CLINICAL RESEARCH STUDY

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Angiotensin Receptor Blockers Versus Angiotensin Converting Enzyme Inhibitors in Acute Myocardial Infarction Without Heart Failure

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ABSTRACT

BACKGROUND: Whether angiotensin II receptor blockers (ARBs) can be an alternative to angiotensin-converting enzyme inhibitors (ACEIs) in patients without heart failure (HF) after acute myocardial infarction (MI) remains controversial. The aim of this study was to compare clinical outcomes between initial ARB and ACEI therapy in patients with MI without HF.

METHODS: Between 2010 and 2016, a total of 31,013 patients who underwent coronary revascularization for MI with prescription of ARBs or ACEIs at hospital discharge were enrolled from the Korean nationwide medical insurance data. Patients who had HF at index MI were excluded. The primary outcome was all-cause death. The secondary outcomes included recurrent MI, hospitalization for new heart HF, stroke, and a composite of each outcome.

RESULTS: Of 31,013 patients, ARBs were prescribed in 12,685 (40.9%) and ACEIs in 18,328 (59.1%). Patients receiving ARBs had a lower discontinuation rate compared with those receiving ACEIs (28.2% vs 43.5%, adjusted hazard ratio [HR] 0.34; 95% confidence interval [CI] 0.31-0.37; $P < .01$). During a median follow-up of 2.2 years, 2480 patients died. The incidence rate of all-cause death in patients receiving ARBs and those receiving ACEIs was 27.7 and 22.9 per 1000 person-years, respectively (adjusted HR 1.04; 95% CI 0.95-1.13; $P = .40$). There were no significant differences in the secondary outcomes between patients receiving ARBs and those receiving ACEIs, except stroke (19.2 vs 13.6 per 1000 person-years; adjusted HR 1.17; 95% CI 1.04-1.32; $P = .01$). In a subgroup analysis, a higher mortality was observed with ARBs compared with ACEIs in patients with diabetes.

CONCLUSIONS: In this nationwide cohort, there was no significant difference in the incidence of all-cause death between ARBs and ACEIs as discharge medications in patients with myocardial infarction without heart failure. Angiotensin II receptor blockers would be an alternative to ACEIs for those intolerant to ACEI therapy.

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KEYWORDS: Angiotensin II receptor blockers; Angiotensin-converting enzyme inhibitors; myocardial infarction; heart failure

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INTRODUCTION

Renin-angiotensin-aldosterone system (RAAS) blockade has become the first-line strategy in the management of cardiovascular disease. Angiotensin-converting enzyme inhibitors (ACEIs) block angiotensin II, which plays an essential role in regulation of blood pressure and vascular remodeling.[1] With solid data regarding its safety and benefits for cardiovascular disease,[1,2] ACEIs remain a gold standard renin-angiotensin system blocker. However, ACEIs are associated with higher rates of drug-related adverse symptoms and drug discontinuation compared with angiotensin II receptor blockers (ARBs), another class of RAAS blockade drugs.[3-5]

In patients with myocardial infarction (MI) with heart failure (HF) or left ventricular (LV) systolic dysfunction, current guidelines recommend ACEI therapy during and after hospitalization[6,7] and ARB therapy in those who are ACEI intolerant, based on the results of a large randomized trial.[4] In patients with MI but without HF, ACEI therapy should be considered in the absence of contraindications.[8,9] However, the evidence for ARB therapy is limited in these patients, and the guidelines do not specifically cover the use of ARBs. In patients with ST-segment-elevation MI (STEMI) with preserved LV ejection fraction, ARBs showed beneficial effects, comparable with ACEIs.[10] However, follow-up duration was limited to 12 months. In addition, outcome was limited to death or MI and event rates were relatively low. Therefore, in the present study, we sought to compare the long-term clinical outcomes between ARB and ACEI in patients without HF using recent nationwide medical insurance data of the Korean population.

CLINICAL SIGNIFICANCE

- Angiotensin II receptor blockers were frequently prescribed to approximately 31% of patients with myocardial infarction without heart failure.
- The persistence rate was higher with angiotensin II receptor blockers compared with angiotensin-converting enzyme inhibitors.
- No significant difference in all-cause death was observed between patients receiving angiotensin II receptor blockers and those receiving angiotensin-converting enzyme inhibitors, but there was a higher incidence of stroke with angiotensin II receptor blockers.
- In patients with diabetes mellitus, mortality was lower with angiotensin-converting enzyme inhibitors.

METHODS

Study Population

Korea has a single-payer national health system, and the National Health Insurance Service (NHIS) maintains national records of all covered inpatient and outpatient visits, procedures, and prescriptions. This was a population-based retrospective cohort study built using the NHIS data. The NHIS provides 50% of the random sample of the national data if the study includes information about specific drugs. The Institutional Review Board of Samsung Medical Center approved this study and informed consent was waived as we used de-identified administrative data.

Among all Korean males and females over 18 years old between January 1, 2010, and November 31, 2016, we selected patients who underwent revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) for MI (n = 64,934) during index hospitalization. Because our objective was to compare the clinical outcomes between ARB and ACEI after hospital discharge among patients without HF, we excluded the patients who had HF at index MI (n = 12,169). We also excluded the patients who had a history of MI (I21-I23, I25.2) (n = 3984), stroke (I60-I63) (n = 5315), or renal disease (N18, N19) (n = 2359). Then we excluded the patients without prescriptions of either ARBs or ACEIs (n = 13,111) or those with a prescription for both medications at discharge (n = 236). In addition, we excluded the patients who had death, recurrent MI, HF, or stroke within 30 days after index MI (n = 6551) or those without any medical records available (n = 542). Finally, 31,013 patients were included in this study (Figure 1).

Outcomes and Definitions

The NHIS claims for inpatient and outpatient visits and procedures, and the prescriptions were coded using the International Classification of Diseases, 10th Revision. As the NHIS routinely audits the claims, such data are considered reliable and used in numerous peer-reviewed publications. With regard to the diagnosis of MI, the validation study in 2013 showed the value of 93%.[11]

The primary outcome was all-cause death. Vital status and cause of death were obtained from the death certification collected by Statistics Korea at the Ministry of Strategy and Finance of South Korea. This vital information was linked to the NHIS database using a unique number provided for each participant. The secondary outcomes were all-cause death, recurrent MI, hospitalization for new HF, stroke, and a composite of individual components. Because the patients who had death, recurrent MI, HF, or stroke within 30 days after the index MI were excluded, the outcomes that occurred beyond 30 days after discharge were counted.

