Comparison of clinical outcomes between angiotensin-converting-enzyme inhibitors and ARBs in patients with acute myocardial infarction with dyslipidemia after a successful stent implantation

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Abstract

Objective: Currently, there are limited comparative data concerning long-term major clinical outcomes following the angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II type 1 (AT1) receptor blockers (ARBs) therapy in patients with acute myocardial infarction (AMI) with dyslipidemia after a successful stent implantation. Therefore, we investigated major clinical outcomes for 2 years following the ACEIs and ARBs therapy in these patients.

Methods: A total of 3015 patients with AMI who underwent a successful stent implantation and were prescribed ACEIs (n=2175) or ARBs (n=840) were enrolled into the study from the Korea AMI Registry (KAMIR). The major clinical endpoint was the occurrence of major adverse cardiac events (MACEs) defined as all-cause death, recurrent myocardial infarction (Re-MI), and any repeat-revascularization-comprised target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR.

Results: After the adjustment, the cumulative incidence of all-cause death in the ARBs group was significantly higher than in the ACEIs group [adjusted hazard ratio (aHR), 2.277; 95% confidence interval (CI), 1.154–4.495; p=0.018]. The cumulative incidences of MACEs (aHR, 1.305; 95% CI, 0.911–1.869; p=0.146), cardiac death, Re-MI, any repeat revascularization, TLR, TVR, and non-TVR were similar between the two groups. In addition, an advanced age (≥65 years), decreased left ventricular ejection fraction (<50%), and cardiopulmonary resuscitation on admission were meaningful independent predictors for all-cause death in this study.

Conclusion: ACEIs were a preferred treatment modality when compared to ARBs for patients with AMI with dyslipidemia who underwent a successful stent implantation to reduce the incidences of all-cause death during a 2-year follow-up. However, additional research is required to determine the clinical implications of these results. *(Anatol J Cardiol 2020; 23: 86-98)*

Keywords: dyslipidemia, myocardial infarction, renin-angiotensin system

Introduction

Dyslipidemia is a major risk factor for the development of cardiovascular disease, and the proper treatment and prevention of dyslipidemia can reduce the cardiovascular morbidity and mortality (1). Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce the incidence of major adverse cardiac events (MACEs) and death following myocardial infarction through the enhancement of the endothelial function, cardiovascular remodeling, and the inhibition of the progression of atherosclerosis (2, 3). Angiotensin II type I (AT1) receptor blockers (ARBs) are an alternative to ACEIs for patients intolerant to ACEIs (4-7). Although previous studies, such as the Heart Outcomes Prevention Evaluation Study (HOPE) (8), EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) (9), and Valsartan in Acute

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Myocardial Infarction Trial (VALIANT) (10) trials, showed the beneficial roles of ACEIs or ARBs in improving cardiovascular outcomes, these comparative studies were not focused on dyslipidemia. Furthermore, Borghi et al. (11) and other investigators (12-14) suggested that the overexpressed AT1 receptor, as well as an increased affinity of such receptors for circulating and locally released angiotensin II, is present in patients with hypercholesterolemia. Therefore, ACEIs and ARBs inhibit the production of angiotensin II or it's binding to the AT1 receptor in these patients.

The Survival of Myocardial Infarction Long-Term Evaluation trial (15) and its post-hoc analysis (16) have suggested that the early treatment with zofenopril was more effective in reducing the morbidity and mortality in patients with acute myocardial infarction (AMI) and hypercholesterolemia compared to patients in the placebo and the normocholesterolemic groups. Another study reported that candesartan was better than felodipine with regard to its capacity to improve hypercholesterolemia-associated endothelial dysfunction (17). Currently, there are limited comparative data concerning the long-term major clinical outcomes following ACEIs and ARBs therapy in AMI patients with dyslipidemia. Hence, we investigated 2-year major clinical outcomes of the ACEIs and ARBs therapy in patients with AMI with dyslipidemia after a successful stent implantation.

Methods

Study population
The present nonrandomized, multicenter, observational, and retrospective cohort study is based on data from the Korea AMI Registry (KAMIR). The characteristics and detailed information of this registry have already been published (18). A total of 5185 patients with AMI in the KAMIR from November 2005 to June 2015 were evaluated. Patients were excluded from the study based on the following criteria: (1) incomplete laboratory results (n=1321, 25.5%); (2) loss to follow-up or those who did not participate (n=113, 2.2%); (3) ACEIs or ARBs had not been prescribed (n=732, 14.1%); and (4) concomitant use of ACEIs and ARBs (n=26, 0.5%). Finally, a total of 3015 AMI patients who underwent a successful stent implantation and were prescribed ACEIs (n=2175, 72.1%) or ARBs (n=840, 27.9%) were enrolled (Fig. 1). The selection of treatment strategies, i.e., either ACEIs or ARBs, after a percutaneous coronary intervention (PCI) was based on the physician's preferences. All data were collected at each participating center using a web-based case report form. This study protocol was approved by the Institutional Review Board of each participating center. In addition, this study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all patients prior to their enrollment. We tracked the enrolled patients via face-to-face interviews, phone calls, and chart reviews (19).
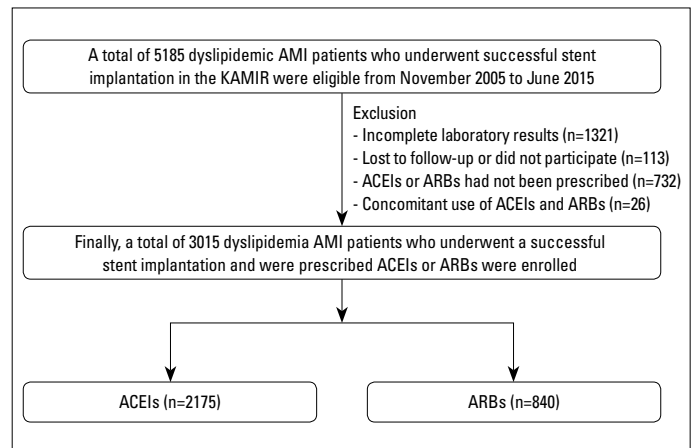

Figure 1. Flow chart

AMI - acute myocardial infarction, KAMIR - Korea Acute Myocardial Infarction Registry, ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin II type I receptor blockers

PCI procedure and medical treatment
The diagnostic coronary angiography and PCI were performed through the femoral and the radial artery approach using the standard technique (20). Before CAG, the loading of dual antiplatelet therapy (DAPT) was as follows: 200 to 300 mg of aspirin and 300 to 600 mg of clopidogrel; and 180 mg ticagrelor or 60 mg prasugrel could also be used as alternatives to clopidogrel. The total duration of DAPT recommended for patients who underwent PCI was >12 months (21).

