Reevaluating the effect of ACEI/ARB therapy on discharged patients with STEMI in the contemporary reperfusion era

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ABSTRACT

Background: Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) had beneficial effects on clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) in the pre-reperfusion or thrombolytic era. It is unknown if the benefits persist in the contemporary reperfusion era.

Aims: We sought to determine if ACEI/ARB improve clinical outcomes for STEMI patients in the contemporary reperfusion era according to the reperfusion strategy.

Methods: In total, we analyzed 12 596 patients from the prospective, nationwide, multicenter China Acute Myocardial Infarction Registry. These patients were classified into the no-reperfusion group (n = 6004) and the primary percutaneous coronary intervention (PCI) group (n = 6592). Two-year all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE) were compared.

Results: In the no-reperfusion group, ACEI/ARB therapy on discharge may reduce the incidence of 30-day MACCE (4.7% vs. 7.4%; adjusted hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.53–0.85; P <0.001), stroke (0.5% vs. 1.1%; adjusted HR, 0.41; 95% CI, 0.21–0.83; P = 0.01), and re-vascularization (2.1% vs. 3.1%; adjusted HR, 0.66; 95% CI, 0.46–0.94; P = 0.02), compared to patients not treated with ACEI/ARB. Patients treated with ACEI/ARB also showed a lower rate of 2-year MACCE (17.0% vs. 19.1%; adjusted HR, 0.87; 95% CI, 0.76–0.99; P = 0.04). No differences were observed in the remaining outcomes. In the primary PCI group, no differences were observed for all examined outcomes before and after multivariate adjustments.

Conclusions: Initiating ACEI/ARB treatment on discharge may reduce cardiovascular events in STEMI patients not receiving reperfusion, while no significant benefits were observed in those receiving primary PCI.

Key words: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, percutaneous coronary intervention, ST-segment elevation myocardial infarction

INTRODUCTION

The effects of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) on prognosis in patients with ST-segment elevation acute myocardial infarction (STEMI) have been confirmed in randomized controlled trials and meta-analyses for the past two decades [1, 2]. Based on these findings, the European Society of Cardiology (ESC) guidelines for the management of STEMI recommend that if there are no contraindications, ACEI should be considered in all patients (class IIa, level A) [3]. Similarly, the American College of Cardiology Foundation/American Heart Association (AHA)guidelines also recommend ACEI for all STEMI patients without contraindications (class IIa, level A) [4]. However, this recommendation is primarily based on results of studies performed in the pre-percutaneous coronary intervention (PCI) era and in patients treated with thrombolytics [1, 2, 5–7]. In this context, it may be inappropriate to extrapolate the conclusions derived from the pre-PCI era to the contemporary reperfusion

WHAT'S NEW?

In ST-segment elevation acute myocardial infarction (STEMI) patients not receiving reperfusion, treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) on discharge may reduce 30-day major adverse cardiac and cerebrovascular events, stroke, and revascularization. Two-year major adverse cardiac and cerebrovascular events were also decreased. In contrast, in STEMI patients who underwent primary percutaneous coronary intervention, no significant benefits were observed from ACEI/ARB therapy on discharge. Therefore, the effect of ACEI/ARB therapy on discharged STEMI patients should be reevaluated in the contemporary primary percutaneous coronary intervention era.

era when primary PCI is given a high recommendation and is widely used. For example, beta-blockers, which are also recommended in the ESC and AHA guidelines based on evidence from the pre-PCI era, showed no benefits in patients with STEMI after primary PCI [8, 9]. It is assumed that recent advances in the management of STEMI, particularly primary PCI, have substantially reduced clinical events [10]. However, in the era of primary PCI, studies examining the independent effects of ACEI/ARB on clinical outcomes for STEMI patients are lacking. As a result, it is unclear whether patients receiving primary PCI after STEMI will benefit from ACEI/ARB therapy. Therefore, we sought to investigate whether ACEI/ARB therapy on discharge improves clinical outcomes in the contemporary reperfusion era and whether the outcomes varied according to treatment strategies (no reperfusion versus primary PCI) in patients enrolled in the China Acute Myocardial Infarction (CAMI) Registry.

METHODS

Study population

The present analysis was based on the CAMI Registry, which is a prospective, nationwide, multicenter observational study of patients with acute myocardial infarction from January 2013 to September 2014 and has been described in detail elsewhere [11, 12]. This study has been registered on ClinicalTrials.gov (NCT01874691). Before enrolling, eligible patients provided written informed consent, and the study methodology complied with the 1975 Declaration of Helsinki. The third universal definition of myocardial infarction was used to diagnose acute myocardial infarction [13]. Data were collected, validated, and submitted through a secure, web-based electronic data capture system. Follow-up was performed by trained physicians at each participating site in a real-time manner to ensure data accuracy and reliability. Senior cardiologists were responsible for the data quality control, and periodic database checking was undertaken [12]. From 19 354 STEMI patients, we excluded patients who died in the hospital (n = 1297) or were discharged with severe conditions (n = 42). Patients who underwent thrombolysis (n = 1224) or urgent coronary artery bypass grafting (n = 4) were also excluded. Besides, those without information on ACEI/ARB (n = 910) or left ventricular ejection fraction (LVEF, n = 3281) were also excluded. Eventually, 12 596 patients were studied in this analysis, including 6004 patients not receiving reperfusion and 6592 patients receiving primary PCI. We further classified patients into the ACEI/ARB group and no-ACEI/ARB group in separate no-reperfusion and primary PCI groups (Figure 1).

Study outcomes

The primary outcome was 2-year all-cause mortality. The secondary outcome was major adverse cardiac and cerebrovascular events (MACCE), which were determined by a composite of all-cause mortality, cardiac death (death was considered as cardiac unless an unequivocal noncardiac cause could be established), recurrent myocardial infarction (MI), stroke (ischemic and hemorrhagic stroke), revascularization (PCI and coronary artery bypass grafting), and major bleeding (as determined by the Thrombolysis in Myocardial Infarction classification) [14].

