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ORIGINAL ARTICLE

The impact of angiotensin-converting-enzyme inhibitors versus angiotensin receptor blockers on 3-year clinical outcomes in elderly (≥ 65) patients with acute myocardial infarction without hypertension

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Abstract

Objective This study aimed to investigate the impact of angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin II type 1 receptor blockers (ARB) on 3-year clinical outcomes in elderly (≥ 65) acute myocardial infarction (AMI) patients without a history of hypertension who underwent successful percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Methods A total of 13,104 AMI patients who were registered in the Korea AMI registry (KAMIR)-National Institutes of Health (NIH) were included in the study. The primary endpoint was 3-year major adverse cardiac events (MACE), which was defined as the composite of all-cause death, recurrent myocardial infarction (MI), and any repeat revascularization. To adjust baseline potential confounders, an inverse probability weighting (IPTW) analysis was performed.

Results The patients were divided into two groups: the ACEI group, $n = 872$ patients and the ARB group, $n = 508$ patients. After IPTW matching, baseline characteristics were balanced. During the 3-year clinical follow-up, the incidence of MACE was not different between the two groups. However, incidence of stroke (hazard ratio [HR], 0.375; 95% confidence interval [CI], 0.166–0.846; $p = 0.018$) and re-hospitalization due to heart failure (HF) (HR, 0.528; 95% CI, 0.289–0.965; $p = 0.038$) in the ACEI group were significantly lower than in the ARB group.

Conclusion In elderly AMI patients who underwent PCI with DES without a history of hypertension, the use of ACEI was significantly associated with reduced incidences of stroke, and re-hospitalization due to HF than those with the use of ARB.

Keywords Angiotensin-converting-enzyme inhibitors · Angiotensin II type 1 receptor blockers · Acute myocardial infarction · Elderly · Geriatric medicine

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Abbreviations

BP	Blood pressure
RAAS	Renin–angiotensin–aldosterone system
ACEI	Angiotensin-converting-enzyme inhibitors
ARB	Angiotensin II type 1 receptor blockers
BB	Beta-blockers
CCB	Calcium channel blockers
MI	Myocardial infarction
AMI	Acute myocardial infarction
STEMI	ST-segment elevation myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
LV	Left ventricle
CAD	Coronary artery disease
PCI	Percutaneous coronary intervention

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CABG	Coronary artery bypass graft
DES	Drug-eluting stents
MACE	Major adverse cardiac events
HF	Heart failure
TLR	Target lesion revascularization
TVR	Target vessel revascularization
KAMIR	Korea AMI Registry
NIH	National Institutes of Health
IPTW	Inverse probability weighting
HR	Hazard ratio
CI	Confidence interval
EUROPA	European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease
HOPE	Heart Outcomes Prevention Evaluation
PEACE	Prevention of Events with Angiotensin-Converting Enzyme Inhibition
VALIANT	Valsartan in Acute Myocardial Infarction

Introduction

Patients after acute myocardial infarction (AMI) remain at high risk for ischemic events. Therefore, appropriate choices of medical therapy are necessary for a successful secondary prevention [1, 2]. Renin–angiotensin–aldosterone system (RAAS) inhibitors are well known for their risk reduction of major cardiovascular events for those who are at high risk [3]. In current European guidelines, angiotensin-converting-enzyme inhibitors (ACEI) are recommended in all patients with ST-segment elevation myocardial infarction (STEMI), and angiotensin II type 1 receptor blockers (ARB) are recommended as an alternative if ACEI is not tolerable due to adverse effects [4–6]. Non-ST-segment elevation myocardial infarction (NSTEMI) with hypertension, heart failure (HF) or diabetes is also an indication for ACEI [5, 7, 8].

Recently, in a meta-analysis of several randomized controlled trials, significant risk reduction of cardiovascular events (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.85–0.93) was demonstrated among patients with history of cardiovascular disease without hypertension treated with ACEI or ARB [9], additional to the well-known benefits of ACEI or ARB in high risk patients with hypertension demonstrated in many previous studies [8, 10–12]. The significance of this finding is added by the fact that large proportion of AMI patients are prehypertensive or normotensive (varying from 40 to 70%) [13, 14]. Although unprevented cardiovascular events would have larger negative impact on quality of life of the elderly population (≥65), hence making optimal choices of medication even more important, there are limited data on the relative superiority of the effects of ACEI and ARB on the long-term clinical outcomes in these patients.

This study aims to evaluate the effect of ACEI and ARB on 3-year clinical outcomes in elderly AMI patients without hypertension who underwent successful percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Materials and methods

Study population

The study population was enrolled from the Korea AMI registry (KAMIR). The design of the KAMIR study has been described in our previous studies [15, 16]. To introduce briefly, it is a prospective, multicenter online registry designed to reflect the "real world" practice in a series of Korean AMI patients treated since November 2005 to investigate the clinical outcomes. For this study, a total of 13,104 patients were enrolled, through November 2011 to December 2015, from KAMIR-National Institutes of Health (NIH) registry. 9829 of these patients underwent successful PCI with second generation DES and among them, 5039 patients did not have a history of hypertension. Patients who were under the age of 65 ($n=2613$) and who were treated with combined ACEI and ARB ($n=1046$) were excluded. The remaining 1380 patients were classified into two groups; the ACEI group ($n=872$) and the ARB group ($n=508$) (Fig. 1).

All patients were provided written informed consent prior to enrollment. All 1380 patients completed 3-year follow-up through face-to-face interviews, phone calls, or chart reviews. This study protocol was approved by the Korea University Guro Hospital Institutional Review Board (IRB) (#2016GR0740) according to the ethical guidelines of the 1975 Declaration of Helsinki.

PCI and medical treatment

Standard technique was used during PCI [17]. All patients received 200–300 mg of loading doses of aspirin and other anti-platelet agents (clopidogrel, ticagrelor, and prasugrel) before the procedure. The use of anti-coagulation during the procedure was left to each physician's discretion. DES were deployed after balloon angioplasty. A successful PCI was defined as achieving an angiographic residual stenosis of less than 10% without major adverse cardiac events (MACE) in the presence of a thrombolysis in myocardial infarction blood flow grade 3. Beta-blockers (BB), calcium channel blockers (CCB), and statins along with ACEI and ARB were also prescribed to patients while in-hospital period. Patients were encouraged to maintain the same medication upon discharge, and dual anti-platelet therapy was also maintained for at least one year.