Study definitions and clinical outcomes
The presence of dyslipidemia was defined as the positive history of having dyslipidemia regardless of the presence or absence of receiving lipid-lowering agents or receiving lipid-lowering agents regardless of the presence or absence of having history of dyslipidemia. Although some patients did not have a previous history of dyslipidemia or were not administered with lipid-lowering agents, their laboratory results were compatible with the diagnostic criteria of dyslipidemia, they were considered as patients with dyslipidemia in this study (22). Because the definition of dyslipidemia varies according to different guidelines and races, we defined dyslipidemia according to the Asian guideline (23), i.e., the patients with 12-hour fasting serum low-density lipoprotein (LDL) cholesterol concentrations of at least 140 mg/dL, high-density lipoprotein (HDL) cholesterol concentrations <40 mg/dL, and triglyceride (TG) concentrations ≥150 mg/dL. We defined STEMI and NSTE-MI according to the current guidelines (5-7). MACEs were the major clinical endpoint of this study; they were defined as all-cause death, recurrent myocardial infarction (Re-MI), and any coronary repeat revascularization during the 2-year follow-up period. All-cause death was classified as cardiac (CD) or non-CD. Any repeat-revascularization-comprised TLR, TVR, and non-TVR. Previously (22), we have published the definitions of Re-MI, TLR, TVR, and non-TVR.

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Statistical analysis

For continuous variables, in this study, the normality test was performed using the Kolmogorov–Smirnov normality test. According to the normality results, the independent samples t-test or Mann–Whitney U test were applied to examine the difference of continuous variables means or medians of the two groups, and the data were expressed as the mean±standard deviations. For categorical variables, the differences between the two groups were analyzed using the chi-squared test or, if not applicable, Fisher's exact test, and the data were expressed as counts and percentages. Various clinical outcomes were estimated using the Kaplan–Meier method, and differences between the two groups were compared using the log-rank test. We included only meaningful confounding covariates (p<0.001, or those having predictive values) during the multiple Cox proportional hazard regression analysis, as shown in Table 1. For all analyzes, two-sided p-values <0.05 were considered statistically significant. All statistical analyzes were performed using the SPSS software, version 20 (IBM; Armonk, NY, USA).

Results

Baseline characteristics

The baseline, laboratory, angiographic, and procedural characteristics of this study population are summarized in Table 2. This study population comprised patients who had a relatively well preserved left ventricular ejection fraction (LVEF; mean, 53.3%±10.9%). The mean age of the patients in the ARBs group was higher than that of those in the ACEIs group (62.6±11.7 years vs. 59.9±11.9 years, p<0.001). The numbers of male patients, STEMI cases, and NSTEMI cases; the peak levels of creatine kinase myocardial band (CK-MB) and troponin-I; the total cholesterol

and LDL-cholesterol levels; the prescription rates of clopidogrel, cilostazol, beta-blockers (BBs), and calcium-channel blockers (CCBs); and the number of cases with American College of Cardiology/American Heart Association (ACC/AHA) type C lesions were higher in case of the ACEIs group than in case of the ARBs group. In contrast, the ARBs group showed higher mean values of body mass index; a greater number of cases with hypertension, diabetes mellitus (DM), and previous history of heart disease (MI, PCI, and cerebrovascular accidents); higher levels of blood N-terminal pro-brain natriuretic peptide and serum creatinine; higher prescription rates of ticagrelor and prasugrel; higher incidence of the left anterior descending coronary artery being as the infarct-related artery (IRA) and the left circumflex coronary artery being the treated vessel; and a greater number of cases with the ACC/AHA type B2 lesions than in the ACEIs group. Even though newly developed antiplatelet agents (ticagrelor, prasugrel) were more frequently prescribed among patients in the ARBs group, the total number of patients in who these agents were prescribed was small. The first-generation DESs (sirolimus-eluting stent and paclitaxel-eluting stent) were more frequently deployed among patients from the ACEIs group, and the biolimus-eluting stent was more frequently deployed among patients from the ARBs group. The incidence of the deployment of the zotarolimus-eluting stent and everolimus-eluting stent among the patients from the two groups was similar. Even though the length of the deployed stents and the number of deployed stents were similar between the two groups, the diameter of the deployed stent was larger in case of patients from the ACEIs group than in cases of those from the ARBs group. In addition, the numbers of cases showing cardiogenic shock, and cardiopulmonary resuscitation (CPR) on admission, and the incidence of the use of intravascular ultrasound (IVUS), optical

Table 1. Clinical outcomes at 2-year

Outcomes	Cumulative Events at 2-year (%)			Unadjusted		*Adjusted	
	ACEIs	ARBs	Log-rank	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
MACEs	150 (7.1)	79 (10.2)	0.010	1.424 (1.085–1.871)	0.011	1.305 (0.911–1.869)	0.146
All-cause death	39 (1.8)	30 (3.7)	0.003	2.044 (1.269–3.290)	0.003	2.277 (1.154–4.495)	0.018
Cardiac death	34 (1.6)	24 (3.0)	0.017	1.870 (1.109–3.154)	0.019	2.019 (0.979–4.163)	0.057
Re-MI	32 (1.5)	19 (2.6)	0.101	1.600 (0.907–2.824)	0.105	1.203 (0.539–2.685)	0.652
Any revascularization	88 (4.3)	39 (5.2)	0.309	1.216 (0.834–1.772)	0.310	1.159 (0.720–1.866)	0.543
TLR	23 (1.1)	16 (2.1)	0.045	1.900 (1.004–3.596)	0.049	2.058 (0.881–4.809)	0.096
TVR	47 (2.3)	28 (3.8)	0.036	1.640 (1.027–2.618)	0.038	1.551 (0.854–2.816)	0.149
Non-TVR	42 (2.0)	12 (1.6)	0.448	0.780 (0.411–1.482)	0.449	0.733 (0.326–1.651)	0.454

*Adjusted by age, gender, LVEF, BMI, STEMI, NSTEMI, hypertension, diabetes, previous MI, previous PCI, previous CVA, peak CK-MB, peak troponin-I, serum level of NT-ProBNP, creatinine, total cholesterol, LDL cholesterol, discharge medications (aspirin, clopidogrel, ticagrelor, prasugrel, cilostazole, BB, CCB), infarct-related artery (IRA), treated vessel (LCx), ACC/AHA lesion type B2 and C, types of stent (BMS, SES, PES, BES), and stent diameter.
CI - confidence interval; MACE - major adverse cardiac events; Re-MI - re-myocardial infarction; TLR - target lesion revascularization; TVR - target vessel revascularization;
LVEF - left ventricular ejection fraction; BMI - body mass index; STEMI - ST-segment elevation myocardial infarction; NSTEMI - non-ST-segment elevation myocardial infarction;
PCI - percutaneous coronary intervention; CVA - cerebrovascular accident; CK-MB - creatine kinase myocardial band; NT-ProBNP - N-terminal pro-brain natriuretic peptide;
LDL - low-density lipoprotein; BBs - beta-blockers; CCBs - calcium-channel blockers; LAD - left anterior descending coronary artery; LCx - left circumflex coronary artery;
ACC/AHA - American College of Cardiology/American Heart Association; BMS - bare-metal stent; SES - sirolimus-eluting stent; PES - paclitaxel-eluting stent; BES - biolimus-eluting stent