Statistical analysis

For continuous variables with normal distribution, the t-test was used to compare means and standard deviations; otherwise, the Mann–Whitney U test was used to compare median and interquartile ranges. Categorical variables were expressed as numbers and percentages. The χ^2 test was used to compare categorical variables when suitable; otherwise, Fisher's exact test was applied. Kaplan–Meier survival curves were created for the cumulative incidences of primary and secondary outcomes at 2 years, comparing ACEI/ARB with no ACEI/ARB with a log-rank test. A multivariable adjustment analysis was performed to adjust potential confounders with a Cox proportional-hazards model. Variables showing a $P < 0.05$ in univariate analysis or deemed to be associated with the outcome of interest according to clinical judgment were used as candidate predictors for multivariate analysis. Ultimately, the variables that were considered to be potentially relevant were age, sex, body mass index (BMI), smoking, hypertension, diabetes, prior myocardial infarction, prior stroke, prior heart failure, prior chronic kidney disease, grade of hospital, symptoms onset to admission time, heart rate, systolic pressure, Killip class, LVEF, Global Registry of Acute Coronary Events (GRACE) risk score, anterior myocardial infarction, prescribed with aspirin, $P2Y_{12}$ blockers, statins, or beta-blockers on discharge. The results of the use of ACEI/ARB for the primary and secondary outcomes were presented as hazard ratios (HR) and their 95% confidence intervals (CI). All analyses

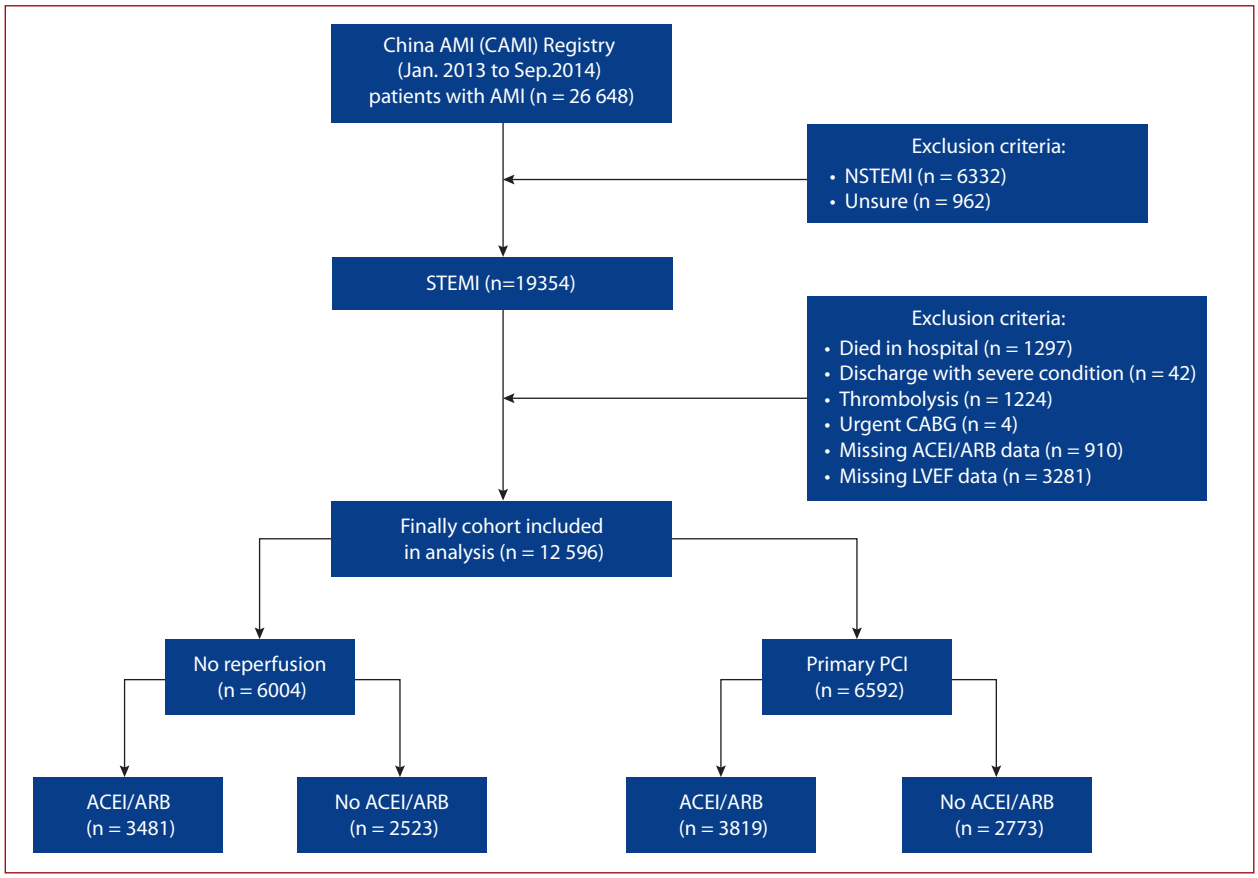

Figure 1. Flowchart of populations from the CAMI Registry

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CAMI, China Acute Myocardial Infarction; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, US). P <0.05 was regarded as statistically significant, and all the reported P-values were 2-sided.

RESULTS

ACEI/ARB use in the no-reperfusion group

The median follow-up in the CAMI Registry was two years (23.3–24.7 months). In the no-reperfusion group (n = 6004), 3481 patients received ACEI/ARB, while 2523 patients did not (Figure 1). ACEI/ARB patients were younger. They were less likely to be current smokers, be admitted to higher-grade hospitals, have a malignant arrhythmia, cardiogenic shock, or receive GP IIb/IIIa receptor antagonist on admission. The in-hospital days were also lower in ACEI/ARB patients. However, ACEI/ARB patients tended to have higher BMI, heart rate, and systolic pressure. The anterior MI was more commonly seen in ACEI/ARB patients. They were also more likely to receive aspirin, beta-blockers, ACEI/ARB on admission, and aspirin, $P2Y_{12}$ blockers, statins, beta-blockers, nitrate, and calcium channel blockers after hospital discharge (Table 1).