The study exposure was an initial use of ARBs or ACEIs at hospital discharge. The initial use of study drugs was defined as the prescription for at least 7 days among the admission claims or as the first outpatient clinic prescription within 30 days after discharge. If a new prescription had been redeemed within 180 days after expiration of prior

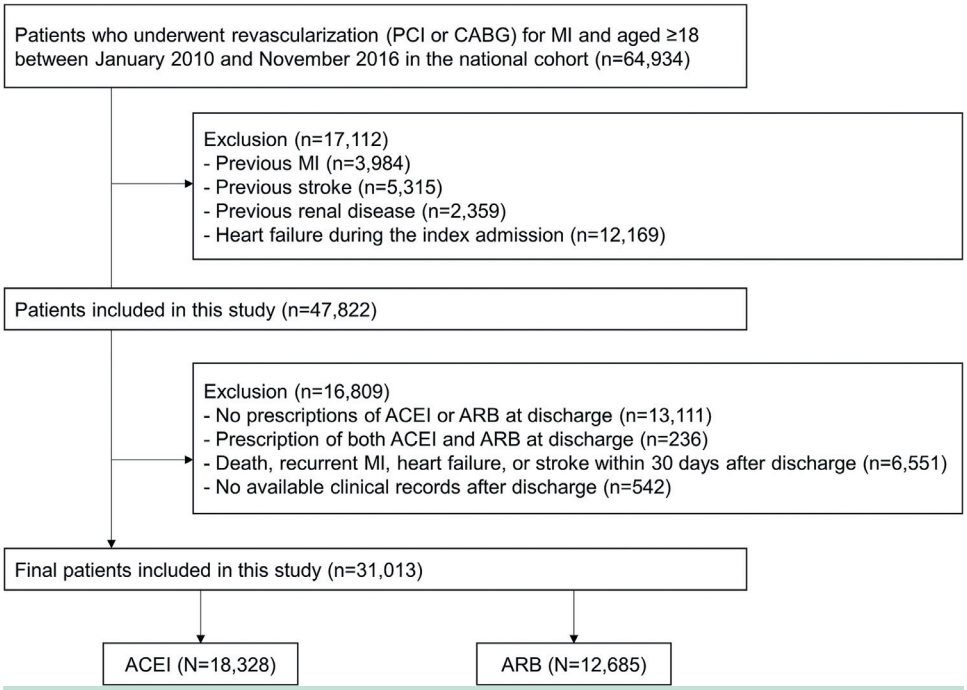

Figure 1 Study flow.
ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CABG = coronary artery bypass graft surgery; MI = acute myocardial infarction; PCI = percutaneous coronary intervention.

prescription, the study drug was considered to be continued. Switching from ACEIs to ARBs or vice versa was considered drug discontinuation.

Previous ACEI or ARB therapy was defined as the presence of prescription during 6 months prior to the index MI. Comorbidities were summarized using the Charlson index. We included diabetes mellitus (E11-E14), hypertension (I10-I13, I15), atrial fibrillation or flutter (I48), chronic obstructive pulmonary disease (J43-J46), and peripheral artery disease (I73, I701, I702, I708, I709, I771, I792, K551, K558, K559). Comorbidities were defined as the presence of codes in claims within a year before index MI. We identified medications of calcium channel blockers, statins, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulants, beta-blockers, and spironolactone at discharge. The medications were identified using the Korean Drug and Anatomical Therapeutic Chemical Codes (Supplementary Table 1, available online).

Statistical Analysis

Patients were followed-up until the development of study outcomes, or the end of the study period (December 31, 2016). Cumulative incidence of each outcome was estimated by the Kaplan-Meier method and log rank tests were applied to evaluate differences between the groups. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) for incidence of clinical outcome using a mixed-effects Cox regression model including an admitted hospital as a random intercept to adjust hospital effect. We also compared the compliance between ARB and ACEI using a Cox regression model with the endpoint defined as discontinuation of initial class of study drugs, development of study outcomes, or end of study period. Furthermore, to account for potential confounding factors, we adjusted for age, sex, previous revascularization, previous ARB or ACEI therapy, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation or flutter, chronic obstructive pulmonary disease, peripheral artery disease, malignancy, admission at tertiary hospital, and discharge medications including calcium channel blockers, statins, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulant, beta-blockers, or spironolactone in multivariable Cox analysis. We examined the proportional hazards assumption using plots of the log-log survival function and Schoenfeld residuals.

We also used an inverse probability of treatment weighting approach on the basis of propensity scores for confounding adjustment.[12] Propensity scores for ARB use were created for each participant using logistic regression, with baseline covariates listed in Table 1 as independent variables. Stabilized weights were calculated from the propensity scores to reweight the study population and achieve covariate balance by creating a pseudo-population. To limit the influence of extreme weights, we truncated the weights at the 1st and 99th percentiles.[13]

We conducted subgroup analyses by age (aged $<$ 65 years vs $\geq$ 65 years), sex, hypertension, diabetes, types of hospital (tertiary hospital vs others), and use of beta-blockers. In addition, we compared the clinical outcomes according to presence of previous ACEI or ARB therapy.