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Table 2. Baseline clinical, laboratory, and procedural characteristics

Variables	ACEIs (n=2175)	ARBs (n=840)	*P*-value
Age (years)	59.9±11.9	62.6±11.7	<0.001
Gender (men)	1641 (75.4)	599 (71.3)	0.020
LVEF (%)	53.0±10.8	54.1±10.8	0.010
Body mass index (kg/m²)	24.8±3.1	25.1±3.3	0.021
Systolic blood pressure (mm Hg)	134.0±27.0	133.2±28.3	0.483
Diastolic blood pressure (mm Hg)	81.0±16.2	80.0±16.7	0.180
Cardiogenic shock, n (%)	73 (3.4)	33 (3.9)	0.444
CPR on admission, n (%)	50 (2.3)	21 (2.5)	0.744
STEMI, n (%)	1199 (55.1)	384 (45.7)	<0.001
Primary PCI, n (%)	1121 (93.5)	354 (92.2)	0.377
CABG, n (%)	3/1199 (0.3)	2/384 (0.5)	0.600
NSTEMI, n (%)	976 (44.9)	456 (54.3)	<0.001
PCI within 24 hours	758 (77.7)	357 (78.3)	0.791
CABG, n (%)	2/976 (0.2)	3/456 (0.7)	0.335
Hypertension, n (%)	1237 (56.9)	603 (71.8)	<0.001
Diabetes mellitus, n (%)	685 (31.5)	340 (40.5)	<0.001
Previous myocardial infarction, n (%)	118 (5.4)	88 (10.5)	<0.001
Previous PCI, n (%)	194 (8.9)	148 (17.6)	<0.001
Previous CABG, n (%)	15 (0.7)	7 (0.8)	0.678
Previous CVA, n (%)	131 (6.0)	91 (10.8)	<0.001
Previous heart failure, n (%)	35 (1.6)	19 (2.3)	0.226
Peak CK-MB (mg/dL)	119.0±170.0	103.5±173.2	0.027
Peak troponin-I (ng/mL)	46.9±139.7	34.9±51.4	0.002
NT-ProBNP (pg/mL)	1280.4±3715.1	2235.5±5687.6	0.001
hs-CRP (mg/dL)	10.7±68.0	14.5±70.8	0.237
Serum creatinine (mg/L)	1.03±0.81	1.26±1.53	<0.001
Blood glucose (mg/dL)	165.5±71.9	169.9±81.0	0.176
Total cholesterol (mg/dL)	192.3±50.1	178.9±50.2	<0.001
Triglyceride (mg/L)	156.8±117.4	150.8±116.9	0.222
HDL cholesterol (mg/L)	43.6±13.8	42.5±15.7	0.098
LDL cholesterol (mg/L)	121.5±41.7	111.0±42.7	<0.001
Discharge medications			
Aspirin, n (%)	2165 (99.5)	832 (99.0)	0.115
Clopidogrel, n (%)	2016 (92.7)	718 (85.5)	<0.001
Ticagrelor, n (%)	79 (3.6)	78 (9.3)	<0.001
Prasugrel, n (%)	61 (2.8)	36 (4.3)	0.039
Cilostazole, n (%)	545 (25.1)	174 (20.7)	0.012
Beta-blocker, n (%)	1939 (89.1)	713 (84.9)	0.001
Calcium channel blockers, n (%)	147 (6.8)	112 (13.3)	<0.001
Lipid lowering agents	1943 (89.3)	742 (88.3)	0.430
Angiographic & procedural characteristics			
Infarct-related artery			
Left main, n (%)	26 (1.2)	22 (2.6)	0.005

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Table 2. Cont.

Variables	ACEIs (n=2175)	ARBs (n=840)	*P*-value
Left anterior descending, n (%)	1001 (46.0)	382 (45.5)	0.787
Left circumflex, n (%)	398 (18.3)	156 (18.6)	0.862
Right coronary artery, n (%)	750 (34.5)	280 (33.3)	0.551
Treated vessel			
Left main, n (%)	48 (2.2)	29 (3.5)	0.052
Left anterior descending, n (%)	1196 (55.0)	466 (55.5)	0.809
Left circumflex, n (%)	578 (26.6)	262 (31.2)	0.011
Right coronary artery, n (%)	901 (41.4)	341 (40.6)	0.678
ACC/AHA lesion type			
Type B1, n (%)	288 (13.2)	131 (15.6)	0.094
Type B2, n (%)	587 (27.0)	285 (33.9)	<0.001
Type C, n (%)	1086 (49.9)	333 (39.6)	<0.001
Extent of coronary artery disease			
1-vessel, n (%)	1037 (47.7)	393 (46.8)	0.660
2-vessel, n (%)	665 (30.6)	273 (32.5)	0.306
≥ 3-vessel, n (%)	473 (21.7)	174 (20.7)	0.536
Multivessel disease, n (%)	1138 (52.3)	447 (53.2)	0.660
IVUS, n (%)	360 (21.9)	170 (24.0)	0.247
OCT, n (%)	7 (1.3)	7 (2.0)	0.438
FFR, n (%)	11 (2.1)	2 (0.6)	0.069
Stents			
BMS, n (%)	185 (8.5)	37 (4.4)	<0.001
SES, n (%)	323 (14.8)	84 (10.0)	<0.001
PES, n (%)	311 (14.3)	89 (10.6)	0.007
ZES, n (%)	501 (23.0)	205 (24.4)	0.426
EES, n (%)	643 (29.6)	272 (32.4)	0.131
BES, n (%)	117 (5.4)	105 (12.5)	<0.001
Others, n (%)	280 (12.9)	85 (10.1)	0.021
Stent diameter (mm)	3.15±0.43	3.11±0.43	0.027
Stent length (mm)	26.0±9.3	26.5±10.5	0.248
Number of stent	1.49±0.81	1.53±0.84	0.278

Values are presented as the mean±SD or numbers and percentages. The *P*-values for continuous data were obtained from the analysis of the unpaired t-test. The *P*-values for categorical data were obtained from the chi-squared test.
LVEF - left ventricular ejection fraction; STEMI - ST-segment elevation myocardial infarction; NSTEMI - non-STEMI; PCI - percutaneous coronary intervention; CABG - coronary artery bypass graft; CVA - cerebrovascular accidents; 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; ACC/AHA - American College of Cardiology/American Heart Association; IVUS - intravascular ultrasound; OCT - optical coherence tomography; FFR - fractional flow reserve, BMS - bare-metal stent; SES - sirolimus-eluting stents; PES - paclitaxel-eluting stents; ZES - zotarolimus-eluting stents; EES - everolimus-eluting stents; BES - biolimus-eluting stents

coherence tomography (OCT), and fractional flow reserve (FFR) among the patients from the two groups were similar.