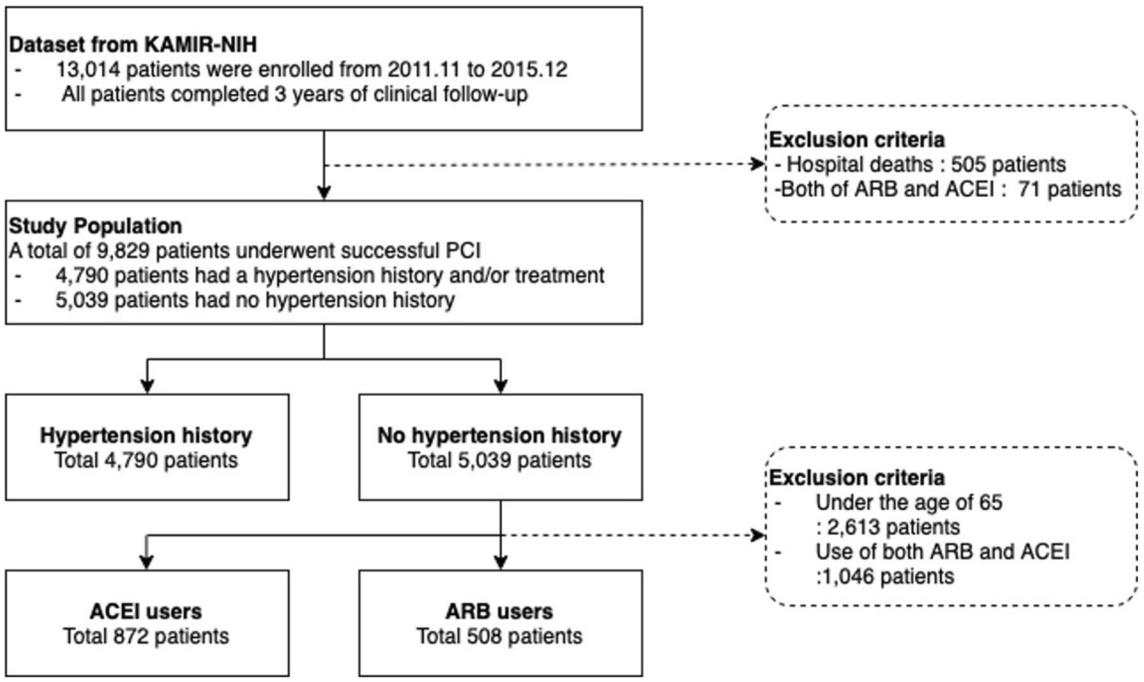

Fig. 1 Patient selection of this study

Study definition and endpoint

The primary endpoint of this study was MACE, a composite of all-cause death, recurrent myocardial infarction (MI), and any repeat revascularization. Recurrent MI was defined as recurred clinical symptoms associated with newly developed ST-segment elevation or newly elevated cardiac markers, twice the upper normal limit at least. Any repeat revascularization was defined as any repeat PCI or coronary artery bypass graft (CABG) of any vessel. The secondary endpoints include all-cause death, recurrent MI, any repeat revascularization, target lesion failure, target lesion revascularization (TLR), target vessel revascularization (TVR), stent thrombosis, stroke, and re-hospitalization due to HF. Repeated PCI within the index procedure stent or 5 mm edge was defined as TLR and repeated PCI or CABG of any segment in target vessel was defined as TVR. Target lesion failure was defined as the composite of TLR, recurrent MI, and cardiac death associated with the target vessel. All patients were encouraged to visit after a month and then every six months after the PCI procedure.

Statistical analysis

Continuous variables were expressed as mean ± standard deviations and discrete variables were expressed as counts and percentages. The differences between two groups for continuous variables were analyzed by unpaired *t* test or Mann–Whitney rank test and for discrete variables, χ^2 or Fisher's exact test were used. Inverse probability weighting (IPTW) analysis was performed using the logistic regression model to adjust the confounding factors. Age, sex, body mass index, Killip class on admission, left ventricular ejection fraction, and risk factors of cardiovascular disease (e.g., hypertension, dyslipidemia, diabetes, prior coronary artery disease (CAD), smoking history) were included for the IPTW. Also, other medications (e.g., aspirin, anti-platelets, CCB, BB, and statins), and PCI procedural characteristics (e.g., target vessel, lesion type and DES type) were also considered.

3-year clinical outcomes were analyzed by Kaplan–Meier analysis, and the differences between the groups were compared with the log-rank test. Hazard ratio (HR) of the ACEI group compared to the ARB group were calculated in the IPTW population using binary logistic regression. Cumulative survival curve was analyzed using Cox-proportional regression analysis with the IPTW adjustment. All analyses were performed with SPSS (version 20.0, SPSS-PC, Inc. Chicago, Illinois) and two-sided $p < 0.05$ was considered statistically significant.

Results

Baseline clinical characteristics

Table 1 shows the baseline clinical characteristics of the patients included in the study. The mean systolic blood