Table 1 Baseline Characteristics*

Variables	ARBs (n = 12,685)	ACEIs (n = 18,328)	*P* Value	SMD
Age, year, mean (SD)	63.5 (12.6)	61.7 (12.6)	<.001	-0.143
Sex, male	9269 (73.1)	14,343 (78.3)	<.001	0.121
Previous revascularization	812 (6.4)	732 (4.0)	<.001	-0.109
Previous ACEIs/ARBs	5250 (41.4)	5295 (28.9)	<.001	-0.264
Charlson index, median (IQR)	1 (0-1)	1 (0-1)	<.001	0
Comorbidity				
Diabetes mellitus	2833 (22.3)	3454 (18.8)	<.001	-0.086
Hypertension	5306 (41.8)	6538 (35.7)	.03	-0.127
Hyperlipidemia	678 (5.3)	1089 (5.9)	<.001	0.026
Atrial fibrillation of flutter	141 (1.1)	93 (0.5)	<.001	-0.067
COPD	944 (7.4)	1139 (6.2)	<.001	-0.049
Peripheral artery disease	262 (2.1)	294 (1.6)	.003	-0.034
Malignancy	608 (4.8)	856 (4.7)	.62	-0.006
Tertiary hospital	5458 (43.0)	9842 (53.7)	<.001	0.215
Medications at discharge				
Calcium channel blockers	3941 (31.1)	3927 (21.4)	<.001	-0.22
Statins	11,477 (90.5)	17,076 (93.2)	<.001	0.098
Aspirin	12,389 (97.7)	17,717 (96.7)	<.001	-0.06
Clopidogrel	9332 (73.6)	14,543 (79.3)	<.001	0.137
Ticagrelor or prasugrel	3703 (29.2)	4,855 (26.5)	<.001	-0.06
Anticoagulant	330 (2.6)	401 (2.2)	.02	-0.027
Beta-blockers	10,760 (84.8)	15,964 (87.1)	<.001	0.066
Spironolactone	1625 (12.8)	2246 (12.3)	.15	-0.017

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor II blockers; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; SD = standard deviation.

*Values are presented as n (%), mean (SD), or median (IQR).

All *P* values were 2-sided, and a *P* value of less than .05 was considered significant. Analyses were performed with the use of SAS Visual Analytics (SAS Institute Inc, Cary, NC).

RESULTS

Clinical Characteristics

Among 31,013 eligible patients, 12,685 (40.9%) received ARBs. Compared with patients receiving ACEIs, those receiving ARBs were more likely to be older and female, and have comorbidities and previous ARB or ACEI therapy (Table 1). There were significant differences in the discharge medications between patients receiving ARBs and those receiving ACEIs.

Persistence Rate of Initial Drug

During the study period, the median duration of persistence of initial drugs in patients receiving ARBs and those receiving ACEIs was 614 and 186 days, respectively ($P < .01$). Patients receiving ARBs had a lower discontinuation rate compared with those receiving ACEIs (28.2% vs 43.5%; adjusted HR 0.34; 95% CI 0.31-0.37; $P < .01$; Table 2). The ACEI to ARB switching rate was 20.7%, whereas the ARB to ACEI switching rate was 3.1% (Figure 2).

Outcomes

During the follow-up (median 2.2 years, interquartile range 1.0-3.9), 2480 patients died. The incidence rate of all-cause death in patients receiving ARBs and those receiving

Table 2 Discontinuation of Initial Therapy

		Discontinuation*			
	Duration (Days) Median (IQR)	Percent	Crude HR (95% CI)	Adjusted† HR (95% CI)	IPTW HR (95% CI)
ACEIs (n = 18,328)	186 (35-739)	43.5%	*Reference*	*Reference*	*Reference*
ARBs (n = 12,685)	614 (209-1299)	28.2%	0.35 (0.34-0.36)	0.34 (0.31-0.37)	0.54 (0.39-0.75)
P value	<.01	<.01	<.01	<.01	<.01

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor II blockers; CI = confidence interval; HR = hazard ratio; IPTW = inverse probability treatment weight; IQR = interquartile range.

*Drug switching (ACEIs to ARBs, or ARBs to ACEIs) was not included in the discontinuation.

†Adjusted for age, sex, previous revascularization, Previous ACEI or ARB therapy, presence of diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation or flutter, chronic obstructive pulmonary disease, peripheral artery disease, or malignancy, admission at tertiary hospital, and other medications including calcium channel blockers, statins, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulant, beta-blockers, or spironolactone at discharge.

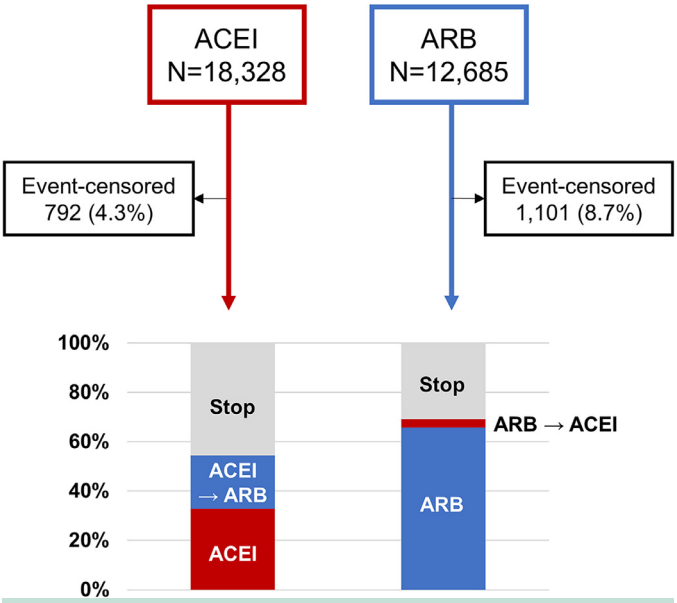

Figure 2 Prescription status of ACEIs or ARBs during follow-up period.
Among patients receiving ACEIs at discharge, 43.5% discontinued ACEIs, 20.7% switched to ARBs, and 31.4% continued ACEIs at the time of follow-up. Among patients receiving ARBs at discharge, 28.2% discontinued ARBs, 3.1% switched to ACEIs, and 60.1% continued ARBs. ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers.

ACEIs was 27.7 and 22.9 per 1000 person-years, respectively (Table 3 and Figure 3). Compared with patients receiving ACEIs, the adjusted HR for all-cause death in patients receiving ARBs was 1.04 (95% CI 0.95-1.13; $P = .40$), which was not statistically significant.

The incidence rate of stroke was significantly higher in patients receiving ARBs compared with those receiving ACEIs (19.2 vs 13.6 per 1000 person-years; adjusted HR 1.17; 95% CI 1.04-1.32; $P = .01$). There were no significant differences in the incidence rate of recurrent MI, hospitalization for HF, or composite of all-cause death, recurrent MI, hospitalization for HF, and stroke between patients receiving ARBs and those receiving ACEIs.