For 30-day outcomes (Table 2), ACEI/ARB therapy on discharge may reduce the incidence of MACCE (4.7% vs. 7.4%; HR, 0.63; 95% CI, 0.51–0.78; P <0.001), stroke (0.5% vs. 1.1%; HR, 0.38; 95% CI, 0.20–0.72; P = 0.003), revascularization (2.1% vs. 3.1%; HR, 0.66; 95% CI, 0.48–0.92; P = 0.01), and major bleeding (1.2% vs. 2.0%; HR, 0.59; 95% CI, 0.39–0.90; P = 0.01) in the unadjusted model. After multivariable adjustment, the differences remained for MACCE (HR, 0.67; 95% CI, 0.53–0.85; P <0.001), stroke (HR, 0.41; 95% CI, 0.21–0.83; P = 0.01), revascularization (HR, 0.66; 95% CI, 0.46–0.94; P = 0.02) except for major bleeding (HR, 0.79; 95% CI, 0.49–1.26; P = 0.32). No differences were observed for all-cause mortality, cardiac death, and recurrent MI in the unadjusted or multivariable adjustment models. One-year outcomes were also similar between ACEI/ARB therapy and no ACEI/ARB therapy (Supplementary material, *Table S1*). For two-year outcomes (Table 3), ACEI/ARB therapy on discharge consistently reduced the incidence of MACCE in the unadjusted (17.0% vs. 19.1%; HR, 0.86; 95% CI, 0.76–0.97; P = 0.02) and multivariable adjustment models (HR, 0.87; 95% CI, 0.76–0.99; P = 0.04). No differences were observed in the remaining outcomes. The Kaplan–Meier survival curves for all-cause mortality (Figure 2), MACCE (Figure 3), cardiac death (Supplementary material, *Figure S1*), recurrent MI (Supplementary material, *Figure S2*), stroke (Supplementary material, *Figure S3*), revascularization

Table 1. Demographic and clinical characteristics of STEMI patients according to ACEI/ARB treatment