Table 1 Baseline clinical characteristics

	Crude population				IPTW			
Variables, N (%)	ACEI ($n=872$)	ARB ($n=508$)	P value	S.diff	ACEI ($n=1390$)	ARB ($n=1371$)	P value	S.diff
Sex, male	604 (69.3)	353 (69.5)	0.931	0.03	973 (70.0)	961 (70.1)	0.957	0.01
Age, year	73.3 ± 5.8	73.9 ± 6.1	0.103	0.09	73.5 ± 5.9	73.4 ± 5.8	0.810	−0.01
Blood pressure; BP, mmHg								
Systolic	131 ± 27	128 ± 25	0.043	−0.11	129 ± 26	129 ± 25	0.930	0.00
Diastolic	78 ± 15	77 ± 15	0.422	−0.05	77 ± 15	77 ± 15	0.618	−0.02
Heart rate, beat per minutes	75 ± 18	78 ± 19	0.021	0.13	76 ± 19	76 ± 18	0.846	0.01
Body mass index, kg/m2	22.7 ± 2.9	22.8 ± 3.0	0.331	0.05	22.7 ± 2.9	22.7 ± 3.0	0.869	−0.01
LV ejection fraction, %	49.9 ± 10.3	52.4 ± 11.0	< 0.001	0.23	50.7 ± 10.2	50.6 ± 11.5	0.864	−0.01
Final diagnosis			0.016	−0.94			0.830	0.06
STEMI	479 (54.9)	245 (48.2)			736 (52.9)	731 (53.3)		
NSTEMI	393 (45.1)	263 (51.8)			655 (47.1)	640 (46.7)		
Killip class								
I	684 (78.4)	400 (78.7)	0.896	0.03	1085 (78.1)	1075 (78.4)	0.822	0.04
II	89 (10.2)	52 (10.2)	0.986	0.01	144 (10.4)	135 (9.9)	0.659	−0.16
III	61 (7.0)	36 (7.1)	0.949	0.03	100 (7.2)	101 (7.4)	0.857	0.07
IV	38 (4.4)	20 (3.9)	0.707	−0.21	61 (4.4)	59 (4.3)	0.913	−0.04
History of patients								
Diabetes mellitus	170 (19.5)	119 (23.4)	0.084	0.85	297 (21.4)	297 (21.7)	0.842	0.07
Dyslipidemia	58 (6.7)	28 (5.5)	0.398	−0.46	85 (6.1)	77 (5.6)	0.577	−0.21
Prior CAD								
Myocardial infarction	48 (5.5)	28 (5.5)	0.995	0.00	82 (5.9)	77 (5.6)	0.753	−0.12
Angina pectoris	76 (8.7)	44 (8.7)	0.973	−0.02	119 (8.6)	123 (9.0)	0.703	0.14
Stroke	37 (4.2)	18 (3.5)	0.522	−0.35	53 (3.8)	45 (3.3)	0.451	−0.28
Infarction	2 (0.2)	1 (0.2)	> 0.999	−0.07	3 (0.2)	2 (0.1)	> 0.999	−0.16
Hemorrhage	35 (4.0)	17 (3.3)	0.530	−0.35	51 (3.7)	43 (3.1)	0.440	−0.29
Heart failure	11 (2.2)	10 (1.1)	0.136	−0.79	20 (1.5)	22 (1.6)	0.790	−0.10
Smoking								
Currently	257 (29.5)	136 (26.8)	0.284	−0.51	399 (28.7)	404 (29.5)	0.650	0.15
Ex-smoker	193 (22.1)	133 (26.2)	0.088	0.82	330 (23.7)	313 (22.8)	0.571	−0.19
Laboratory findings								
Fasting blood sugar, mg/dL	158 ± 69	161 ± 71	0.375	0.05	159 ± 70	158 ± 67	0.810	−0.01
HbA1c, %	6.2 ± 1.2	6.3 ± 1.3	0.074	0.12	6.2 ± 1.2	6.2 ± 1.1	0.450	−0.03
Total cholesterol, mg/dL	178 ± 40	175 ± 44	0.207	−0.07	175 ± 40	174 ± 43	0.516	−0.03
Triglyceride, mg/dL	106 ± 68	101 ± 59	0.149	−0.08	103 ± 66	104 ± 62	0.856	0.01
HDL-cholesterol, mg/dL	44 ± 12	43 ± 12	0.061	−0.11	44 ± 12	43 ± 12	0.294	−0.04
LDL-cholesterol, mg/dL	114 ± 41	114 ± 40	0.974	0.00	113 ± 45	113 ± 39	0.993	0.00
NT-pro BNP, pg/mL	1855 ± 4406	2382 ± 4472	0.100	−0.12	1807 ± 4322	2499 ± 4750	0.002	−0.15
Creatinine, mg/dL	0.96 ± 0.73	0.91 ± 0.53	0.135	−0.09	0.96 ± 0.79	0.92 ± 0.63	0.181	−0.05
eGFR-MDRD	82.9 ± 50.2	88.3 ± 33.3	0.032	−0.13	84.3 ± 88.2	88.2 ± 33.4	0.022	−0.09

Data are presented as N (%) or mean ± standard deviation

IPTW inverse probability weighting, *ACEI* angiotensin-converting-enzyme inhibitors, *ARB* angiotensin II type 1 receptor blocker, *S.diff* standardized mean difference, *LV* left ventricle, *STEMI* ST-segment elevation myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *CAD* coronary artery disease, *HbA1c* hemoglobin A1c, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *NT-pro BNP* N-terminal-pro hormone B-type natriuretic peptide, *eGFR-MDRD* estimated glomerular filtration rate – Modification of Diet in Renal Disease

pressure (BP) was higher in the ACEI group (131 ± 27 vs. 128 ± 25 mmHg; $p=0.043$). The mean heart rate was higher in the ARB group (78 ± 19 vs. 75 ± 18 beats per minute; $p=0.021$). The average left ventricle (LV) ejection fraction was more preserved in the ARB group (52.4 ± 11.0 vs. 49.9 ± 10.3%; $p<0.001$) and the incidence of STEMI

at final diagnosis was higher in the ACEI group (54.9 vs. 48.2%; $p = 0.016$). The prevalence of heart failure was similar between the two groups, but the estimated glomerular filtration rate—Modification of Diet in Renal Disease (eGFR-MDRD) was lower in the ACEI group (82.9 ± 50.2 vs. 88.3 ± 33.3; $p = 0.032$). These differences in baseline characteristics were all balanced after the IPTW adjustment except eGFR-MDRD and N-terminal-pro hormone B-type natriuretic peptide (NT-pro BNP) (eGFR-MDRD: 84.3 ± 88.2 vs. 88.2 ± 33.4; $p = 0.022$, NT-pro BNP: 1807 ± 4322 vs. 2499 ± 4750 pg/mL; $p = 0.002$).

Angiographic and procedural characteristics

Table 2 presents the angiographic and procedural characteristics and medication at discharge. The incidence of left circumflex artery being the infarcted artery was higher in the ARB group (14.4 vs. 20.5%; $p = 0.004$). The incidence of multi-vessel disease was more frequent in the ACEI group (56.1 vs. 48.4%; $p = 0.006$). Both maximum stent diameter (3.13 ± 0.40 vs. 3.08 ± 0.40 mm; $p = 0.043$) and total stent length were higher in the ACEI group (31.0 ± 13.7 vs. 28.8 ± 13.3 mm; $p = 0.003$). Clopidogrel and BB were more frequently prescribed to ACEI group (clopidogrel: 76.6 vs. 69.3%; $p = 0.003$, BB: 90.7 vs. 80.3%; $p < 0.001$), and cliostazol, prasugrel, CCB, and statins were more frequently prescribed in ARB group (cliostazol: 8.5 vs. 17.7%; $p < 0.001$, prasugrel: 4.0 vs 8.9%; $p < 0.001$, CCB: 1.8 vs. 4.9%; $p = 0.001$, statin: 94.2 vs. 96.9%; $p = 0.024$). These differences in medication and angiographic procedural characteristics were all balanced after the IPTW adjustment.