Clinical outcomes

Table 1 and Figure 2 show the cumulative incidences of the major clinical outcomes during the 2-year follow-up period. Before the adjustment, the cumulative incidences of MACEs [hazard ratio (HR), 1.424; 95% confidence interval (CI), 1.085–1.871; p=0.011], all-cause death (HR, 2.044; 95% CI, 1.269–3.290; p=0.003), CD (HR, 1.870; 95% CI, 1.109–3.154; p=0.019), TLR (HR, 1.900; 95% CI, 1.004–3.596; p=0.049) and TVR (HR, 1.640; 95% CI, 1.027–2.618; p=0.038) were significantly higher in the ARBs group than in the ACEIs group. However after the adjustment, the cumulative incidences of MACEs [adjusted HR (aHR), 1.305; 95% CI, 0.911–1.869;
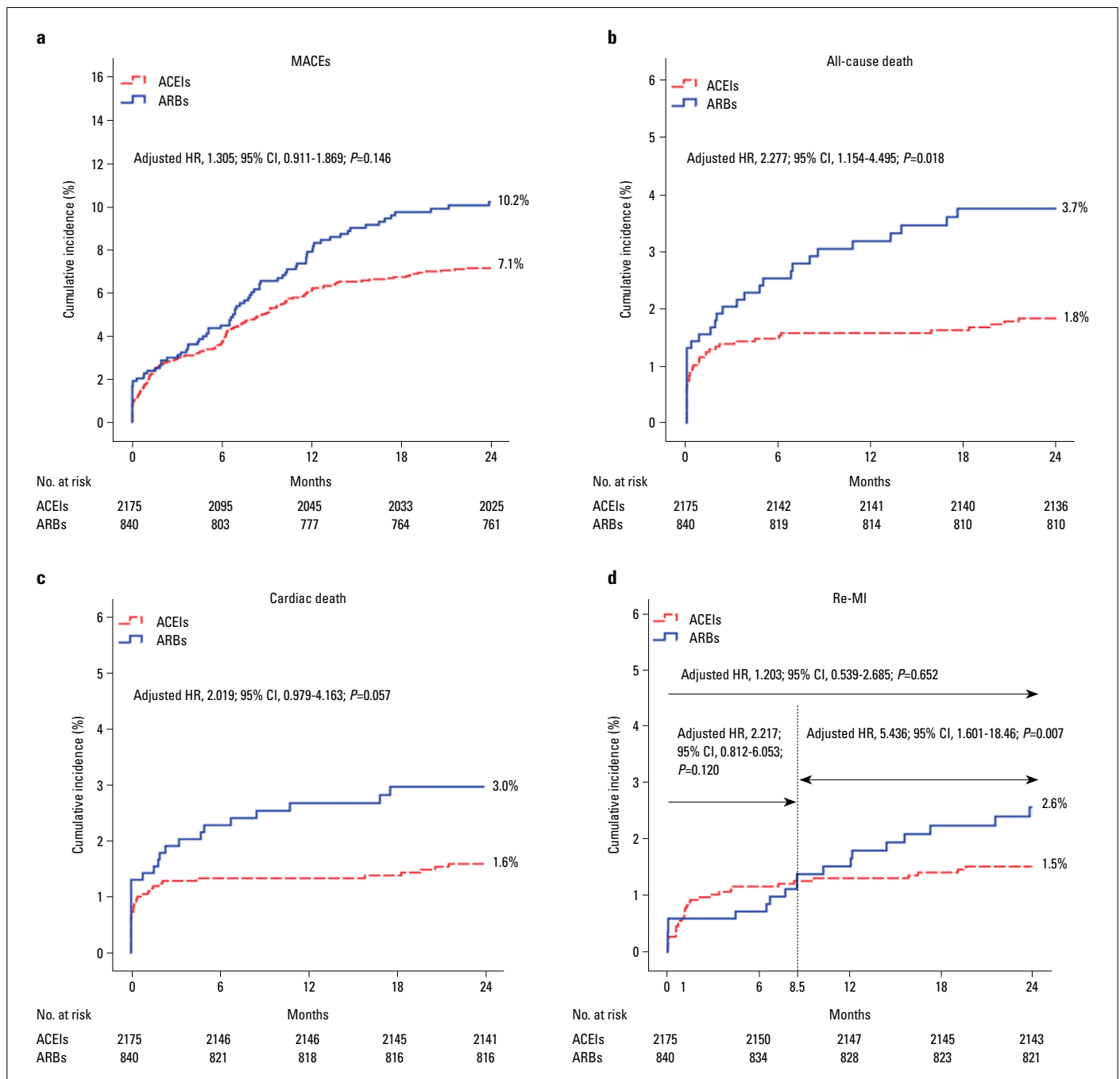
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Figure 2. Kaplan–Meier curved analysis for MACEs (a), all-cause death (b), cardiac death (c), Re-MI (d), any repeat revascularization (e), TLR (f), TVR (g), and non-TVR (h)

MACEs - major adverse cardiac event, ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin II type I receptor blockers, re-MI - recurrent myocardial infarction, TLR - target lesion revascularization, TVR - target vessel revascularization

p=0.146], cardiac death (aHR, 2.019; 95% CI, 0.979–4.163; p=0.057), Re-MI (aHR, 1.203; 95% CI, 0.539–2.685; p=0.652), any repeat revascularization (aHR, 1.159; 95% CI, 0.720–1.866; p=0.543), TLR (aHR, 2.058; 95% CI, 0.881–4.809; p=0.096), TVR (aHR, 1.551; 95% CI, 0.854–2.816; p=0.149), and non-TVR (aHR, 0.733; 95% CI, 0.326–1.651; p=0.454) among the two groups were similar. However, the cumulative incidence of all-cause death in the ARB group was significantly higher than that in the ACEI group (aHR, 2.277; 95% CI, 1.154–4.495; p=0.018). Table 3 shows the independent predictors for MACEs and all-cause death at the 2-year time point. An advanced age (≥65 years, aHR, 1.431; 95% CI, 1.071–1.911; p=0.015) CPR on admission (aHR, 1.951; 95% CI, 1.009–3.776; p=0.047), and multivessel disease (aHR, 1.698; 95% CI, 1.275–2.262; p<0.001) were significant independent predictors for MACEs. An advanced age (≥65 years, aHR, 2.765; 95% CI, 1.584–4.826; p<0.001), decreased LVEF (<50%, aHR, 1.859; 95% CI, 1.144–3.022; p=0.012),