Subgroup Analysis

The association between the use of ARBs and risk of all-cause death were consistent in various subgroups (Figure 4). However, there was a significant interaction for the risk of all-cause death between diabetes and ARB therapy (interaction $P = .03$). With diabetes, the risk of all-cause death was significantly higher in patients receiving ARBs than those receiving ACEIs, but without diabetes, the risk of all-cause death was not significantly different between the groups.

The incidence rate of all-cause death was not significantly different between patients receiving ARBs and those receiving ACEIs regardless of previous ARB or ACEI therapy (Supplementary Table 2, available online).

Primary Outcomes Compared with those of Patients Not Receiving Either ACEIs or ARBs

Supplementary Table 3 (available online) presents the baseline characteristics, including patients not receiving either ACEIs or ARBs (n = 9494). Compared with patients not receiving ACEIs or ARBs, those receiving ACEIs had a significantly lower incidence rate of all-cause death (adjusted HR 0.86; 95% CI 0.79-0.93, $P < .001$). However, statistical significance was not reached for those receiving ARBs (adjusted HR 0.89; 95% CI 0.75-1.05, $P = .18$, Supplementary Table 4, available online).

DISCUSSION

In the present study, we investigated clinical outcomes of ARB therapy compared with ACEI in patients with MI but without HF. The main findings were as follows: First, in real-world practice, ARBs were frequently prescribed at hospital discharge in patients with MI without HF. Second, the persistence rate was substantially higher with ARBs than ACEIs during the study period. Third, there was no significant difference in the incidence of all-cause death in patients receiving ARBs and those ACEIs, but the incidence of stroke was higher in those with ARBs.

In patients with MI, early ACEI therapy reduces mortality and adverse events including recurrent MI, HF progression, and stroke.[2,14,15] However, adverse reactions to ACEI are frequently reported. The incidence of cough was

Table 3 Clinical Outcomes Between ACEIs and ARBs

Outcomes	ARBs		ACEIs		Risk of ARBs Compared with ACEIs					
					Unadjusted		Adjusted†		IPTW	
	Number of Cases	Incidence Rate (per 1000 Person-Years)	Number of Cases	Incidence Rate (per 1000 Person-Years)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death	1077	27.7	1403	22.9	1.22 (1.11−1.34)	<.001	1.04 (0.95−1.13)	.40	1.06 (0.97-1.15)	.18
Recurrent MI	493	12.0	652	10.3	1.14 (0.99−1.31)	.07	1.12 (0.97−1.28)	.13	1.12 (0.97-1.29)	.14
Hospitalization for HF	464	11.3	586	9.1	1.19 (1.04−1.36)	.009	1.01 (0.88−1.14)	.93	1.02 (0.88-1.17)	.83
Stroke	780	19.2	860	13.6	1.37 (1.22−1.54)	<.001	1.17 (1.04−1.32)	.01	1.17 (1.04−1.32)	.01
Composite*	2049	56.3	2661	45.9	1.22 (1.14−1.29)	<.001	1.07 (1.00−1.14)	.05	1.09 (1.03-1.15)	<.001

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CI = confidence interval; HF = heart failure, HR = hazard ratio; MI = myocardial infarction; IPTW = inverse probability treatment weight.

*A composite of all-cause death, recurrent MI, hospitalization for HF, and stroke.

†Adjusted for age, sex, previous revascularization, previous ACEI or ARB therapy, presence of diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation or flutter, chronic obstructive pulmonary disease, peripheral artery disease, or malignancy, admission at tertiary hospital, and other medications including calcium channel blockers, statins, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulant, beta-blocker, or spironolactone at discharge.

reported in half of East Asians taking ACEIs.[16] Consequently, up to 20% of patients cannot tolerate ACEI therapy.[16,17] Angiotensin II receptor blockers are another class of drugs for RAAS blockade with beneficial effects on cardiovascular protection.[17] In the Valsartan in Acute Myocardial Infarction (VALIANT) trial, valsartan was as effective as captopril with less drug-related adverse events in patients with MI complicated by HF or evidence of LV systolic dysfunction.[4] Therefore, the current practice guidelines recommend ARB therapy after acute MI in patients who are intolerant of ACEIs.[7-9] However, in patients with MI but without HF, there are limited data on the effectiveness of ARB therapy compared with ACEI therapy. There is no relevant randomized trial on this topic. Although several observational studies reported favorable outcomes of ARB therapy compared with ACEI therapy in patients with MI,[18,19] the inclusion criteria were not limited to those without HF. Therefore, we investigated the long-term clinical outcomes between ARB and ACEI therapy in a broad spectrum of patients with MI without HF using large nationwide data. Considering that a majority of patients experiencing MI do not have HF or LV dysfunction in the primary percutaneous coronary intervention era,[20] the results of our study are of great clinical importance.

In the present study, the crude incidence of all-cause death was higher in patients receiving ARBs than those receiving ACEIs. However, the adjusted risk for all-cause death was not significantly different between ARB and ACEI therapy because patients receiving ARB had a higher risk profile at baseline, such as older age and comorbidities, than those receiving ACEIs. These findings are consistent with a previous study by Yang et al[10] In that study including 6698 patients with STEMI with preserved LV systolic function, those with ARBs were older and were more likely to be female and have hypertension than those with ACEIs. After adjusting for risk factors, ARBs showed beneficial effects comparable with ACEIs with regard to all-cause death or MI at 1 year after index MI. Compared with the study by Yang et al,[10] our study included a much larger number of subjects receiving ARBs (12,685 vs 1185) with STEMI as well as non-STEMI, and had longer duration of follow-up. In addition, hospitalization for new HF and stroke were added for the outcome analysis in our study. Unexpectedly, the incidence rate of stroke was significantly lower in patients receiving ACEIs than those receiving ARBs. Both ACEIs and ARBs are known to have a protective effect against stroke development.[21,22] In MI patients, however, there was a report that favors ACEIs over ARBs with regard to the stroke prevention.[23] ACEIs' biological action on circulating angiotensin II, angiotensin 1-7 and bradykinin, potentially related with vasculopathy and thrombus formation may explain the different outcomes between ACEI and ARB.[24,25] Future studies are needed to compare the effectiveness of ARBs and ACEIs for stroke prevention in patients with MI.