	No reperfusion			Primary PCI		
	ACEI/ARB (n = 3481)	No ACEI/ARB (n = 2523)	*P*-value	ACEI/ARB (n = 3819)	No ACEI/ARB (n = 2773)	*P*-value
Demographic characteristics						
Age, years, mean (SD)	62.52 (12.31)	62.97 (12.56)	0.16	59.55 (11.88)	60.49 (11.73)	0.001
Age ≥75 years, n (%)	643 (18.5)	546 (21.6)	0.002	443 (11.6)	356 (12.8)	0.13
Male, n (%)	2615 (75.1)	1904 (75.5)	0.76	3155 (82.6)	2199 (79.3)	<0.001
BMI, kg/m^2, mean (SD)	24.10 (3.24)	23.93 (3.28)	0.047	24.63 (3.32)	24.28 (3.12)	<0.001
Risk factors, n (%)						
Smoker	1905 (54.7)	1431 (56.7)	0.13	2339 (61.2)	1705 (61.5)	0.84
Current smoker	1504 (43.2)	1178 (46.7)	0.007	1985 (52.0)	1477 (53.3)	0.30
Hypertension	1942 (55.8)	1040 (41.2)	<0.001	2094 (54.8)	1061 (38.3)	<0.001
Diabetes	652 (18.7)	440 (17.4)	0.20	710 (18.6)	467 (16.8)	0.07
Hyperlipemia	213 (6.1)	126 (5.0)	0.06	364 (9.5)	149 (5.4)	<0.001
Prior MI	204 (5.9)	146 (5.8)	0.90	178 (4.7)	132 (4.8)	0.85
Prior PCI	110 (3.2)	95 (3.8)	0.20	190 (5.0)	122 (4.4)	0.28
Prior CABG	6 (0.2)	5 (0.2)	>0.99	9 (0.2)	3 (0.1)	0.22
Prior heart failure	54 (1.6)	38 (1.5)	0.89	25 (0.7)	14 (0.5)	0.43
Prior stroke	338 (9.7)	243 (9.6)	0.92	271 (7.1)	193 (7.0)	0.83
Prior peripheral artery diseases	18 (0.5)	13 (0.5)	0.99	13 (0.3)	18 (0.6)	0.07
Prior chronic kidney disease	28 (0.8)	26 (1.0)	0.36	14 (0.4)	21 (0.8)	0.03
Prior COPD	68 (2.0)	52 (2.1)	0.77	49 (1.3)	30 (1.1)	0.46
Hospital level, n (%)			<0.001			<0.001
Provincial level	1084 (31.1)	860 (34.1)		1789 (46.8)	1464 (52.8)	
Municipal level	1982 (56.9)	1433 (56.8)		1832 (48.0)	1210 (43.6)	
County level	415 (11.9)	230 (9.1)		198 (5.2)	99 (3.6)	
Symptoms onset to admission time ≥12 h, n (%)	2150 (61.8)	1521 (60.3)	0.25	448 (11.7)	277 (10.0)	0.03
Admission status						
Heart rate, (beats/min), mean (SD)	79 (17)	77 (18)	<0.001	77 (17)	75 (17)	<0.001
Systolic pressure, (mm Hg), mean (SD)	131 (24)	122 (23)	<0.001	131 (25)	124 (24)	<0.001
Malignant arrhythmia, n (%)	163 (4.7)	167 (6.6)	0.001	257 (6.7)	242 (8.7)	0.003
Atrial flutter/fibrillation	34 (1.0)	46 (1.8)	0.005	32 (0.8)	33 (1.2)	0.16
Atrial-ventricular block	56 (1.6)	62 (2.5)	0.02	83 (2.2)	80 (2.9)	0.07
Ventricular flutter/fibrillation	39 (1.1)	23 (0.9)	0.43	91 (2.4)	68 (2.5)	0.86
Other	34 (1.0)	35 (1.4)	0.14	51 (1.3)	59 (2.1)	0.01
Killip class II–IV, n (%)	930 (26.7)	730 (28.9)	0.058	687 (18.0)	470 (16.9)	0.27
Cardiogenic shock, n (%)	108 (3.1)	122 (4.8)	<0.001	120 (3.1)	131 (4.7)	0.001
GRACE risk score ≥155, n (%)	1259 (36.2)	1110 (44.0)	<0.001	1115 (29.2)	951 (34.3)	<0.001
eGFR ≤60 ml/min/1.73 m^2, n (%)	617 (17.7)	496 (19.7)	0.057	511 (13.4)	405 (14.6)	0.16
LVEF (%)			0.66			0.21
≤40	466 (13.4)	356 (14.1)		365 (9.6)	236 (8.5)	
41–49	775 (22.3)	569 (22.6)		745 (19.5)	575 (20.7)	
≥50	2240 (64.3)	1598 (63.3)		2709 (70.9)	1962 (70.8)	
Location of MI, n (%)			<0.001			<0.001
Anterior	2093 (60.1)	1259 (49.9)		2060 (53.9)	1278 (46.1)	
Right ventricular	164 (4.7)	200 (7.9)		332 (8.7)	377 (13.6)	
Other	1224 (35.2)	1064 (42.2)		1427 (37.4)	1118 (40.3)	
In-hospital medications, n (%)						
Aspirin	3367 (96.7)	2410 (95.5)	0.02	3768 (98.7)	2725 (98.3)	0.19
$P2Y_{12}$ blockers	3349 (96.2)	2412 (95.6)	0.24	3745 (98.1)	2715 (97.9)	0.66
GP IIb/IIIa receptor antagonist	618 (17.8)	550 (21.8)	<0.001	2249 (58.9)	1671 (60.3)	0.26
Heparin	3163 (90.9)	2266 (89.8)	0.17	3359 (88.0)	2540 (91.6)	<0.001
Statins	3366 (96.7)	2417 (95.8)	0.07	3721 (97.4)	2702 (97.4)	0.99
Beta-blockers	2787 (80.1)	1571 (62.3)	<0.001	3137 (82.1)	1799 (64.9)	<0.001
ACEI/ARB	3051 (87.6)	688 (27.3)	<0.001	3348 (87.7)	834 (30.1)	<0.001
Discharge medications, n (%)						
Aspirin	3390 (97.4)	2267 (89.9)	<0.001	3764 (98.6)	2394 (86.3)	<0.001
$P2Y_{12}$ blockers	3265 (93.8)	2225 (88.2)	<0.001	3630 (95.1)	2301 (83.0)	<0.001
Statins	3371 (96.8)	2232 (88.5)	<0.001	3689 (96.6)	2269 (81.8)	<0.001
Beta-blockers	2793 (80.2)	1335 (52.9)	<0.001	3172 (83.1)	1431 (51.6)	<0.001
Nitrate	2208 (63.4)	1401 (55.5)	<0.001	1953 (51.1)	1144 (41.3)	<0.001
Calcium channel blockers	375 (10.8)	161 (6.4)	<0.001	281 (7.4)	103 (3.7)	<0.001
In-hospital days, median (IQR)	11.00 (8.02–14.42)	12.00 (8.02–16.00)	<0.001	9.01 (7.01–12.00)	9.01 (7.01–12.00)	0.14

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CCU, intensive care unit; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation acute myocardial infarction

Table 2. Comparison of 30-day outcomes according to ACEI/ARB treatment

	ACEI/ARB	No ACEI/ARB	Unadjusted HR (95% CI)	*P*-value	Multivariable adjusted HR (95% CI)	*P*-value
All-cause mortality						
No reperfusion	31 (0.9)	31 (1.2)	0.72 (0.44–1.19)	0.20	0.94 (0.53–1.67)	0.84
Primary PCI	15 (0.4)	15 (0.6)	0.72 (0.35–1.47)	0.37	0.90 (0.39–2.06)	0.80
MACCE						
No reperfusion	162 (4.7)	182 (7.4)	0.63 (0.51–0.78)	<0.001	0.67 (0.53–0.85)	<0.001
Primary PCI	151 (4.0)	121 (4.5)	0.90 (0.70–1.14)	0.37	0.86 (0.66–1.12)	0.28
Cardiac death						
No reperfusion	16 (0.5)	18 (0.7)	0.64 (0.33–1.26)	0.20	0.79 (0.36–1.72)	0.56
Primary PCI	5 (0.1)	9 (0.3)	0.40 (0.13–1.19)	0.10	0.56 (0.16–1.90)	0.35
Recurrent MI						
No reperfusion	20 (0.6)	17 (0.7)	0.85 (0.45–1.63)	0.63	0.73 (0.36–1.45)	0.36
Primary PCI	22 (0.6)	11 (0.4)	1.45 (0.70–2.99)	0.31	1.06 (0.49–2.31)	0.88
Stroke						
No reperfusion	16 (0.5)	27 (1.1)	0.38 (0.20–0.72)	0.003	0.41 (0.21–0.83)	0.01
Primary PCI	15 (0.4)	12 (0.4)	0.85 (0.39–1.83)	0.67	0.69 (0.29–1.66)	0.41
Revascularization						
No reperfusion	70 (2.1)	76 (3.1)	0.66 (0.48–0.92)	0.01	0.66 (0.46–0.94)	0.02
Primary PCI	56 (1.5)	51 (1.9)	0.79 (0.54–1.16)	0.23	0.66 (0.44–0.99)	0.047
Major bleeding						
No reperfusion	40 (1.2)	49 (2.0)	0.59 (0.39–0.90)	0.01	0.79 (0.49–1.26)	0.32
Primary PCI	61 (1.6)	47 (1.7)	0.94 (0.64–1.38)	0.76	1.10 (0.71–1.70)	0.66