Clinical outcomes

The 3-year cumulative major clinical outcomes after acute myocardial infarction are presented in Table 3. Without IPTW adjustment, the cumulative incidence of stroke was significantly higher in the ARB group (3.0 vs. 1.4%; $p = 0.041$). No significant difference could be found in MACE, target lesion failure, all-cause death, recurrent MI, any repeat revascularization, and stent thrombosis between two groups before and after the IPTW adjustment. However, stroke and re-hospitalization due to HF were significantly lower in the ACEI group (stroke: 1.2 vs. 2.9%; $p = 0.001$, re-hospitalization due to HF: 2.6 vs 4.5%; $p = 0.006$) after the adjustment. The cumulative survival curve of the stroke and re-hospitalization due to HF is presented in Fig. 2. Compared to the ARB group, ACEI group reduced risk for stroke and re-hospitalization due to HF (stroke: HR 0.375, 95% CI, 0.166–0.846; $p = 0.018$, HF: HR 0.528, 95% CI, 0.289–0.965; $p = 0.038$).

No significant differences were observed in systolic BP, diastolic BP, heart rate, and LV ejection fraction compared in initial, 1-year, 2-year, and 3-year follow-up between the two groups (Fig. 3)

The sub-analyses of clinical outcomes were also performed and are demonstrated in Table 4. Compared to the ARB group, the risks for total death in patients with eGFR-MDRD ≥ 90 were lower in the ACEI group (HR 0.52, 95% CI, 0.30–0.90; $p = 0.020$). For stroke and re-hospitalization due to HF, which showed significant risk reduction in analyses without sub-grouping (Fig. 2), numerous sub-groups have also demonstrated risk reduction. For re-hospitalization due to HF, male gender, diabetics, 40% ≤ LVEF < 50%, NT-pro BNP ≥ 400 pg/mL, or 60 ≤ eGFR-MDRD < 90 were at lower risk in the ACEI group (male: HR 0.42, 95% CI, 0.24–0.73; $p = 0.002$, diabetes: HR 0.29, 95% CI, 0.12–0.70; $p = 0.006$, 40% ≤ LVEF < 50%: HR 0.55, 95% CI, 0.36–0.84; $p = 0.006$, NT-pro BNP ≥ 400 pg/mL: HR 0.42, 95% CI, 0.25–0.73; $p = 0.002$, 60 ≤ eGFR-MDRD < 90: HR 0.44, 95% CI, 0.23–0.84; $p = 0.013$). For stroke, male gender, 40% ≤ LVEF, 30 ≤ eGFR-MDRD < 60, or eGFR-MDRD ≥ 90 demonstrated lesser risk in the ACEI group compared to the ARB group (male: HR 0.35, 95% CI, 0.17–0.72; $p = 0.004$, 40% ≤ LVEF < 50%: HR 0.39, 95% CI, 0.21–0.70; $p = 0.002$, 50% ≤ LVEF: HR 0.25, 95% CI, 0.10–0.58; $p = 0.001$, 30 ≤ eGFR-MDRD < 60: HR 0.22, 95% CI, 0.05–0.88; $p = 0.033$, 90 ≤ eGFR-MDRD: HR 0.31, 95% CI, 0.10–0.93; $p = 0.037$).

Discussion

The main findings of this study are as follows: in elderly AMI patients without hypertension, (1) ACEI shows more benefit in risk reduction for stroke and re-hospitalization due to HF; (2) these benefits of ACEI could be maximized when prescribed to patients with LVEF ≥ 40% or NT-pro BNP ≥ 400 pg/mL; (3) the relative superiority of ACEI is maintained throughout a wide range of renal function (eGFR-MDRD ≥ 30); (4) there were no significant differences in cumulative incidences of MACE, target lesion failure, all-cause death, recurrent MI, any repeat revascularization, and stent thrombosis between two groups.

The current guidelines recommend that ACEI should be considered first in all patients after STEMI in the absence of contraindications [18] and also in NSTEMI [19]. ARB is recommended when patients show intolerability with ACEI [19]. Despite the recommended guidelines, many clinicians in Korea prefer ARB as their first choice due to the frequent development of adverse side effects of ACEI such as coughing [20], which could lead to worse compliance among patients. Current controversy about the relative efficacy of ACEI and ARB on the long-term clinical outcomes would