Patients receiving ARBs had a higher drug persistence rate than those receiving ACEIs. This finding may be

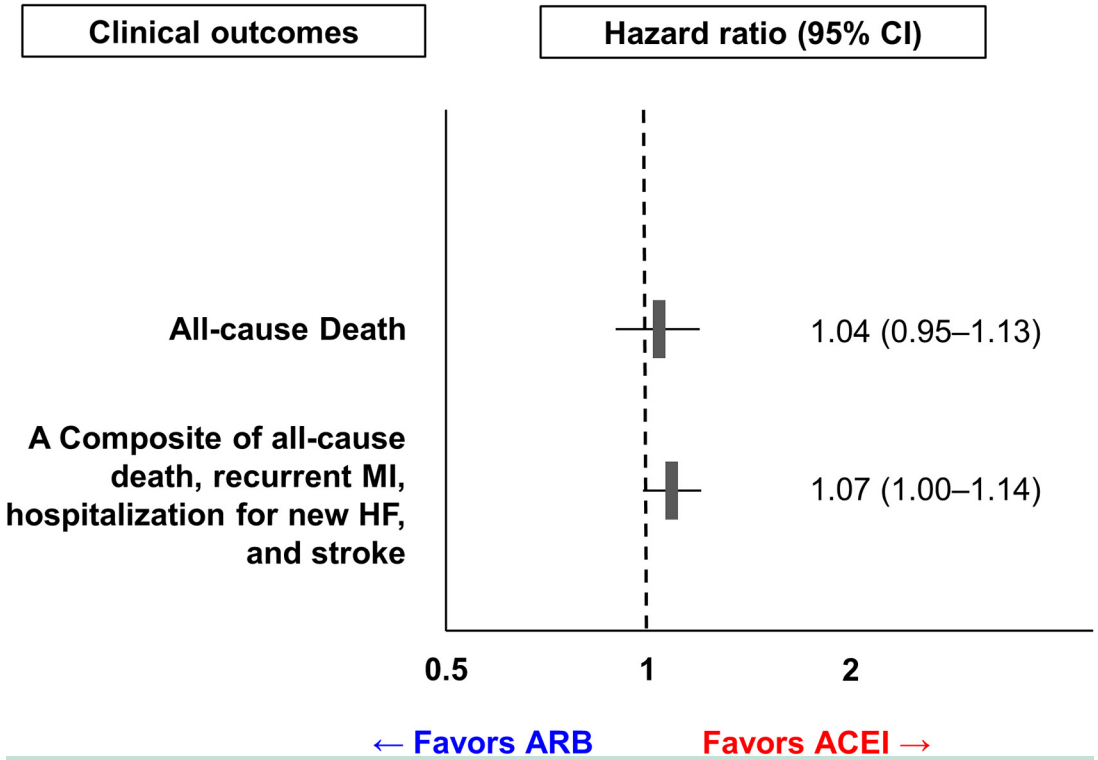

Figure 3 Adjusted hazard ratios for clinical outcomes between ARBs and ACEIs.
ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CI = confidence interval; HF = heart failure; MI = myocardial infarction.

related to the drug-related adverse reactions to ACEIs, as the VALIANT study showed higher rates of drug-related adverse events and subsequent discontinuation of captopril than valsartan.[4] Given the drug intolerance of ACEIs, evidence of ARB therapy in patients with MI is required in real-world practice. In our study, the longer duration of ARB therapy than ACEI therapy might have contributed to the favorable outcomes with ARBs. In contrast with ARB users, more than half of patients who discontinued initial ACEIs during follow-up switched to ARB therapy, which may be one of the reasons for no significant difference in clinical outcomes between ACEI and ARB users. Our findings would give practical evidence of ARB therapy as an alternative to ACEI therapy in patients MI without HF who are intolerant of ACEI therapy.

The effectiveness of ARB therapy for all-cause death was consistent in various subgroups, except for diabetes. This finding is in line with a previous meta-analysis demonstrating the mortality benefit of ACEIs, but not ARBs, in patients with diabetes.[26] Several trials have also raised concerns about the cardiovascular mortality related with ARB use in diabetic patients with coronary heart disease.[27,28] For this high-risk patient group, ACEIs should be considered as the first-line renin-angiotensin-aldosterone blockade, as current guidelines recommend.

Our study had several limitations. First, this was an observational study. The choice of drug was at the physicians' discretion. Although we only included patients who had received ARBs or ACEIs at hospital discharge, there was a potential selection bias induced by unrecorded confounders other than renal dysfunction or hypotension. Information on type of MI and angiographic severity, anthropometric and behavioral factors was lacking, and we had only limited information on disease management based on claims. Second, we did not consider the changes of medication during follow up other than ARB or ACEI. Third, there was a high discontinuation rate of the study drugs, and the reasons for discontinuation of initial ARBs or ACEIs were unclear. Although the drug intolerance of ACEIs is well known, the early discontinuation of ACEIs in our study might have been caused by physician or patient preference in the absence of side effects. However, the discontinuation rates of ACEIs in real-world practice have been reported as high as 47%, similar to our study, mainly due to drug intolerance.[29] In any case, our study provides the real-world discontinuation rates of ACEIs and ARBs in patients without HF after MI, which may contribute to clinical outcomes. Nevertheless, it is important to note that there may be ethnic differences in response or tolerance to ACEIs,[16] so that the initial use of ARBs in patients with MI without HF should be determined with caution in those anticipated to be tolerant to ACEIs. Last, there was no information on LV ejection fraction. However, as recent data demonstrated that the majority of patients with MI, particularly those without HF, have preserved LV ejection fraction,[20,30] the inclusion of patients with reduced LV

