRA) (HR, 1.26; 95% CI, 1.11–1.43; $p < 0.001$), with or without lipid lowering agents receiving, and cardiogenic shock (HR, 1.18; 95% CI, 1.08–1.30; $p = 0.001$), RASI showed a more beneficial effect on MACE in patients with STEMI compared with NSTEMI. In addition, old age (≥65 years), decreased LVEF (< 50%), SBP, DBP, hypertension, DM, cardiogenic shock, CPR on admission, CK-MB, lipid lowering agents, and PCI within 24 h were independent predictors of all-cause of death. Taken together, old age (≥65 years), decreased LVEF (< 50%),

hypertension, CK-MB, cardiogenic shock, CPR on admission and PCI within 24 h were meaningful common independent risk factors for both all-cause death and cardiac death in PSM patients (Table 3).

4. Discussion

The principal findings of this study are as follows [1]: the cumulative incidences of all-cause death and CD were significantly lower in patients with STEMI compared with NSTEMI after RASI therapy [2], however, the cumulative incidences of MACE, re-MI, total revascularization (TLR, TVR, and non-TVR) were similar between the two groups after PSM [3], In addition, old age (≥65 years), decreased LVEF (< 50%), hypertension, CK-MB, cardiogenic shock, CPR on admission, and PCI within 24 h were common significant independent risk factors of all-cause death and CD in PSM patients.

Conversion of angiotensin I to angiotensin II formation is inhibited by ACEI, ACEI catalyze the breakdown of bradykinin to inactive peptides, thus accumulated bradykinin plays some important beneficial roles in cardiovascular protection, including vasodilation, and stimulation of nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor, and tissue plasminogen activator production [12]. Furthermore, in the AIRE study, ACEI could enhance endothelial function and cardiovascular remodeling and reduce the progression of atherosclerosis leading to beneficial effects on cardiovascular outcomes such as MI or HF [13]. Therefore, the European Society of Cardiology (ESC) guidelines and the American Heart Association (AHA) guidelines recommend ACEI as Class 1A drug in AMI patients with decreased LVEF (≤40%) and suggest ARB as Class 1B recommendation in STEMI patients and Class 1A recommendation in NSTEMI patients. In this regard, RAI (RASI) may play an important role in AMI patients. RASI provides a mortality benefit by decreasing the worsening of progressive LV dilation and remodeling, especially in patients with LV dysfunction under AMI [14,15].

Many previous studies demonstrated that the long-term prognosis of STEMI was worse than NSTEMI [16,17]. Although NSTEMI may be a less severe clinical disease in the long term compared with STEMI, NSTEMI can show a higher risk profile during the acute phase [18]. The worse in-hospital outcome in STEMI could be caused by the relatively higher incidence of cardiogenic shock. However, the reasons for the higher incidence of death in NSTEMI during a long-term follow-up period was not well assessed [19]. One report [20] showed that STEMI was associated with a higher risk of short-term mortality (≤2 months after index PCI, adjusted HR, 1.85; 95% CI, 1.45–2.38), but NSTEMI was associated with a higher risk of long-term mortality (> 2 months after index PCI, adjusted HR, 0.68; 95% CI, 0.59–0.83). Montalescot et al. [21] reported that among 1878 patients, in-hospital mortality (4.6% *vs.* 4.3%) and 1-year mortality (9.0% *vs.* 11.6%, $p = 0.09$) were not significant between STEMI and NSTEMI groups. In the GRACE registry [16], the authors suggested the need for better long-term medical treatment and more intense follow-up in patients with ACS to improve long-term outcomes. In case of NSTEMI, more early invasive strategy and secondary prevention treatments including antiplatelet agents, beta-blockers, and lipid lowering agents can reduce the incidence of adverse clinical outcomes [22–25].