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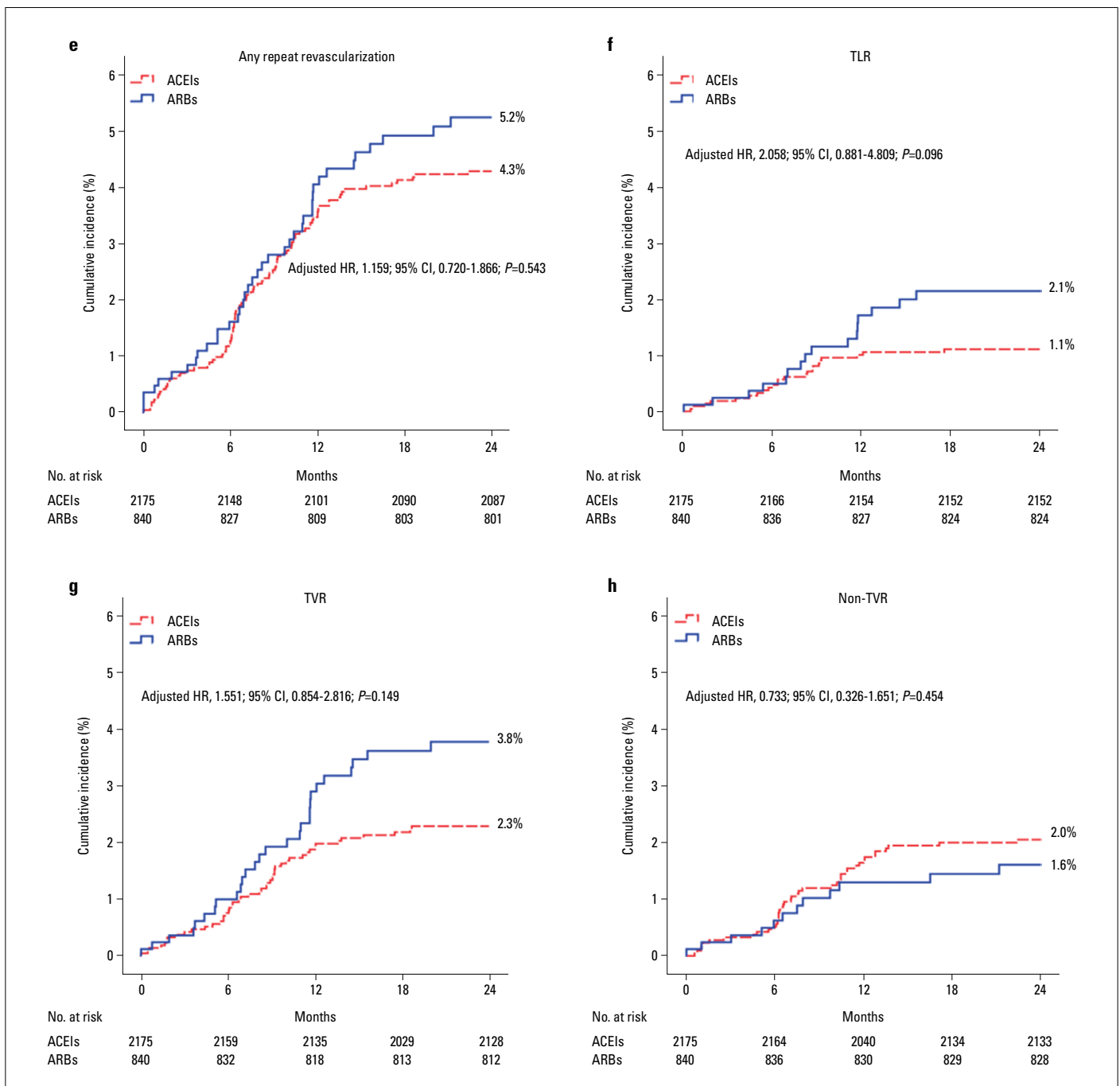DOI:10.14744/AnatolJCardiol.2019.60374

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), TVR (g), and non-TVR (h)

MACEs - major adverse cardiac event, ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin II type I receptor blockers, re-MI - recurrent myocardial infarction, TLR - target lesion revascularization, TVR - target vessel revascularization

and CPR on admission (aHR, 2.916; 95% CI, 1.114–7.630; p=0.029) were meaningful independent predictors for all-cause death. In female patients, and patients with decreased LVEF and non-cardiogenic shock, ACEIs may be preferred instead of ARBs to reduce the incidence of MACEs after stent implantation (Fig. 3a). In addition, ACEIs are preferred to ARBs in male patients and patients with decreased LVEF and non-cardiogenic shock to reduce the incidence of all-cause death (Fig. 3b).

Discussion

The main findings of this study are the following: (1) the cumulative incidence all-cause death in the ARBs group was significantly higher than that in the ACEIs group, (2) the cumulative incidences of MACE, CD, Re-MI, and any repeat revascularization including TLR, TVR, and non-TVR were similar between the two groups, and (3) an advanced age (≥65 years), decreased

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Table 3. Independent predictors for MACEs and all-cause death at 2 years in total study population

| | MACEs | | | | All-Cause Death | | | |
| | Univariate | | Multiple | | Univariate | | Multiple | |
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ACEIs vs. ARBs	1.424 (1.085–1.871)	0.011	1.371 (1.035–1.817)	0.028	2.044 (1.269–3.290)	0.003	1.840 (1.127–3.003)	0.015
Age (≥65 years)	1.676 (1.293–2.171)	<0.001	1.431 (1.071–1.911)	0.015	3.875 (2.320–6.471)	<0.001	2.765 (1.584–4.826)	<0.001
Gender (men)	1.290 (0.974–1.708)	0.076	1.056 (0.776–1.437)	0.728	2.115 (1.311–3.411)	0.002	1.307 (0.779–2.193)	0.310
LVEF (<50%)	1.324 (1.016–1.726)	0.037	1.160 (0.881–1.527)	0.289	2.315 (1.442–3.751)	0.001	1.859 (1.144–3.022)	0.012
Hypertension	1.330 (1.009–1.753)	0.043	1.132 (0.846–1.514)	0.405	1.819 (1.063–3.113)	0.029	1.304 (0.748–3.273)	0.350
Diabetes mellitus	1.512 (1.164–1.964)	0.002	1.286 (0.965–1.665)	0.088	1.792 (1.117–2.874)	0.015	1.339 (0.823–2.177)	0.239
Cardiogenic shock	1.590 (0.889–2.842)	0.118	1.378 (0.758–2.503)	0.293	1.714 (0.624–4.705)	0.296	1.197 (0.420–3.408)	0.736
CPR on admission	2.018 (1.070–3.803)	0.030	1.951 (1.009–3.776)	0.047	3.377 (1.359–8.390)	0.009	2.916 (1.114–7.630)	0.029
Beta-blocker	0.875 (0.599–1.278)	0.490	1.102 (0.750–1.618)	0.621	0.812 (0.415–1.587)	0.542	0.963 (0.486–1.911)	0.915
Prasugrel	1.376 (0.567–3.337)	0.481	1.217 (0.495–2.993)	0.669	2.144 (0.289–15.45)	0.449	1.777 (0.239–13.20)	0.574
Ticagrelor	1.576 (0.700–3.550)	0.272	2.029 (0.824–4.998)	0.124	-	-	-	-
Lipid-lowering agent	1.283 (0.883–1.864)	0.191	1.170 (0.798–1.716)	0.422	1.860 (1.017–3.400)	0.044	1.637 (0.888–3.017)	0.114
ACC/AHA type B2/C lesion	1.240 (0.902–1.704)	0.186	1.290 (0.925–1.798)	0.133	1.068 (0.610–1.867)	0.819	1.246 (0.691–2.248)	0.465
MVD	1.887 (1.430–2.489)	<0.001	1.698 (1.275–2.262)	<0.001	1.476 (0.907–2.402)	0.117	1.134 (0.688–1.868)	0.956
Stent diameter	0.799 (0.584–1.093)	0.161	0.931 (0.673–1.289)	0.667	0.682 (0.381–1.222)	0.199	0.955 (0.522–1.750)	0.883
Stent length	1.006 (0.993–1.020)	0.343	1.002 (0.987–1.016)	0.832	1.006 (0.983–1.031)	0.600	1.001 (0.974–1.029)	0.945

ACEIs - angiotensin-converting-enzyme inhibitors; ARBs - angiotensin II type 1 receptor blockers; HR - hazard ratio; LVEF - left ventricular ejection fraction; CPR - cardiopulmonary resuscitation; ACC/AHA - American College of Cardiology/American Heart Association; MVD - multivessel disease

LVEF(<50%), and CPR on admission were statistically significant independent predictors for all-cause death.