Table 2 Angiographic, procedural characteristics and medication at discharge

Variables, *N* (%)	Crude population				IPTW			
	ACEI ($n=872$)	ARB ($n=508$)	*P* value	S.diff	ACEI ($n=1390$)	ARB ($n=1371$)	*P* value	S.diff
Angiographic and procedural characteristics								
Infarct-related artery								
LAD	432 (49.5)	241 (47.4)	0.452	−0.30	678 (48.8)	664 (48.4)	0.856	−0.05
LCX	126 (14.4)	104 (20.5)	0.004	1.44	228 (16.4)	228 (16.6)	0.872	0.06
RCA	302 (34.6)	152 (29.9)	0.072	−0.83	462 (33.2)	457 (33.3)	0.957	0.02
Left main	12 (1.4)	11 (2.2)	0.269	0.59	22 (1.6)	23 (1.7)	0.844	0.07
Multi-vessel disease	489 (56.1)	246 (48.4)	0.006	−1.06	729 (52.4)	712 (51.9)	0.787	−0.07
Number of vessels, *N*	1.77 ± 0.77	1.63 ± 0.73	0.001	−0.18	1.71 ± 0.76	1.69 ± 0.75	0.589	−0.02
Drug-eluting stents								
Everolimus	452 (51.8)	261 (51.4)	0.870	−0.06	727 (52.3)	701 (51.1)	0.538	−0.16
Zotarolimus	2 (0.2)	0 (0.0)	0.534	−0.68	2 (0.1)	0 (0.0)	0.500	−0.54
Biolimus A9	164 (18.8)	116 (22.8)	0.073	0.88	272 (19.6)	283 (20.6)	0.482	0.24
Sirolimus	23 (2.6)	23 (4.5)	0.059	1.00	49 (3.5)	46 (3.4)	0.806	−0.09
Stent diameter, mm (max)	3.13 ± 0.40	3.08 ± 0.40	0.043	−0.11	3.11 ± 0.39	3.11 ± 0.42	0.721	0.01
Stent diameter, mm (mean)	3.08 ± 0.38	3.06 ± 0.40	0.199	−0.07	3.07 ± 0.38	3.07 ± 0.40	0.933	0.00
Total stent length, mm	31.0 ± 13.7	28.8 ± 13.3	0.003	−0.17	30.3 ± 13.2	30.9 ± 14.7	0.312	0.04
Discharge medication								
RAAS inhibitors								
Perindopril	403 (46.2)	0 (0.0)			634 (45.6)	0 (0.0)		
Ramipril	390 (44.7)	0 (0.0)			628 (45.2)	0 (0.0)		
Captopril	60 (6.9)	0 (0.0)			91 (6.5)	0 (0.0)		
Cilazapril	11 (1.3)	0 (0.0)			27 (1.9)	0 (0.0)		
Enalapril	6 (0.7)	0 (0.0)			8 (0.6)	0 (0.0)		
Tanatril	1 (0.1)	0 (0.0)			1 (0.1)	0 (0.0)		
Zofenopril	1 (0.1)	0 (0.0)			1 (0.1)	0 (0.0)		
Candesartan	0 (0.0)	202 (39.8)			0 (0.0)	561 (40.9)		
Losartan	0 (0.0)	130 (25.6)			0 (0.0)	346 (25.2)		
Telmisartan	0 (0.0)	97 (19.1)			0 (0.0)	243 (17.7)		
Valsartan	0 (0.0)	65 (12.8)			0 (0.0)	180 (13.1)		
Fimasartan	0 (0.0)	9 (1.8)			0 (0.0)	23 (1.7)		
Olmesartan	0 (0.0)	3 (0.6)			0 (0.0)	8 (0.6)		
Irbesartan	0 (0.0)	1 (0.2)			0 (0.0)	3 (0.2)		
Eprosartan	0 (0.0)	1 (0.2)			0 (0.0)	7 (0.5)		
Aspirin	867 (99.4)	505 (99.4)	> 0.999	0.00	1382 (99.4)	1362 (99.3)	0.786	−0.01
Clopidogrel	668 (76.6)	352 (69.3)	0.003	−0.86	1018 (73.2)	1016 (74.2)	0.582	0.11
Cilostazol	74 (8.5)	90 (17.7)	< 0.001	2.55	167 (12.0)	163 (11.9)	0.919	−0.04
Prasugrel	35 (4.0)	45 (8.9)	< 0.001	1.91	89 (6.4)	80 (5.8)	0.534	−0.23
Ticargrelor	161 (18.5)	106 (20.9)	0.276	0.54	270 (19.4)	259 (18.9)	0.729	−0.12
Ca-channel blockers	16 (1.8)	25 (4.9)	0.001	1.68	48 (3.5)	45 (3.3)	0.803	−0.09
Beta-blockers	791 (90.7)	408 (80.3)	< 0.001	−1.13	1210 (87.1)	1189 (86.7)	0.800	−0.04
Statin	821 (94.2)	492 (96.9)	0.024	0.28	1325 (95.3)	1307 (95.3)	0.992	0.00

Data are presented as *N* (%) or mean ± standard deviation

IPTW inverse probability weighting, *ACEI* angiotensin-converting-enzyme inhibitors, *ARB* angiotensin II type 1 receptor blocker, *S.diff* standardized mean difference, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *RAAS* renin-angiotensin-aldosterone system

Table 3 Major clinical outcomes after acute myocardial infarction at 3 years

Variables, *N* (%)	Crude population			IPTW		
	ACEI (*n* = 872)	ARB (*n* = 508)	*P* value	ACEI (*n* = 1390)	ARB (*n* = 1371)	*P* value
LV ejection fraction, %						
Discharge	49.9 ± 10.3	52.4 ± 11.0	0.277	50.7 ± 10.2	50.6 ± 11.5	0.868
1-year	55.0 ± 9.8	56.3 ± 9.7	0.379	55.5 ± 9.6	55.1 ± 10.3	0.974
2-year	54.0 ± 11.8	54.6 ± 10.8	0.370	54.4 ± 11.6	54.1 ± 11.0	0.580
3-year	54.7 ± 11.2	54.7 ± 13.2	0.061	55.4 ± 10.9	52.9 ± 13.6	0.398
MACE	132 (15.1)	80 (15.7)	0.762	207 (14.9)	203 (14.8)	0.956
Target lesion failure	48 (5.5)	32 (6.3)	0.542	75 (5.4)	80 (5.8)	0.613
Total death	62 (7.1)	47 (9.3)	0.155	102 (7.3)	107 (7.8)	0.643
Cardiac death	34 (3.9)	23 (4.5)	0.571	55 (4.0)	57 (4.2)	0.789
Non-cardiac death	28 (3.2)	24 (4.7)	0.154	47 (3.4)	50 (3.6)	0.705
Myocardial infarction	18 (2.1)	15 (3.0)	0.297	31 (2.2)	35 (2.6)	0.575
STEMI	3 (0.3)	2 (0.4)	> 0.999	4 (0.3)	5 (0.4)	0.752
NSTEMI	15 (1.7)	13 (2.6)	0.286	27 (1.9)	31 (2.3)	0.557
Revascularization	71 (8.1)	33 (6.5)	0.264	106 (7.6)	97 (7.1)	0.583
CABG	1 (0.1)	1 (0.2)	> 0.999	1 (0.1)	2 (0.1)	0.622
PCI	70 (8.0)	32 (6.3)	0.237	104 (7.5)	95 (6.9)	0.574
TLR	13 (1.5)	10 (2.0)	0.504	19 (1.4)	26 (1.9)	0.272
TVR	28 (3.2)	16 (3.1)	0.950	41 (2.9)	39 (2.8)	0.869
Non-TVR	45 (5.2)	17 (3.3)	0.117	68 (4.9)	58 (4.2)	0.410
Stent thrombosis	4 (0.5)	2 (0.4)	> 0.999	5 (0.4)	6 (0.4)	0.745
Stroke	12 (1.4)	15 (3.0)	0.041	16 (1.2)	40 (2.9)	0.001
Hemorrhage	0 (0.0)	5 (1.0)	0.007	0 (0.0)	12 (0.9)	< 0.001
Infarction	11 (1.3)	10 (2.0)	0.301	15 (1.1)	28 (2.0)	0.041
Transient ischemic attack	1 (0.1)	0 (0.0)	> 0.999	1 (0.1)	0 (0.0)	> 0.999
Re-hospitalization due to HF	27 (3.1)	22 (4.3)	0.232	36 (2.6)	62 (4.5)	0.006

Data are presented as *N* (%) or mean ± standard deviation

IPTW inverse probability weighting, *ACEI* angiotensin-converting-enzyme inhibitors, *ARB* angiotensin II type 1 receptor blocker, *LV* Left Ventricle, *MACE* major adverse cardiac events, *STEMI* ST-segment elevation myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary interventions, *TLR* target lesion revascularization, *TVR* target vessel revascularization, *HF* heart failure