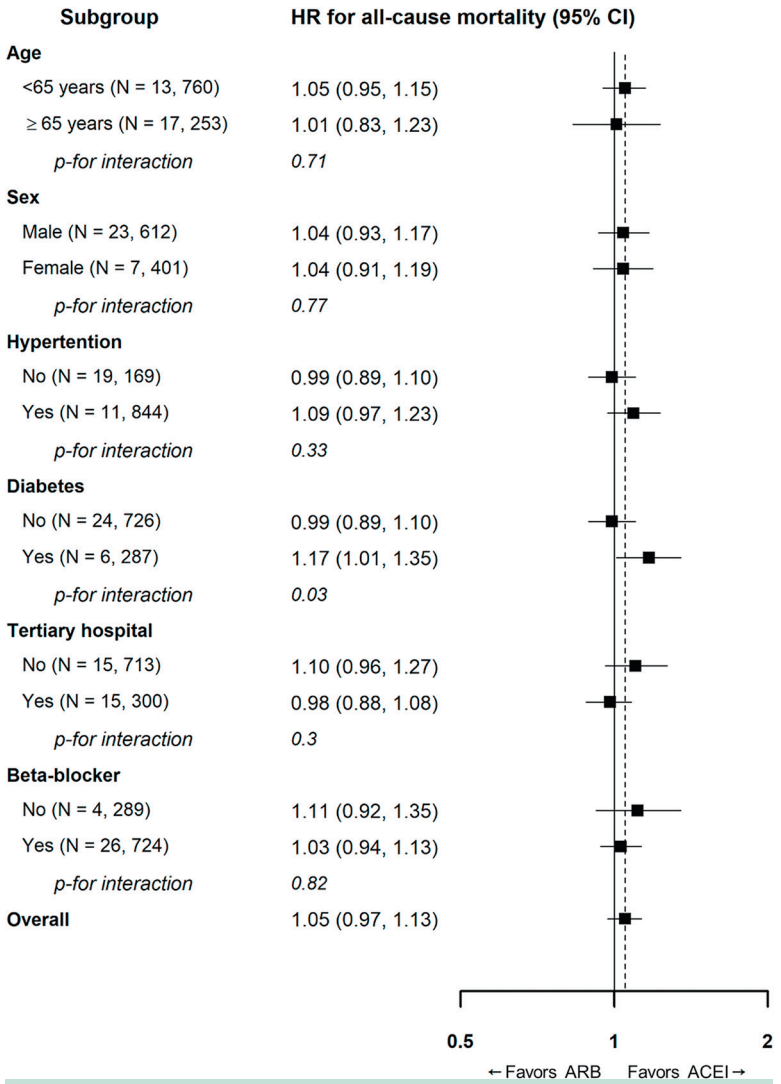

Figure 4 Subgroup analysis for all-cause death.
Adjusted for age, sex, previous revascularization, previous ACEI/ARB therapy, presence of diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation of flutter, chronic obstructive pulmonary disease, peripheral artery disease, or malignancy, admission at tertiary hospital, and discharge medication including calcium channel blockers, statins, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulant, beta-blockers, or spironolactone. ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CI = confidence interval; HR = hazard ratio.

ejection fraction might have had trivial effects on the conclusions of this study. However, the interpretation of this study should be based on the absence of HF.

CONCLUSIONS

In this nationwide registry, there was no significant difference in the incidence of all-cause death between ARB and ACEI therapy in patients with MI but without HF. Our study presents the long-term outcomes of ARB therapy, providing real-world evidence of ARB use as an alternative for those intolerant to ACEIs. However, it is important note that ARBs were associated with a higher risk of stroke in overall population and a higher mortality in patients with diabetes, supporting the recommendation that ACEIs should be considered as the first-line therapy. A large, randomized study is needed to confirm the current findings.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2024.07.020.