ACEIs are recommended with Class I, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or anterior infarct. Also, ACEIs should be considered in all patients in the absence of contraindications as Class IIa according to the ESC STEMI guidelines 2017 (4).

Dyslipidemia is a major predictor for cardiovascular clinical outcomes after AMI (22). Recently, many studies have focused on a high-dose statin therapy to reduce the risk of cardiovascular death, Re-MI, and coronary revascularization in AMI patients (24-26), but not on the important roles of ACEIs or ARBs (4-7). It has been reported that circulating LDL-cholesterol/apolipoprotein B particles may be involved in promoting the upregulation of AT1 receptor genes and this leads to the structural overexpression of vascular AT1 receptors for angiotensin II in cultured vascular smooth muscle cells, as well as in hypercholesterolemic rabbits (13, 27). The relationship between the renin-angiotensin system (RAS) and lipid disorders has been investigated in humans (28). The increased availability of angiotensin II triggers the atherosclerotic process and promotes the further activation of the RAS (29). Hence, these previous reports support the rationale for the use of RAS inhibitors in patients with lipid disorders. A Japanese study (30) has shown that compared to amlodipine, telmisartan could treat both the hemodynamic and metabolic aberrations seen in patients with metabolic syndrome. Considering previous reports

(15-17, 30) the possibility of a favorable interaction between RAS inhibitors and the prevention of cardiovascular disease in patients with hypercholesterolemia has been suggested.

Even though the beneficial effects of ACEIs and ARBs on reducing the incidence of MACEs in patients with AMI have been well established (3, 31, 32), the relative superiority of ACEIs and ARBs with regard to long-term clinical outcomes is still debatable (32, 33). ACEIs play important roles in the conversion of angiotensin I to angiotensin II and catalyze the breakdown of bradykinin to inactive peptides, and the process leads to the accumulation of bradykinin. Bradykinin exerts numerous beneficial effects on cardiovascular protection, including vasodilation, stimulation of nitric oxide (NO), and production of prostacyclin, endothelium-derived hyperpolarizing factor, and tissue plasminogen activator (34). ARBs selectively block the AT1 receptor. Unfortunately, this blockage induces the unwanted elevation of the circulating angiotensin II level through the stimulation of angiotensin II type 2 (AT2) receptors; this increase in the AT2 receptor levels is the main cause of cardiac myocyte hypertrophy and apoptosis, inflammation, plaque instability, and thrombus formation (35). In one study, ACEIs were reported to be associated with better survival than ARBs in AMI patients 2–5 years after survival discharge (aHR, 0.53; 95% CI, 0.38–0.74; p<0.001) (36). In terms of reducing the incidence of death, MI, angina, revascularization, or stroke, ARBs and ACEIs have similar capacities (HR, 0.97; 95% CI, 0.91–1.03; p=0.286), as per the VALIANT study (32).
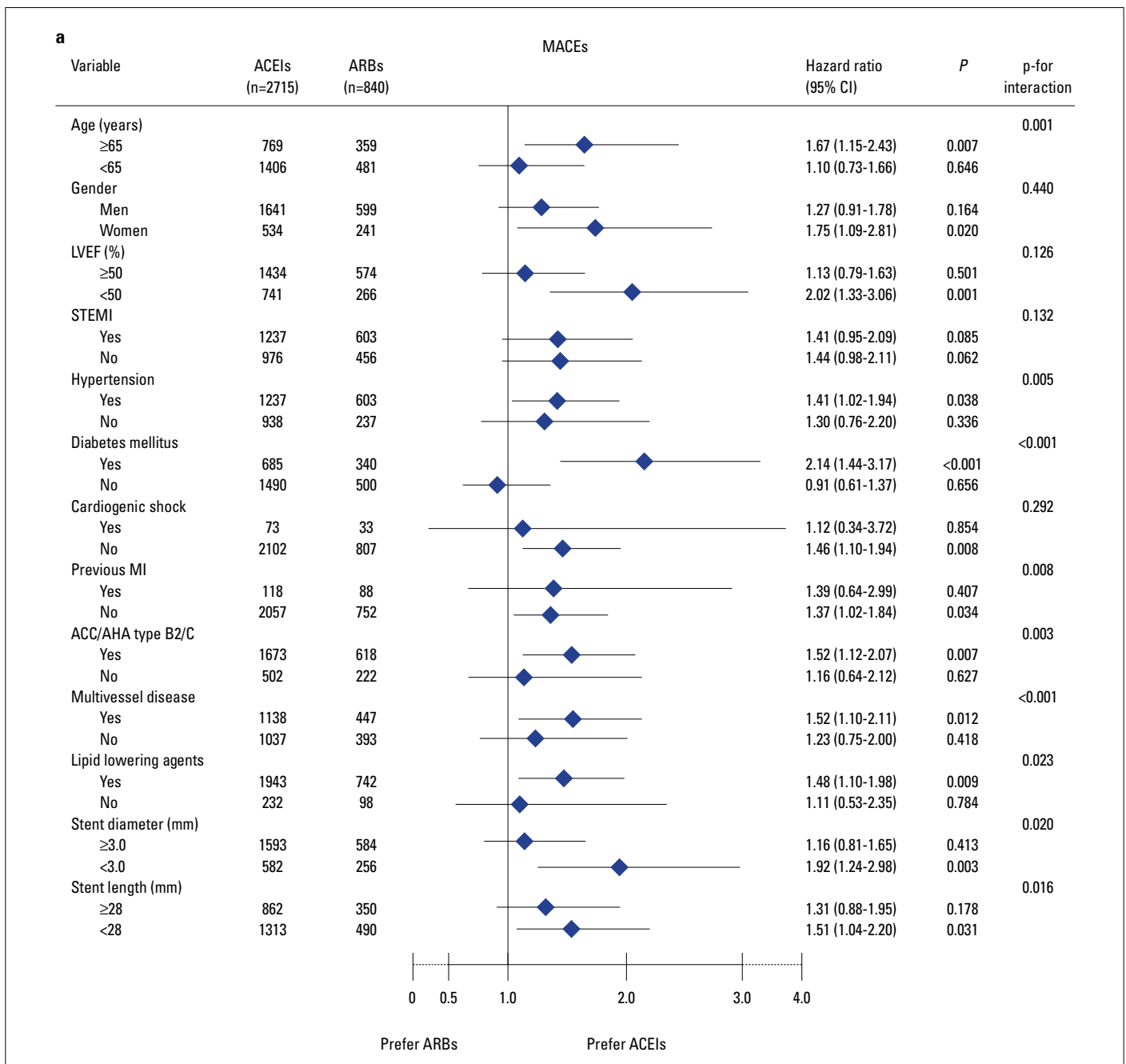
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a