*Age, sex, body mass index, smoking, hypertension, diabetes, prior myocardial infarction, prior stroke, prior heart failure, prior chronic kidney disease, hospital level, symptoms onset to admission time, heart rate, systolic pressure, Killip class, left ventricular ejection fraction, GRACE risk score, anterior myocardial infarction, prescribed with aspirin, $P2Y_{12}$ blockers, statins, or beta-blockers at discharge were included in the adjustment model

Abbreviations: CI: confidence interval; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular event; other — see Table 1

Table 3. Comparison of two-year outcomes according to ACEI/ARB treatment

	ACEI/ARB	No ACEI/ARB	Unadjusted HR (95% CI)	*P*-value	Multivariable adjusted HR (95% CI)	*P*-value
All-cause mortality						
No reperfusion	231 (7.0)	200 (8.2)	0.84 (0.69–1.01)	0.07	0.89 (0.72–1.10)	0.28
Primary PCI	110 (3.0)	91 (3.4)	0.87 (0.66–1.15)	0.32	0.95 (0.69–1.29)	0.73
MACCE						
No reperfusion	561 (17.0)	463 (19.1)	0.86 (0.76–0.97)	0.02	0.87 (0.76–0.99)	0.04
Primary PCI	496 (13.6)	362 (13.7)	0.99 (0.86–1.13)	0.86	0.95 (0.82–1.11)	0.55
Cardiac death						
No reperfusion	96 (3.0)	65 (2.8)	1.07 (0.78–1.46)	0.68	1.19 (0.84–1.69)	0.32
Primary PCI	35 (1.0)	25 (1.0)	1.01 (0.60–1.68)	0.98	1.23 (0.69–2.21)	0.48
Recurrent MI						
No reperfusion	81 (2.5)	60 (2.6)	0.98 (0.70–1.36)	0.89	0.85 (0.59–1.22)	0.38
Primary PCI	73 (2.0)	47 (1.8)	1.12 (0.78–1.62)	0.54	1.07 (0.72–1.60)	0.74
Stroke						
No reperfusion	50 (1.6)	46 (2.0)	0.74 (0.49–1.12)	0.15	0.77 (0.49–1.21)	0.25
Primary PCI	63 (1.7)	28 (1.1)	1.62 (1.04–2.53)	0.03	1.46 (0.89–2.40)	0.14
Revascularization						
No reperfusion	201 (6.3)	160 (6.9)	0.90 (0.73–1.11)	0.33	0.89 (0.71–1.11)	0.30
Primary PCI	243 (6.7)	190 (7.3)	0.92 (0.76–1.11)	0.37	0.83 (0.67–1.02)	0.07
Major bleeding						
No reperfusion	70 (2.2)	61 (2.6)	0.83 (0.59–1.17)	0.29	0.98 (0.67–1.44)	0.94
Primary PCI	98 (2.7)	65 (2.5)	1.09 (0.80–1.49)	0.59	1.19 (0.84–1.70)	0.33

*Age, sex, body mass index, smoking, hypertension, diabetes, prior myocardial infarction, prior stroke, prior heart failure, prior chronic kidney disease, hospital level, symptoms onset to admission time, heart rate, systolic pressure, Killip class, left ventricular ejection fraction, GRACE risk score, anterior myocardial infarction, prescribed with aspirin, $P2Y_{12}$ blockers, statins, or beta-blockers at discharge were included in the adjustment model

Abbreviations: see Tables 1 and 2

(Supplementary material, *Figure S4*), and major bleeding (Supplementary material, *Figure S5*) in the no-reperfusion group showed consistent results.

ACEI/ARB use in the primary PCI group

In the primary PCI group (n = 6592), 3819 patients received ACEI/ARB, while 2773 patients did not (Figure 1). ACEI/ARB patients were younger. They were less likely to have a history of chronic kidney disease or be admitted to higher-grade hospitals. They also had a lower prevalence of malignant arrhythmia, cardiogenic shock, or GRACE risk score ≥155. However, ACEI/ARB patients were more likely to be male patients with a higher BMI. Hypertension, hyperlipemia, and anterior MI were more commonly seen in ACEI/ARB patients. The heart rate and systolic pressure were also higher in ACEI/ARB patients. ACEI/ARB patients were also more likely to receive beta-blockers, ACEI/ARB on admission, and aspirin, $P2Y_{12}$ blockers, statins, beta-blockers, nitrate, and calcium channel blockers after hospital discharge (Table 1).

In the primary PCI group, no differences were observed for primary or secondary outcomes between ACEI/ARB patients and no ACEI/ARB patients during 30-day follow-up (Table 2). Although the incidence of stroke was higher in ACEI/ARB patients during two-year follow-up (1.7% vs. 1.1%; HR, 1.62; 95% CI, 1.04–2.53; $P = 0.03$), the difference disappeared after multivariable adjustment (HR, 1.46; 95% CI, 0.89–2.40; $P = 0.14$). No differences were observed in the remaining one-year (Supplementary material, *Table S1*) or two-year outcomes (Table 3). The Kaplan-Meier survival curves for all-cause mortality (Figure 2), MACCE (Figure 3), cardiac death (Supplementary material, *Figure S1*), recurrent MI (Supplementary material, *Figure S2*), stroke (Supplementary material, *Figure S3*), revascularization (Supplementary material, *Figure S4*), and major bleeding (Supplementary material, *Figure S5*) in the primary PCI group showed consistent results.

DISCUSSION

The major findings of this registry analysis were as follows: 1) in patients who had STEMI in the contemporary reperfusion era, ACEI/ARB therapy on discharge had benefits in those who did not receive reperfusion; 2) In contrast, ACEI/ARB therapy was not significantly associated with either 30-day or 2-year clinical outcomes in those who underwent primary PCI.