Supplementary Table 1 List of Medication Codes

Medication	Korean Drug and Anatomical Therapeutic Chemical Codes
ACEIs	104201ATB, 104202ATB, 114701ATB, 122901ATB, 122902ATB, 122903ATB, 133001ATB, 133002ATB, 133003ATB, 140901ATB, 151601ATB, 151602ATB, 151603ATB, 163501ATB, 163502ATB, 173401ATB, 173402ATB, 173403ATB, 184501ATB, 196801ATB, 196802ATB, 211301ATB, 211302ATB, 221901ATB, 222401ACH, 222401ATB, 222402ACH, 222402ATB, 222404ATB, 235002ATB, 262200ATB, 262300ATB, 440300ATB, 447100ATB, 447200ACH, 447200ATB, 448600ATB, 448700ATB, 453600ATB, 453700ATB, 499200ATB, 499300ATB, 501601ATB, 501602ATB, 510401ATB, 510402ATB, 510403ATB, 556200ATB
ARBs	122601ATB, 122602ATB, 122603ATB, 122604ATB, 177301ATB, 177303ATB, 185701ATB, 85702ATB, 247101ATB, 247102ATB, 247103ATB, 247104ATB, 262500ATB, 356400ATB, 378801ATB, 378802ATB, 378900ATB, 385700ATBS, 385800ATB, 423700ATB, 429201ATB, 442600ATB, 443200ATB, 443300ATB, 460500ATB, 468501ATB, 468502ATB, 468503ATB, 486900ATB, 492800ATB, 492900ATB, 495800ATB, 500500ATB, 500600ATB, 502600ATB, 502700ATB, 503000ATB, 509200ATB, 511500ATB, 511600ATB, 511700ATB, 513600ATB, 513900ATB, 515201ATB, 515202ATB, 515203ATB, 519700ATB, 519800ATB, 519900ATB, 520000ATB, 520100ATB, 520901ATB, 520902ATB, 521200ATB, 521300ATB, 521400ATB, 522000ATB, 522200ATB, 522300ATB, 522400ATB, 522600ATB, 522700ATB, 522800ATB, 522900ATB,523000ATB, 523100ATB, 523200ATB, 523300ATB, 523400ATB, 524000ATB, 524100ATB, 525000ATB, 525100ATB, 525200ATB, 525300ATB, 526300ATB, 526400ATB, 526500ATB, 526800ATB, 526900ATB, 527000ATB, 527100ATB, 547500ATB, 547600ATB, 547700ATB, 547800ATB, 547900ATB, 548000ATB, 553800ATB, 556100ATB, 582200ATB, 582400ATB, 629400ATB, 629500ATB, 629600ATB, 629700ATB, 629800ATB, 629900ATB, 630000ATB, 630100ATB, 630200ATB, 631300ATB, 631600ATB, 631700ATB, 632800ATB, 632900ATB, 633000ATB, 634900ATB, 635000ATB, 635100ATB, 635200ATB, 637400ATB, 637500ATB, 637600ATB, 644100ATB, 644200ATB, 644800ATB, 651401ATB, 651402ATB, 651403ATB
Calcium channel blockers	107601ATB, 107601ATD, 107602ATB,107602ATD, 114001ACH,114002ACH, 114003ACH, 115101ATB, 115102ATB, 115103ATB, 115104ATB, 133101ATB, 133102ATB, 145701ACR, 145703ACR, 145704BIJ, 145706ATB, 145707ACR, 145707ATB, 145707ATR, 157501ATR, 157502ATR, 157503ATR,178902A-CR,180301ATB, 180302ATB, 180303ATB, 182001ATB, 182002ATB, 188001ATB, 188002ATB, 188003ATB, 201001ATB, 201002ACR, 201002ATB, 201003ACR, 201004BIJ, 201030BIJ, 201031BIJ, 201401ACS, 201401ATB, 201405ATR, 201407ACS, 201409ATR, 201702ATB, 201901ATB, 201902BIJ, 201930BIJ, 202402ACS, 247603ATR, 247605ATR, 247606ATB, 247607ATB, 247630BIJ, 262400ATR, 356201ATB, 356202ATB, 356202ATR, 356203ATR, 441201ATB, 441202ATB, 447100ATB, 447200ACH, 447200ATB, 459801ACH, 459801ATB, 459802ACH, 459901ATB, 464601ATB, 470801ATB, 470802ATB, 472300ATB, 472400ATB, 472500ATB, 476201ATB, 479701ATB, 483201ATB, 483202ATB, 486501ATB, 486502ATB, 492800ATB, 492900ATB, 495800ATB, 495901ATB, 500500ATB, 500600ATB, 501801ATB, 502700ATB, 503000ATB, 511500ATB, 511600ATB, 511700ATB, 513900ATB, 518900ATB, 519700ATB, 519800ATB, 519900ATB, 520000ATB, 520100ATB, 521200ATB, 521300ATB, 521400ATB, 522200ATB, 522300ATB, 522400ATB, 522600ATB, 522700ATB, 522800ATB, 522900ATB, 523000ATB, 523100ATB, 523200ATB, 523300ATB, 523400ATB, 528201ATR, 528202ATR, 547500ATB, 547600ATB, 547700ATB, 547800ATB, 547900ATB, 548000ATB,582200ATB, 582400ATB, 614500ATB, 629400ATB, 629500ATB, 629600ATB, 631300ATB, 632800ATB, 632900ATB, 633000ATB, 637400ATB, 637500ATB, 637600ATB, 644800ATB
Statins	111501ATB, 111502ATB, 111503ATB, 111504ATB, 162401ACH, 162402ACH, 162403ATR, 185801ATB, 216601ATB, 216602ATB, 216603ATB, 216604ATB, 227801ATB, 227801ATR, 227802ATB, 227803ATB, 227805ATB, 227806ATB, 454001ATB, 454002ATB, 454003ATB, 470901ATB, 470902ATB, 470903ATB, 471000ATB, 471100ATB,472300ATB, 472400ATB, 472500ATB, 502201ATB, 502202ATB, 502203ATB, 502204ATB, 507800ATB ,518900ATB, 519300ACH, 524000ATB, 524100ATB, 525000ATB, 525100ATB, 525200ATB, 525300ATB, 526300ATB, 526400ATB, 526500ATB, 526900ATB, 527000ATB, 527100ATB, 553700ATB, 614500ATB, 629700ATB, 629800ATB, 629900ATB, 630000ATB, 630100ATB, 630200ATB, 631400ATB, 631500ATB, 631600ATB, 631700ATB, 633800ATB, 633900ATB, 634600ATB, 634800ATB, 634900ATB, 635000ATB, 635100ATB, 635200ATB, 640700ATB, 640800ATB, 640900ATB, 644100ATB, 644200ATB, 653200ATB, 654600ATB, 661800ATB, 661900ATB, 662000ATB, 662100ATB, 663400ACS,663900ATB, 664000ATB, 664100ATB,664200ATB, 664300ATB, 664400ATB, 664600ATB, 664700ATB, 664800ATB, 671200ATB, 671300ATB, 671400ATB, 671500ATB, 671600ATB, 671700ATB, 671800ATR, 671900ATR, 672000ATR, 672100ATR, 672500ATR, 672600ATR, 672700ATR, 672800ATR, 672900ATR, 673000ATR
Aspirin	110701ATB, 110701ATE, 110702ATB, 110704ATB, 110705ACE, 110706ATB, 110801ATB, 110802ATB, 111001ACE, 111001ATB, 111001ATE, 111002ATE, 111003ACE, 111003ATE, 256800ATB, 259100ACH, 394500ATB, 489700ACR, 517900ACE, 517900ACH, C75000ATB, C75100ATB, D39300ATB, D87600ATE

Supplementary Table 1 (*Continued*)

Medication	Korean Drug and Anatomical Therapeutic Chemical Codes
Clopidogrel	136901ATB, 495201ATB, 517900ACE, 517900ACH
Ticagrelor or prasugrel	597301ATB, 597302ATB, 615901ATB, 615902ATB
Anticoagulants	249103ATB, 249105ATB, 511401ATB, 511402ATB, 511403ATB, 511404ATB, 613701ACH, 613702ACH, 617001ATB, 617002ATB, 643601ATB, 643602ATB, 643603ATB
Beta-blockers	100801ACH, 107901ATB, 107902ATB, 110201ATB, 110202ATB, 111401ATB, 111402ATB, 111403ATB, 116801ATB, 116803ATB, 117001ATB, 117002ATB, 117901ATB, 117902ATB, 117903ATB, 117904ATB, 124801ATB, 125001ATB, 125002ATB, 125003ATB, 125004ACR, 125005ATB, 125006ACR, 125007ACR, 125008ACR, 129101ATB, 154401BIJ, 154430BIJ, 154431BIJ, 180201BIJ, 180202BIJ, 180230BIJ, 180231BIJ, 193802ATB, 194003ATR, 194004ATR, 219901ATB, 219902BIJ, 219903ATB, 219904ATB, 219905ACR, 219906ACR, 262100ATB, 262400ATR, 262600ATB, 460200ATB, 469800ATB, 469900ATB, 470000ATB, 483101ATB, 483102ATB, 489501ATB, 489502ATB
Spironolactone	231101ATB, 231102ATB, 262700ATB

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers.