MACEs

Variable	ACEIs (n=2715)	ARBs (n=840)		Hazard ratio (95% CI)	P	p-for interaction
Age (years)						0.001
≥65	769	359		1.67 (1.15-2.43)	0.007	
<65	1406	481		1.10 (0.73-1.66)	0.646	
Gender						0.440
Men	1641	599		1.27 (0.91-1.78)	0.164	
Women	534	241		1.75 (1.09-2.81)	0.020	
LVEF (%)						0.126
≥50	1434	574		1.13 (0.79-1.63)	0.501	
<50	741	266		2.02 (1.33-3.06)	0.001	
STEMI						0.132
Yes	1237	603		1.41 (0.95-2.09)	0.085	
No	976	456		1.44 (0.98-2.11)	0.062	
Hypertension						0.005
Yes	1237	603		1.41 (1.02-1.94)	0.038	
No	938	237		1.30 (0.76-2.20)	0.336	
Diabetes mellitus						<0.001
Yes	685	340		2.14 (1.44-3.17)	<0.001	
No	1490	500		0.91 (0.61-1.37)	0.656	
Cardiogenic shock						0.292
Yes	73	33		1.12 (0.34-3.72)	0.854	
No	2102	807		1.46 (1.10-1.94)	0.008	
Previous MI						0.008
Yes	118	88		1.39 (0.64-2.99)	0.407	
No	2057	752		1.37 (1.02-1.84)	0.034	
ACC/AHA type B2/C						0.003
Yes	1673	618		1.52 (1.12-2.07)	0.007	
No	502	222		1.16 (0.64-2.12)	0.627	
Multivessel disease						<0.001
Yes	1138	447		1.52 (1.10-2.11)	0.012	
No	1037	393		1.23 (0.75-2.00)	0.418	
Lipid lowering agents						0.023
Yes	1943	742		1.48 (1.10-1.98)	0.009	
No	232	98		1.11 (0.53-2.35)	0.784	
Stent diameter (mm)						0.020
≥3.0	1593	584		1.16 (0.81-1.65)	0.413	
<3.0	582	256		1.92 (1.24-2.98)	0.003	
Stent length (mm)						0.016
≥28	862	350		1.31 (0.88-1.95)	0.178	
<28	1313	490		1.51 (1.04-2.20)	0.031	

0   0.5   1.0   2.0   3.0   4.0

Prefer ARBs   Prefer ACEIs

Figure 3. Subgroup analysis for MACEs (a) and all-cause death (b)

MACEs - major adverse cardiac events, LVEF - left ventricular ejection fraction, STEMI - ST-segment elevation myocardial infarction, ACC/AHA - American College of Cardiology/American Heart Association, ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin II type I receptor blockers, CI - confidence interval

We assume that the main causative factor of these results is related with the fact that ACEIs can reduce the level of serum angiotensin II and activate the bradykinin system. In contrast, ARBs may cause the prolonged elevation of the level of angiotensin II level and the upregulation of angiotensin I. It is well known that the elevated serum level of angiotensin II plays an important role in the pathogenesis of coronary artery disease (37). Elevated angiotensin II levels may direct an increase in the serum cholesterol levels via the interaction with macrophage AT1 receptors, stimulating 3-hydroxy-3-methylglutaryl coenzyme A reductase gene ex-

pression and ultimately leading to cholesterol accumulation in the macrophages and foam cell formation (38). In this study, despite our attempts to adjust the diverse variables through the multiple Cox proportional hazard analysis, the baseline characteristics (Table 2) showed that the proportions of old age (≥65 years, 42.7% vs. 35.4%, p<0.001), hypertension (71.8% vs. 56.9%, p<0.001), and DM (40.5% vs. 31.5%, p<0.001) were significantly higher in the ARBs group than in the ACEIs group. In contrast, the numbers of STEMI cases, the peak levels of CK-MB, and troponin-I, the total cholesterol, and LDL-cholesterol levels, the number of cases with ACC/
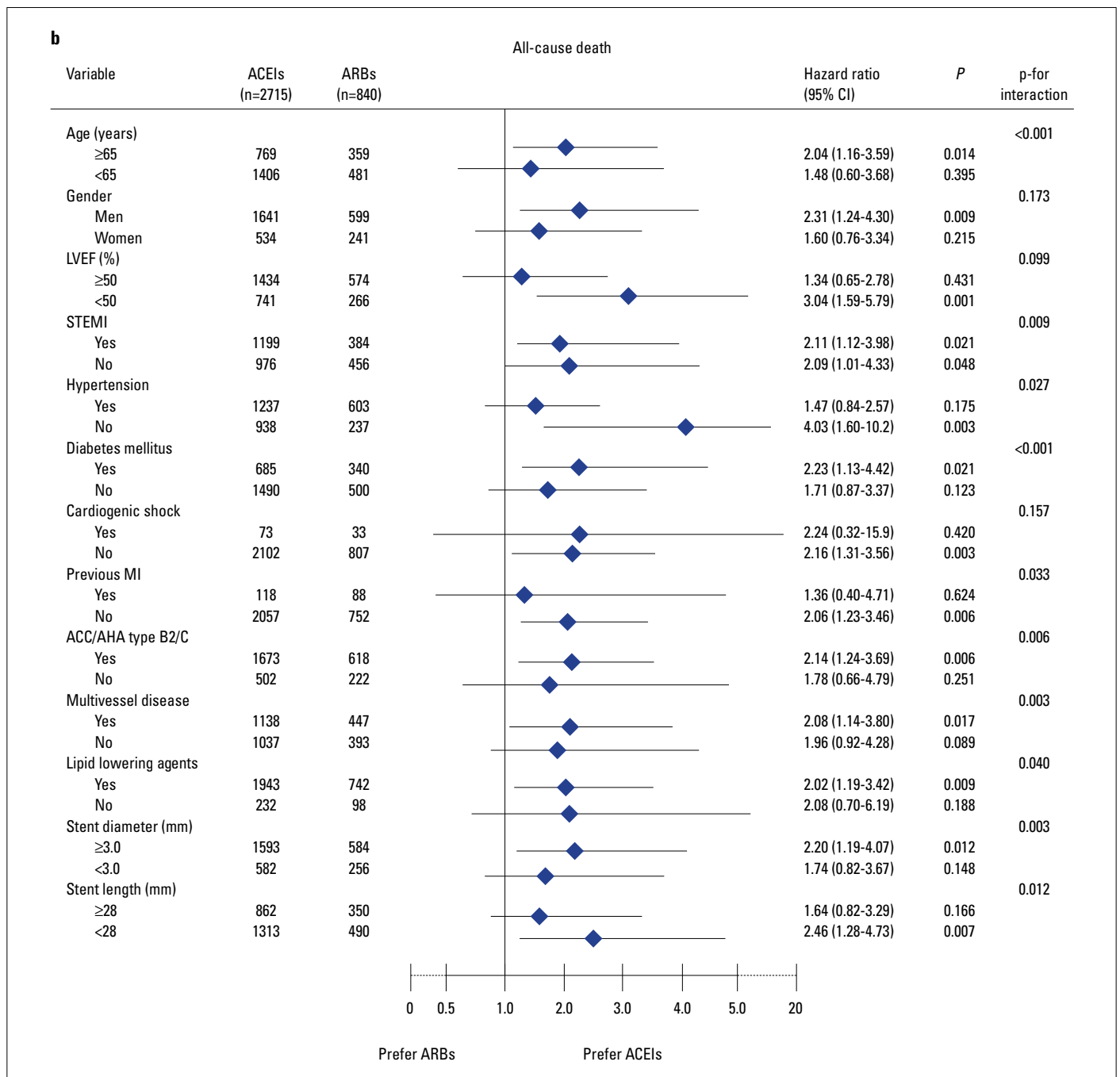
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b — All-cause death