ACEI/ARB therapy on discharge has been long recommended for the treatment of STEMI patients [15–17]. In the Trandolapril Cardiac Evaluation study, 1749 patients with myocardial infarction and left ventricular systolic dysfunction (LVEF ≤35%) were randomly assigned to receive oral trandolapril (876 patients) or a placebo (873 patients). The follow-up period was between 24 and 50 months. The trandolapril group was associated with lower risks of all-cause death (34.7% vs. 42.3%; relative risk [RR], 0.78; 95% CI, 0.67–0.91; $P = 0.001$), death from cardiovascular (CV) causes (RR, 0.75; 95 CI, 0.63–0.89; $P = 0.001$), sudden death (RR, 0.76; 95 CI, 0.59–0.98; $P = 0.03$), and progression to severe heart failure (RR, 0.71; 95 CI: 0.56–0.89; $P = 0.003$), compared with the placebo group. No difference was observed in the risk of recurrent myocardial infarction (RR, 0.86; 95 CI: 0.66–1.13; $P = 0.29$) [15]. Similarly, a meta-analysis based on data from 5 long-term randomized trials also found that ACEI could reduce the risks of death (23.0% vs. 26.8%; odds ratio [OR], 0.80; 95% CI, 0.74–0.87), reinfarction (8.9% vs. 11.0%; OR, 0.79; 95% CI, 0.70–0.89), readmission for heart failure (13.7% vs. 18.9%; OR, 0.67; 95% CI, 0.61–0.74), and the composite of these events (33.8% vs. 41.0%; OR, 0.72; 95% CI, 0.67–0.78), compared with placebo in patients with left ventricular dysfunction or heart failure. The benefits were seen early after the start of therapy and lasted for a very long time [16]. Even in patients who had stable coronary artery disease and no evidence of heart failure or left ventricular dysfunction (LVEF <35%), a meta-analysis including seven randomized controlled trials and a total of 33960 patients also confirmed that treatment with ACEI decreased all-cause mortality (OR, 0.86; 95% CI, 0.79–0.93), CV mortality (OR, 0.81; 95% CI, 0.73–0.90), myocardial infarction (OR, 0.82; 95% CI: 0.75–0.89), and stroke (OR, 0.77; 95% CI, 0.66–0.88) [17]. Based on this evidence, the current ESC guidelines for STEMI management recommend daily oral ACEI/ARB therapy in STEMI survivors unless contraindicated (class IIa, level A) [3]. However, the evidence is largely derived from pre-PCI data. No data have been updated concerning patients in the contemporary reperfusion era who receive primary PCI. Furthermore, compared to current practice, prior studies included several significant flaws, such as a relatively small sample size or a lower rate of use of newer antiplatelet agents. With the increased use of primary PCI, improved PCI procedures, and widespread use of evidence-based prescribing, such as statins and more recent antiplatelet agents, the management of STEMI patients today has evolved significantly from that of two decades ago. All of them have translated into a marked improvement in mortality and morbidity after STEMI [3].

In the current study, we used up-to-date data from China's national CAMI Registry to examine the relationships between ACEI/ARB therapy on discharge and clinical outcomes. We showed that ACEI/ARB medication was linked to a substantial drop in MACCE, stroke, and revascularization in patients not receiving reperfusion. However, these benefits were not observed in patients receiving primary PCI. Given that patients who did not receive ACEI/ARB were described as having somewhat high-risk variables such as older age, higher prevalence of malignant arrhythmia, cardiogenic shock, and higher GRACE risk score, the results may be biased due to the differences in baseline characteristics. We attempted multivariable adjustment to account for the variations in baseline characteristics between the groups to address this, and the results remained consistent. Additionally, this study's design excluded patients who died during the index hospitalization or were discharged in crit-