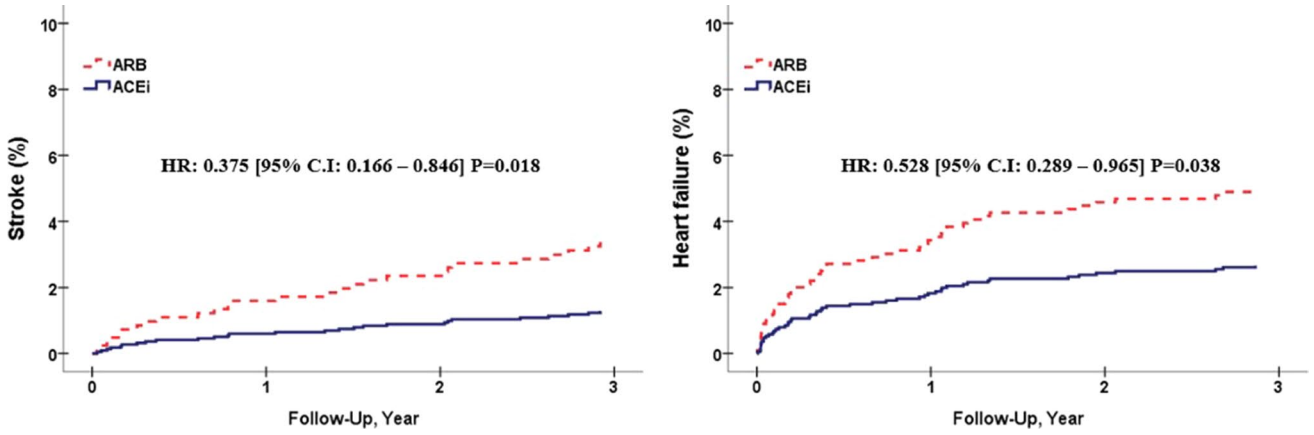

Fig. 2 Cumulative survival curve of the stroke, and re-hospitalization due to heart failure by Cox proportional regression analysis with IPTW adjustment. *IPTW* Inverse probability weighting, *ACEI* angiotensin-converting-enzyme inhibitors, *ARB* angiotensin II receptor blocker, *HR* hazard ratio, *CI* confidence interval)

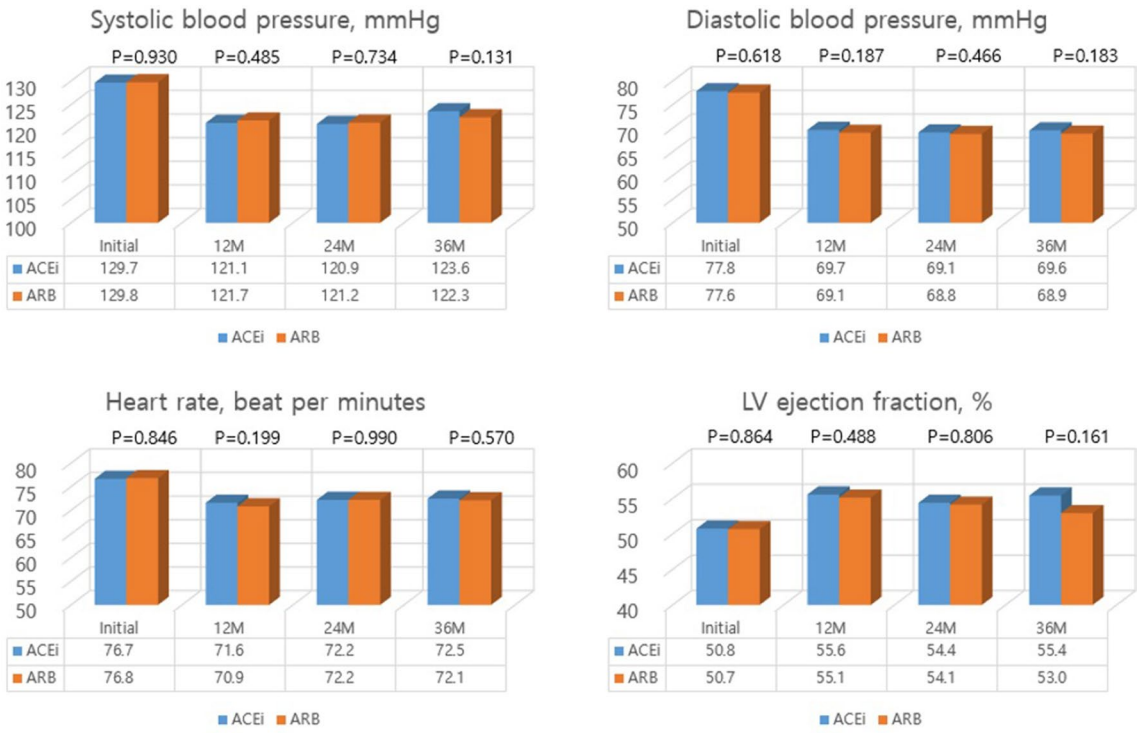

Fig. 3 Comparison of blood pressure, heart rate, and LV ejection fraction between ACEI and ARB group during initial, 1-year, 2-year, 3-year follow-up

Table 4 Sub-analyses of clinical outcomes by comorbidities in ACEI group compared to ARB group