Variable	ACEIs (n=2715)	ARBs (n=840)	Hazard ratio (95% CI)	P	p-for interaction
Age (years)					<0.001
≥65	769	359	2.04 (1.16-3.59)	0.014	
<65	1406	481	1.48 (0.60-3.68)	0.395	
Gender					0.173
Men	1641	599	2.31 (1.24-4.30)	0.009	
Women	534	241	1.60 (0.76-3.34)	0.215	
LVEF (%)					0.099
≥50	1434	574	1.34 (0.65-2.78)	0.431	
<50	741	266	3.04 (1.59-5.79)	0.001	
STEMI					0.009
Yes	1199	384	2.11 (1.12-3.98)	0.021	
No	976	456	2.09 (1.01-4.33)	0.048	
Hypertension					0.027
Yes	1237	603	1.47 (0.84-2.57)	0.175	
No	938	237	4.03 (1.60-10.2)	0.003	
Diabetes mellitus					<0.001
Yes	685	340	2.23 (1.13-4.42)	0.021	
No	1490	500	1.71 (0.87-3.37)	0.123	
Cardiogenic shock					0.157
Yes	73	33	2.24 (0.32-15.9)	0.420	
No	2102	807	2.16 (1.31-3.56)	0.003	
Previous MI					0.033
Yes	118	88	1.36 (0.40-4.71)	0.624	
No	2057	752	2.06 (1.23-3.46)	0.006	
ACC/AHA type B2/C					0.006
Yes	1673	618	2.14 (1.24-3.69)	0.006	
No	502	222	1.78 (0.66-4.79)	0.251	
Multivessel disease					0.003
Yes	1138	447	2.08 (1.14-3.80)	0.017	
No	1037	393	1.96 (0.92-4.28)	0.089	
Lipid lowering agents					0.040
Yes	1943	742	2.02 (1.19-3.42)	0.009	
No	232	98	2.08 (0.70-6.19)	0.188	
Stent diameter (mm)					0.003
≥3.0	1593	584	2.20 (1.19-4.07)	0.012	
<3.0	582	256	1.74 (0.82-3.67)	0.148	
Stent length (mm)					0.012
≥28	862	350	1.64 (0.82-3.29)	0.166	
<28	1313	490	2.46 (1.28-4.73)	0.007	

0   0.5   1.0   2.0   3.0   4.0   5.0   20

Prefer ARBs   Prefer ACEIs

Figure 3. Subgroup analysis for MACEs (a) and all-cause death (b)

MACEs - major adverse cardiac events, LVEF - left ventricular ejection fraction, STEMI - ST-segment elevation myocardial infarction, ACC/AHA - American College of Cardiology/ American Heart Association, ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin II type I receptor blockers, CI - confidence interval

AHA type C lesions, and the incidence of the use of first-generation DESs were higher in the ACEIs group than in the ARBs group. Hence, we speculate that these differences of baseline characteristics may play important roles in explaining the differences in mortality (e.g., all-cause death, CD) between the two groups. According to the OPTIMAAL study (33), the clinical benefits of RAS inhibitors were more profound in the high-risk patients' subgroup, i.e., in patients with anterior MI, decreased LVEF (≤40%), heart failure, prior MI, and tachycardia. Therefore, we thought that these

relatively poorer baseline characteristics of the ACEIs group may be related to a more prominent beneficial effect of RAS inhibitors in this group compared with the ARB group.

Lipid-lowering agents, such as statin, may decrease the expression and density of AT1 receptors caused by hypercholesterolemia (14) through the improvement of the endothelial responses to angiotensin II stimulation (39). In this study, the numbers of patients who were prescribed lipid-lowering agents were similar between the two groups (89.3% vs. 88.3%, p=0.430). Therefore,

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the influence of statins on the major clinical outcomes may be minimized in this study.

Finally, we think that the results of our study may provide some meaningful information to interventional cardiologists during or after PCI and help them ascertain which treatment strategy, i.e., ACEIs or ARBs treatment, is more appropriate for patients with AMI with dyslipidemia to reduce the incidence of all-cause death.

Study limitations

This study had several limitations (21). First, in this study, some data were under-reported or missing due to limitations of the registry data. Especially, the causes of non-CD are very important to understand the main findings of this study. Unfortunately, we could not provide the detailed causes of non-CD due to the above limitations. Therefore, we think that this is a shortcoming of this study. Second, this study was based on medications administered at discharge, and these registry data did not include the complete information concerning the presence or absence of the changes in the prescription doses of each drug during the follow-up period and long-term drug compliance (especially, crossover between ACEIs and ARBs), and drug-related adverse events; this may act as an important factor causing bias in this study. Third, we defined dyslipidemia according to the Asian guidelines such as the Japan Atherosclerosis Society guidelines; these criteria may differ according to the race and region of the patients. Fourth, the information concerning the criteria for the initiation of ACEIs and ARBs administration and the health situation when the ARBs administration was started were very important determinants for long-term clinical outcomes. However, we could not provide this information due to limitations associated with the registry data; these factors may contribute to bias. Fifth, the achievement of the target blood cholesterol level (i.e., LDL cholesterol) was a very important prognostic parameter after statin therapy during the follow-up period. However, we could not present the follow-up results of these lipid profiles due to limitations of the registry data; this may also represent a bias. Sixth, despite the multiple Cox proportional hazard regression analysis, the results of this study may differ according to the variables not included in this registry or in this analysis.

Conclusion

In this study, ACEIs were the preferred treatment modality compared to ARBs for patients with AMI with dyslipidemia, who underwent a successful stent implantation, to reduce the incidence of all-cause death during a 2-year follow-up period. However, additional research is required to determine the clinical implications of these results.

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