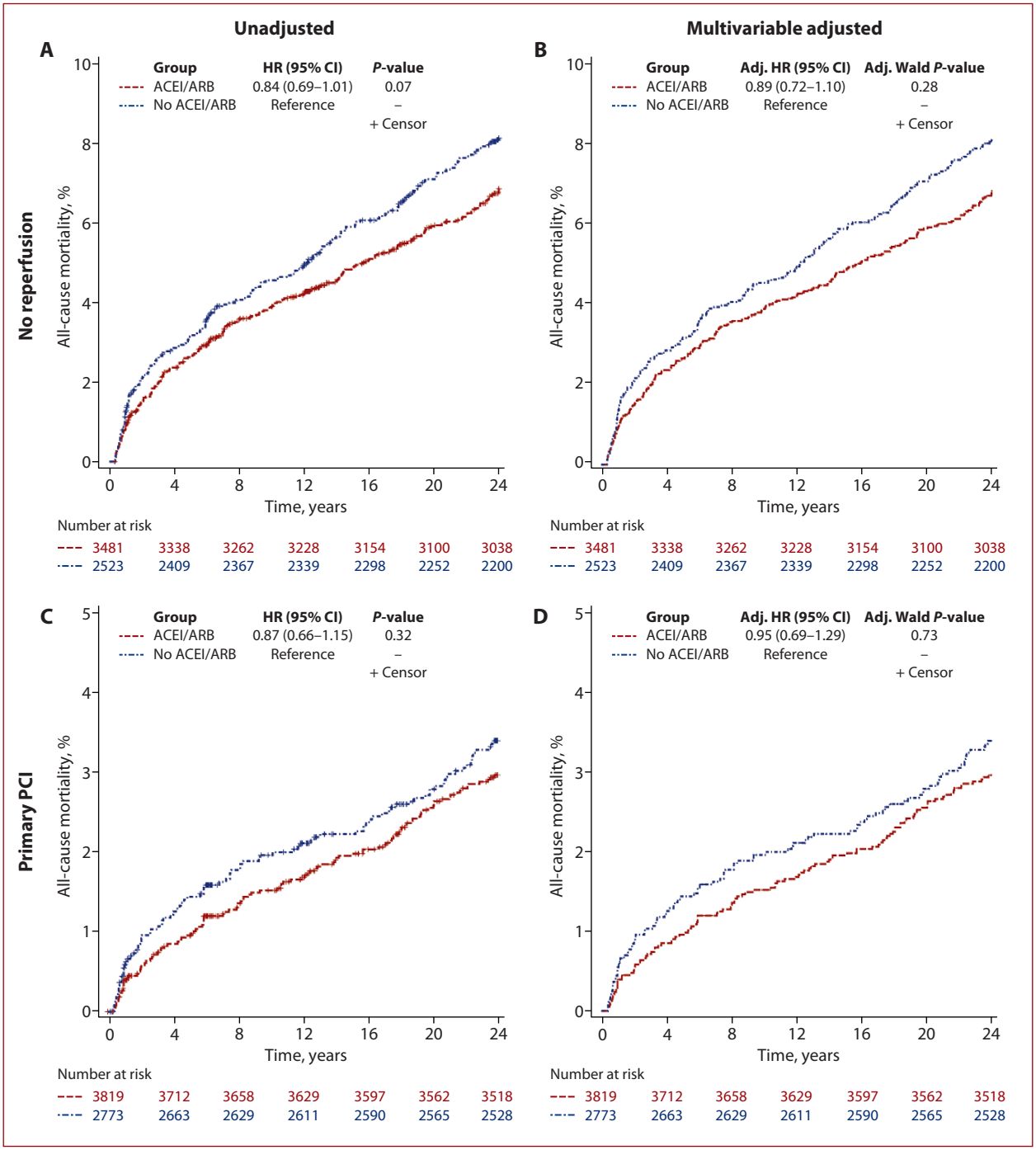

Figure 2. Unadjusted and multivariable-adjusted risk of all-cause mortality according to ACEI/ARB treatment
*Age, sex, body mass index, smoking, hypertension, diabetes, prior myocardial infarction, prior stroke, prior heart failure, prior chronic kidney disease, hospital grade, time from symptoms onset to admission, heart rate, systolic pressure, Killip class, left ventricular ejection fraction, GRACE risk score, anterior myocardial infarction, prescribed with aspirin, $P2Y_{12}$ blockers, statins, or beta-blockers on discharge were included in the adjustment model

Abbreviations: CI, confidence interval; HR, hazard ratio; other — see Figure 1

ical condition, which minimized any potential bias caused by variations in baseline characteristics. Taken together, differences in baseline parameters cannot be the cause of the observed connection between ACEI/ARB and clinical outcomes. The advantages of our study include a large sample size and a reflection of current real-world practice, including high rates of statin use and dual anti-platelet medication.

It has been shown that ACEI alters several aspects of the atherosclerotic process by preventing the production of angiotensin II and minimizing the breakdown of bradykinin [18–20]. Angiotensin II induces the expression of pro-inflammatory genes, increases lipid peroxidation and oxyradical production, and causes endothelial dysfunction. Besides, angiotensin II promotes the growth of vascular smooth muscle and PAI-I production. In contrast, brady-