Supplementary Table 2 Clinical Outcomes Between ARBs and ACEIs Among Patients with and Without Previous ACEI/ARB Therapy

Outcome	Naïve (n = 20,468)				Previous ACEI/ARB Therapy (n = 10,545)			
	Number of Cases	Incidence Rate (per 1000 Person-Years)	Adjusted HR† (95% CI)	*P* Value	Number of Cases	Incidence Rate (per 1000 Person-Years)	Adjusted HR† (95% CI)	*P* Value
All-cause death								
ACEIs	872	19.7	*Reference*		531	31.4	*Reference*	
ARBs	523	22.3	1.04 (0.93-1.16)	.47	554	36.1	1.06 (0.93-1.20)	.39
Composite*								
ACEIs	1683	39.8	*Reference*		978	62.3	*Reference*	
ARBs	1042	46.9	1.10 (1.02-1.18)	.01	1007	71.1	1.04 (0.94-1.14)	.48

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

*A composite of all-cause death, recurrent MI, hospitalization for heart failure, and stroke.

†Adjusted for age, sex, previous revascularization, presence of diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation or flutter, chronic obstructive pulmonary disease, peripheral artery disease, or malignancy, admission at tertiary hospital, and other medications including calcium channel blockers, statins, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulant, beta-blockers, or spironolactone at discharge.

Supplementary Table 3 Baseline Characteristics Including Patients Not Receiving Either ARBs or ACEIs*

Variable	Overall (n = 40,507)	ARBs (n = 12,685)	ACEIs (n = 18,328)	No ARB/ACEI Therapy (n = 9494)
Age, year, mean (SD)	62.5 (12.6)	63.5 (12.6)	61.7 (12.6)	62.8 (12.7)
Sex, male	30,865 (76.2)	9269 (73.1)	14,343 (78.3)	7253 (76.4)
Previous revascularization	2148 (5.3)	812 (6.4)	732 (4.0)	604 (6.4)
Previous ACEI/ARB therapy	12,900 (31.8)	5250 (41.4)	5295 (28.9)	2355 (24.8)
Charlson index, median (IQR)	0 (0−1)	1 (0−1)	1 (0−1)	0 (0−1)
Comorbidity				
Diabetes mellitus	8096 (20.0)	2833 (22.3)	3454 (18.8)	1809 (19.1)
Hypertension	14,569 (36.0)	5306 (41.8)	6538 (35.7)	2725 (28.7)
Hyperlipidemia	2388 (5.9)	678 (5.3)	1089 (5.9)	621 (6.5)
Atrial fibrillation of flutter	320 (0.8)	141 (1.1)	93 (0.5)	86 (0.9)
COPD	2737 (6.8)	944 (7.4)	1139 (6.2)	654 (6.9)
Peripheral artery disease	716 (1.8)	262 (2.1)	294 (1.6)	160 (1.7)
Malignancy	1954 (4.8)	608 (4.8)	856 (4.7)	490 (5.2)
Tertiary hospital	18,564 (45.8)	5458 (43.0)	9842 (53.7)	3264 (34.4)
Medications at discharge				
Calcium channel blockers	10,791 (26.6)	3941 (31.1)	3927 (21.4)	2923 (30.8)
Statins	37,188 (91.8)	11,477 (90.5)	17,076 (93.2)	8635 (91.0)
Aspirin	39,266 (96.9)	12,389 (97.7)	17,717 (96.7)	9160 (96.5)
Clopidogrel	30,779 (76.0)	9332 (73.6)	14,543 (79.3)	6904 (72.7)
Ticagrelor or prasugrel	11,500 (28.4)	3703 (29.2)	4855 (26.5)	2942 (31)
Anticoagulant	960 (2.4)	330 (2.6)	401 (2.2)	229 (2.4)
Beta-blockers	33,862 (83.6)	10,760 (84.8)	15,964 (87.1)	7138 (75.2)
Spironolactone	5184 (12.8)	1625 (12.8)	2246 (12.3)	1313 (13.8)

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor II blockers; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; SD = standard deviation.

*Values were presented n (%), mean (standard deviation) or median (interquartile range).

Supplementary Table 4 Clinical Outcomes According to the Use of Renin-Angiotensin-Aldosterone Blockade

	Number of Cases	Incidence Rate (per 1000 Person-Years)	Comparison with No ACEI/ARB Therapy			
			Unadjusted		Adjusted†	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause mortality						
ACEIs	1403	22.9	0.76 (0.69-0.83)	<.001	0.86 (0.79-0.93)	<.001
ARBs	1077	27.7	0.93 (0.77-1.12)	0.45	0.89 (0.75-1.05)	.18
No ACEI/ARB therapy	802	29.9	Reference		Reference	
Composite*						
ACEIs	2661	45.9	0.86 (0.81-0.93)	<.001	0.93 (0.87-0.99)	.05
ARBs	2049	56.3	1.05 (0.92-1.19)	0.47	1.00 (0.87-1.14)	>.99
No ACEI/ARB therapy	1381	54.2	Reference		Reference	

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CI = confidence interval; HR = hazard ratio.

*A composite of all-cause death, recurrent myocardial infarction, hospitalization for heart failure, and stroke.

†Adjusted for age, sex, previous revascularization, previous ACEI or ARB therapy, presence of diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation or flutter, chronic obstructive pulmonary disease, peripheral artery disease, or malignancy, admission at tertiary hospital, and other medications including calcium channel blockers, statins, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulant, beta-blockers, or spironolactone at discharge.