Subgroup	Population, *N*	MACE HR [95% CI]	*P* value	Total Death HR [95% CI]	*P* value	Heart failure HR [95% CI]	*P* value	Stroke HR [95% CI]	*P* value
Overall	2761	1.00 [0.81–1.24]	0.961	0.93 [0.7–1.24]	0.652	0.56 [0.37–0.86]	0.008	0.38 [0.21–0.69]	0.001
Sex			0.516		0.105		0.030		0.010
Male	1934	1.14 [0.89–1.45]	0.279	0.94 [0.68–1.30]	0.745	0.42 [0.24–0.73]	0.002	0.35 [0.17–0.72]	0.004
Female	827	0.66 [0.43–1.03]	0.069	0.90 [0.49–1.64]	0.731	0.93 [0.46–1.85]	0.843	0.46 [0.16–1.30]	0.145
Diabetes			0.035		0.085		< 0.001		< 0.001
Yes	594	0.89 [0.58–1.35]	0.590	0.92 [0.53–1.59]	0.778	0.29 [0.12–0.70]	0.006	–	0.994
No	2167	1.04 [0.82–1.33]	0.702	0.94 [0.67–1.31]	0.730	0.72 [0.44–1.18]	0.198	0.55 [0.29–1.03]	0.063
LVEF, %			0.136		0.144		0.027		0.001
< 40	430	0.99 [0.60–1.62]	0.980	0.84 [0.46–1.51]	0.565	1.04 [0.56–1.93]	0.884	1.66 [0.43–6.33]	0.455
40–50	836	0.99 [0.80–1.22]	0.953	0.93 [0.70–1.24]	0.666	0.55 [0.36–0.84]	0.006	0.39 [0.21–0.70]	0.002
≥ 50	1448	1.16 [0.86–1.56]	0.306	0.97 [0.66–1.44]	0.918	0.55 [0.23–1.32]	0.186	0.25 [0.10–0.58]	0.001
NT-pro BNP			0.045		0.014		< 0.001		0.002
< 400 pg/mL	756	1.27 [0.79–2.02]	0.308	1.58 [0.76–3.28]	0.220	0.46 [0.12–1.79]	0.270	–	0.993
≥ 400 pg/mL	898	1.01 [0.72–1.41]	0.949	1.08 [0.72–1.61]	0.687	0.42 [0.25–0.73]	0.002	0.53 [0.23–1.21]	0.134
eGFR-MDRD			0.038		0.008		0.067		0.015
≤ 30	50	0.29 [0.07–1.15]	0.079	–	0.998	0.76 [0.12–4.60]	0.773	–	0.998
30–60	466	0.91 [0.57–1.44]	0.690	0.89 [0.51–1.54]	0.694	0.69 [0.27–1.76]	0.445	0.22 [0.05–0.88]	0.033
60–90	1149	1.30 [0.93–1.81]	0.119	1.43 [0.90–2.28]	0.127	0.44 [0.23–0.84]	0.013	0.58 [0.25–1.37]	0.219
≥ 90	1092	0.80 [0.55–1.17]	0.264	0.52 [0.30–0.90]	0.020	0.68 [0.31–1.46]	0.326	0.31 [0.10–0.93]	0.037

ACEI angiotensin-converting-enzyme inhibitors, *ARB* angiotensin II type 1 receptor blocker, *MACE* major adverse cardiac events, *HR* hazard ratio, *CI* confidence interval, *LVEF* left ventricle ejection fraction, *NT-pro BNP* N-terminal-pro hormone B-type natriuretic peptide, *eGFR-MDRD* estimated glomerular filtration rate – Modification of Diet in Renal Disease

contribute to this prescribing pattern even more. According to the Valsartan in Acute Myocardial Infarction (VALIANT) study, ARB showed similar efficacy in reducing death, MI, angina, revascularization, and stroke over a 2-year follow-up (HR, 0.97; 95% CI, 0.91–1.03; $p = 0.286$) [10]. On the other hand, ACEI was analyzed to be more superior in survival than ARB in AMI patients in 2–5-year follow-up by Hara et al. (HR, 0.53; 95% CI, 0.38–0.74; $p < 0.001$) [21]. Also, Korean national registry data suggested use of ACEI was associated with reduced cumulative incidences of MACE, any repeat vascularization, stroke, and re-hospitalization due to HF at 3 years compared to ARB in patients with AMI without hypertension [22]. The subgroup analysis of this study was consistent with our findings in this study, which demonstrated relative benefit of ACEI in preventing stroke in elderly population. Despite the controversy, there are limited studies on direct comparison between ACEI and ARB in elderly population. In elderly population, negative impact of suboptimal prescription would be larger, thus highlighting the importance of optimal medical treatment. The current trend of growing elderly population worldwide [23], would highlight this importance even more.

Although our study did not show significant differences in cumulative incidence of MACE, target lesion failure, all-cause death, recurrent MI, any repeat revascularization, and stent thrombosis, our findings suggest relatively beneficial effect on stroke and HF in the elderly population. From the sub-analyses, these benefits were particularly demonstrated in patients with LVEF ≥ 40% or NT-pro BNP ≥ 400 pg/mL, suggesting potential standards for selecting appropriate medications in similar clinical situations. In addition, ACEI maintained its relative superiority in patients with renal failure (30 ≤ eGFR-MDRD < 90), and because of the high prevalence of comorbidities in the elderly population, these results add further emphasis on importance of using ACEI in this population. These findings would largely contribute to optimal prescription to the elderly, leading to greater patient's quality of life and to the socioeconomic benefits regarding the growing size of the population.

Advantages in risk reduction of stroke and re-hospitalization due to HF could be explained in several ways. Left ventricle remodeling is one of the most important factors of prognosis after AMI. This process of remodeling within few weeks after AMI is well known [24]. General consensus is that both ACEI and ARB have an anti-fibrotic effect, which is the rationale for the current guidelines for recommending ACEI inhibitors as Class I drugs for use within 24 h after MI. Although ARB shares many of the clinical benefits with ACEI in terms of inhibiting RAAS, they have different mechanism of action [25]. ARB causes prolonged elevation of angiotensin II levels, which leads to unopposed stimulation of angiotensin II type 2 receptor. This phenomenon leads to increased thrombus formation [26] and may also lead to increase in serum cholesterol levels through activating macrophage angiotensin II type 1 receptor, which results in accumulation of cholesterol in macrophages and foam cell formation. On the other hand, ACEI inhibits the conversion of angiotensin I to angiotensin II, preventing the possible pathological effects mentioned above. Additionally, it is also known that ACEI reduces the breakdown of bradykinin, which could add to the protective effects of ACEI. These differences in mechanism are a plausible explanation for the superiority of ACEI over ARB in reducing incidences of stroke and re-hospitalization due to HF in elderly patients with AMI.

A meta-analysis compared ACEI versus placebo trials: the vascular disease including Heart Outcomes Prevention Evaluation (HOPE), European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA), and Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trials. Initial BPs in all these trials were within normal range (133/79 to 139/78 mmHg). The analysis demonstrated that there was only a mean of 3/1.5 to 5/3 mmHg of BP reduction, but it still led to reduced cardiovascular mortality by 17.4% ($p < 0.01$)[6, 27–29]. Thus, even small changes in BP are possible of affecting the clinical outcomes. However, as demonstrated in Fig. 3., no significant differences were observed in systolic BP, and diastolic BP between two groups in initial, 1-year, 2-year, and 3-year follow-up. This indicates that additional benefit of ACEI shown in this study was not due to differences in controlling BP. The fact that there were no differences in BP during the follow-up also reflects the "real world" practice in Korea, which would be the result of appropriate BP management of the physicians in Korea. The prospective design and the large multicenter population base are the strengths of the KAMIR study and these observational data from the real world setting could provide additional information, which would not be available in strictly controlled randomized trials.