Until recently, AMI has been increasing and represents one of the main causes of death in Korea associated with prolonged life expectancy, improved socioeconomic status, and westernized diet [26,27]. However, the mortality of coronary heart disease has decreased in advanced countries due to the tight control of cardiovascular risk factors, advancement of effective drugs, improvement of operative skills and equipment during PCI or CABG [28,29]. There were limited data comparing the long-term prognoses of STEMI and NSTEMI in AMI patients, especially focused on the use of RASI. In this study, RASI showed a more potential beneficial effect on MACE (7.0% *vs.* 8.4%, $p < 0.001$), all-cause death (2.0% *vs.* 2.9%, $p < 0.001$), CD (1.4% *vs.* 1.9%, $p = 0.002$) in STEMI patients compared with NSTEMI patients before PSM. After PSM, the beneficial effects of RASI in STEMI patients were also prominent in the cumulative incidences of all-cause death (2.1% *vs.* 3.0%, $p = 0.003$) and CD (1.5% *vs.* 2.0%, $p = 0.023$) than in NSTEMI patients. In addition, after multivariate analysis, the cumulative incidences of all-cause death (HR, 1.359; 95% CI, 1.129–1.637; $p = 0.001$) and cardiac death (HR, 1.294; 95% CI, 1.032–1.621; $p = 0.025$) were also higher in NSTEMI patients. In the OPTIMAAL study [30], the clinical benefit of RASI was larger in the high-risk patients subgroup such as anterior MI, decreased LVEF (≤40%), HF, prior MI, and tachycardia. In our study, the incidence of decreased LVEF (< 50%) (40.4% *vs.* 27.6%, $p < 0.001$), infarction in the LAD (52.9% *vs.* 42.4%, $p < 0.001$), Killip class III (4.7% *vs.* 1.4%, $p < 0.001$), cardiogenic shock (5.1% *vs.* 1.7%, $p < 0.001$), and CPR on admission (3.2% *vs.* 1.4%, $p < 0.001$) was significantly higher in the STEMI group before PSM. Even though we attempted to adjust the diverse variables through PSM or multivariate analysis, we speculate that these baseline characteristics may be play an important role in explaining mortality differences (e.g., all-cause death, CD) between the two groups and may be similar to results of the subgroup analysis of the OPTIMAAL study. The result of multivariate analysis demonstrated decreased LVEF (< 50%), cardiogenic shock, CPR on admission, and PCI within 24 h were meaningful common independent predictors of all-cause death and CD in this study (Table 3). Another important major factor in determining the clinical outcome is the treatment strategy of the NSEMI group. Until now, early invasive treatment showed better clinical outcomes compared with the conservative treatment [31]. Because the proportion of patients who received the conservative treatment was more than that of the patients who received invasive treatment, these biases could affect the results of the study. In this study, 94.2% (13247/14061) of the STEMI patients had received primary PCI, about 78.8% (8591/10899) of the NSTEMI patients had received early invasive treatment strategy. Therefore, even though different treatment strategies exist between the two groups, this comparative study may provide meaningful information.

Although the impact of RASI on the cumulative incidence of MACE, re-MI, total revascularization, TLR, TVR, non-TVR was not significantly different between the STEMI and NSTEMI groups, RASI significantly reduced the cumulative incidences of all-cause death and CD in the STEMI group compared with the NSTEMI group before and after PSM. In addition, the mortality reduction capability of RASI was more prominent in STEMI patients and old age (≥65 years), decreased LVEF (< 50%), hypertension, CK-MB, cardiogenic shock, CPR on admission, and PCI within 24 h were meaningful common independent risk factors for both all-cause death and cardiac death.

This study has several limitations. First, the present study is a non-randomized controlled study, therefore, there may be some under-reporting and/or missed data common to other registry data. Second, these registry data did not include complete data concerning patient adherence or non-adherence to drug or adverse events, this study was based on discharge medications and this may act as an important bias. Third, the 2-year follow-up period of this study was too short to fully determine the long-term major clinical outcomes. Fourth, even though we adopted PSM and multivariate analysis to adjust for numerous confounding factors, a large-scale randomized controlled well-planned trial may be needed.

Conflicts of interest

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

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Appendix A. Supplementary data

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