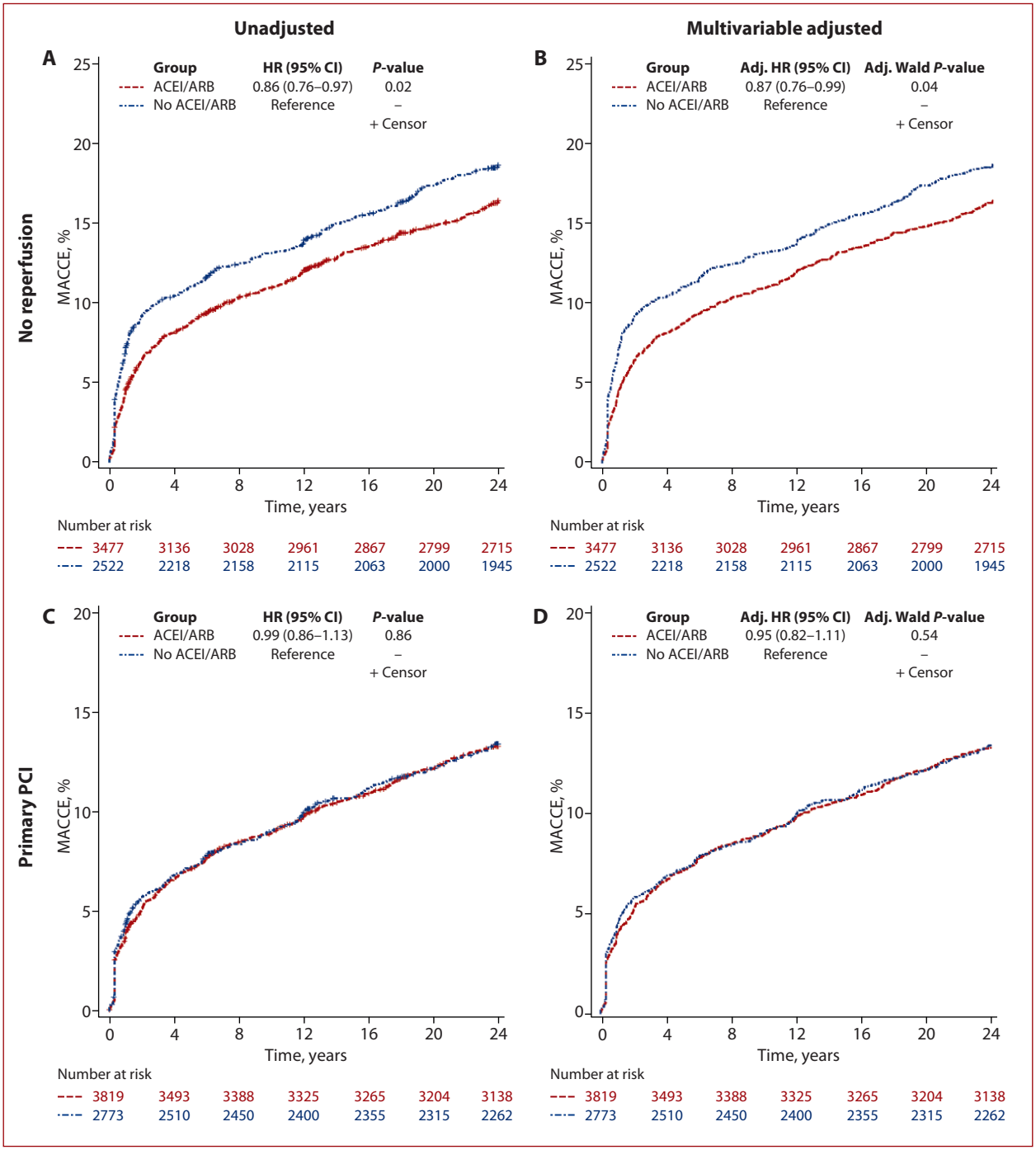

Figure 3. Unadjusted and multivariable-adjusted risk of MACCE according to ACEI/ARB treatment
*Age, sex, body mass index, smoking, hypertension, diabetes, prior myocardial infarction, prior stroke, prior heart failure, prior chronic kidney disease, hospital grade, time from symptoms onset to admission, heart rate, systolic pressure, Killip class, left ventricular ejection fraction, GRACE risk score, anterior myocardial infarction, prescribed with aspirin, $P2Y_{12}$ blockers, statins, or beta-blockers on discharge were included in the adjustment model

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events; other — see Tables 1 and 2

kinin reduces the detrimental effects of angiotensin II and enhances endothelial function by boosting the expression and activity of the constitutive nitric oxide synthase, which can create nitric oxide. Bradykinin also has an antiproliferative impact and stimulates the production of tissue plasminogen activators by inhibiting the expression of monocytes and adhesion molecules. By striking a balance between angiotensin II and bradykinin, ACEI is expected to maintain endothelial function and prevent the onset and progression of atherosclerosis. Therefore, it is not surprising that ACEI/ARB could reduce the risks of MACCE, stroke, and revascularization in the no-reperfusion group. Besides, a meta-analysis concluded that the early benefits of approximately one month of ACEI therapy in STEMI pa-

tients were observed mainly during the first week [1]. The Trandolapril Cardiac Evaluation study also found that the benefits were observed early after the start of treatment and persisted long-term [16]. These results are similar to our findings, which confirm that the benefits were mainly observed during 30-day follow-up and continued at 2 years.

However, in the primary PCI group, we observed no significant differences in MACCE, all-cause mortality, cardiac death, or recurrent MI, which is different from previous studies. After all, with the widespread use of primary PCI, residual myocardial ischemia was significantly decreased [21]. Moreover, evidence-based prescribing, such as statins and dual antiplatelet therapy, was increasingly used and also documented to decrease CV events [3]. As a result, the significant decrease in mortality observed in patients who were treated with primary PCI may diminish the benefits that have been observed with ACEI/ARB in previous reports. Therefore, ACEI/ARB may confer no benefits, or a larger sample size is needed to document the role of ACEI/ARB in patients receiving primary PCI. It is also likely that the apparent neutral results in the PCI group are due to the higher risks of these patients receiving ACEI/ARB, which may counteract the beneficial effects of ACEI/ARB. To control for differences in baseline characteristics, we performed multivariable adjustments and observed consistent results.

Overall, significant benefits of ACEI/ARB therapy on discharge were observed in those patients who did not receive reperfusion. In contrast, no significant benefits were observed in those receiving primary PCI. Thus, all these data together suggest that not all STEMI patients in the contemporary reperfusion era may significantly benefit from additional ACEI/ARB therapy. In particular, the increased daily administration of medications would also worsen patient compliance, increase medical treatment errors, and raise healthcare costs [22]. It is, therefore, crucial to reconsider the role of ACEI/ARB therapy for secondary prevention in addition to primary PCI and other currently available medications. Appropriate classification of STEMI patients who benefit from ACEI/ARB therapy would lower medical expenses and prevent the development of ACEI/ARB side effects. Future large-scale randomized trials will undoubtedly be required to determine which patients with STEMI would mostly benefit from ACEI/ARB therapy.

Limitations

Our study has several limitations inherent in observational studies. First, selection bias for the use of ACEI/ARB is inevitable in observational studies, which may have led healthier or worse patients to receive ACEI/ARB. Although multivariable adjustment was performed to adjust differences in baseline characteristics, it is not possible to completely exclude the influence of unmeasured confounders on clinical outcomes. Second, we had no data on the specific ACEI/ARB used or the dose employed, which might have affected the results. However, considering that this study demonstrated the value of ACEI/ARB treatment in STEMI patients not receiving reperfusion, it appeared reasonable to infer that ACEI/ARB was administered adequately in this study. Third, the prescription of ACEI/ARB on discharge might not represent long-term use of ACEI/ARB after STEMI. In our study, 73.5% of patients continued to use ACEI/ARB one year after STEMI. Fourth, the CAMI registry was conducted between January 2013 and September 2014. Since that time, recommendations for antiplatelet and statin therapies have evolved significantly [23, 24]. This discrepancy may influence the interpretation of our data, as it may not fully reflect the efficacy of contemporary therapies. Consequently, whether our findings can be generalized to STEMI patients treated according to the latest guidelines warrants further investigation in future studies.

CONCLUSIONS

Based on data from the contemporary reperfusion era, our results indicated that ACEI/ARB therapy conferred benefits in STEMI patients not receiving reperfusion, while no significant benefits were observed in those receiving primary PCI. Considering the observational design, the conclusions need to be confirmed or refuted by future prospective clinical trials.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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