The prevalence of prehypertension or normotension is reported to vary from 40 to 70% in AMI patients [13, 14] and consistent with this report, 51% of AMI patients in our registry data did not have a history of hypertension. In addition as mentioned above, population aging is occurring in both developed and developing countries worldwide [23]. Despite these current situations, direct comparison trial of ACEI and ARB in elderly AMI patients without hypertension is very limited, thus making our findings in the present study particularly more meaningful.

However, there are some limitations in our study. First, variations were present in the baseline characteristics of

the patients due to the use of multicenter national prospective registry, but after performing the IPTW adjustment, most of the factors were well balanced. In addition, we performed additional sub-analyses for the factors that were not balanced after the IPTW adjustment (eGFR-MDRD and NT-pro BNP). Second, the classification of two groups (ACEI group vs. ARB group) was based on the medications upon discharge. The specific dose, compliance, incidence of discontinuation, and adverse events were also not collected. Third, study population was based on single race of Korean, only limited application of our study to other races could be made. Due to our limitations, further studies in varied patient populations with randomized controlled trials are needed to confirm our findings in the present study.

In conclusion, the use of ACEI in elderly AMI patients without a history of hypertension undergoing PCI with contemporary DES was associated with reduced cumulative incidences of stroke, and rehospitalization due to HF at 3 years than those with the use of ARB.

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Data availability All data can be checked by sending an email to Correspondence or the website of the Korea AMI Registry-National Institute of Health (http://www.kamir.or.kr).

Declarations

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

References

1. Bramlage P, Messer C, Bitterlich N, Pohlmann C, Cuneo A, Stammwitz E, Tebbenjohanns J, Gohlke H, Senges J, Tebbe U (2010) The effect of optimal medical therapy on 1-year mortality after acute myocardial infarction. Heart 96:604–609
2. Tea V, Bonaca M, Chamandi C, Iliou MC, Lhermusier T, Aissaoui N, Cayla G, Angoulvant D, Ferrieres J, Schiele F, Simon T, Danchin N, Puymirat E, investigators F-M, (2019) Appropriate secondary prevention and clinical outcomes after acute myocardial infarction according to atherothrombotic risk stratification: the FAST-MI 2010 registry. Eur J Prev Cardiol 26:411–419
3. Messerli FH, Bangalore S (2017) Angiotensin receptor blockers reduce cardiovascular events, including the risk of myocardial infarction. Circulation 135:2085–2087
4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, Group ESCSD (2018) 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 39:119–177
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S (2016) 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 37:267–315
6. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342:145–153
7. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC et al (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 327:669–677
8. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM (2003) Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 349:1893–1906
9. McAlister FA (2012) Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in normotensive atherosclerotic patients: a collaborative meta-analysis of randomized trials. Eur Heart J 33:505–514
10. McMurray J, Solomon S, Pieper K, Reed S, Rouleau J, Velazquez E, White H, Howlett J, Swedberg K, Maggioni A, Køber L, Van de Werf F, Califf R, Pfeffer M (2006) The effect of valsartan, captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol 47:726–733
11. Borghi C, Bacchelli S, Esposti DD, Bignamini A, Magnani B, Ambrosioni E (1999) Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension. SMILE Study Investigators. Survival of myocardial infarction long-term evaluation. Am J Hypertens 12:665–672

12. Gustafsson F, Torp-Pedersen C, Køber L, Hildebrandt P (1997) Effect of angiotensin converting enzyme inhibition after acute myocardial infarction in patients with arterial hypertension. TRACE study group. Trandolapril Cardiac Event J Hypertens 15:793–798
13. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364:937–952
14. Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA (2011) Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA 305:913–922
15. Choi SY, Choi BG, Rha SW, Byun JK, Shim MS, Li H, Mashaly A, Choi CU, Park CG, Seo HS, Oh DJ, Jeong MH (2017) Angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers in acute ST-segment elevation myocardial infarction patients with diabetes mellitus undergoing percutaneous coronary intervention. Int J Cardiol 249:48–54
16. Byun JK, Choi BG, Rha SW, Choi SY, Jeong MH (2018) Comparison of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with diabetes mellitus and non-ST-segment elevation myocardial infarction who underwent successful percutaneous coronary intervention. Atherosclerosis 277:130–135
17. Grech ED (2003) ABC of interventional cardiology: percutaneous coronary intervention. II: the procedure. BMJ 326:1137–1140
18. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 61:485–510
19. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Jneid H, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP, Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Zidar JP (2011) 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. J Am Coll Cardiol 57:e215-367
20. Tseng DS, Kwong J, Rezvani F, Coates AO (2010) Angiotensin-converting enzyme-related cough among Chinese-Americans. Am J Med 123:183.e11–15
21. Hara M, Sakata Y, Nakatani D, Suna S, Usami M, Matsumoto S, Sugitani T, Nishino M, Sato H, Kitamura T, Nanto S, Hamasaki T, Hori M, Komuro I (2014) Comparison of 5-year survival after acute myocardial infarction using angiotensin-converting enzyme inhibitor versus angiotensin II receptor blocker. Am J Cardiol 114:1–8
22. Her AY, Choi BG, Rha SW, Kim YH, Choi CU, Jeong MH (2020) The impact of angiotensin-converting-enzyme inhibitors versus angiotensin receptor blockers on 3-year clinical outcomes in patients with acute myocardial infarction without hypertension. PLoS ONE 15:e0242314
23. Bloom DE, Boersch-Supan A, McGee P, Seike A (2011) Population aging: facts, challenges, and responses. Benefits Compens Int 41:22
24. French BA, Kramer CM (2007) Mechanisms of post-infarct left ventricular remodeling. Drug Discov Today Dis Mech 4:185–196
25. Kim YH, Her AY, Jeong MH, Kim BK, Hong SJ, Kim S, Ahn CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y (2020) Comparison of clinical outcomes between angiotensin-converting-enzyme inhibitors and ARBs in patients with acute myocardial infarction with dyslipidemia after a successful stent implantation. Anatol J Cardiol 23:86–98
26. Strauss MH, Hall AS (2006) Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox. Circulation 114:838–854
27. Fox KM (2003) Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 362:782–788
28. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG (2004) Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 351:2795–2804
29. Yusuf S, Pogue J (2005) ACE inhibition in stable coronary artery disease. N Engl J Med 352:937–939