

# Renal Safety and Renin–Angiotensin–Aldosterone System Inhibitors in Patients With Contrast Media Exposure: A Multicenter Randomized Controlled Study

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**Abstract:** There is no clear consensus on the safety of renin–angiotensin–aldosterone system inhibitors in patients with contrast media exposure. We aimed to assess the safety of renin–angiotensin–aldosterone system inhibitors in patients exposed to contrast media at 1-year follow-up. Patients treated with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) were recruited and randomly divided into 2 groups (1:1 ratio): with ACEI/ARB group (ACEI/ARB continued throughout the study period) and without ACEI/ARB group (ACEI/ARB stopped 24 hours before and continued 48 hours after the procedure). The primary endpoint was contrast-induced acute kidney injury (CI-AKI) and secondary endpoints were major adverse cardiovascular events (MACEs), and the need for renal replacement therapy during hospitalization and at 1-year follow-up. The occurrence rates of CI-AKI

were not comparable in the ACEI/ARB group and the without ACEI/ARB group (2.92% and 2.62%, respectively;  $P = 0.866$ ). No significant between-group differences were found with respect to the frequency of MACEs or renal replacement therapy during hospitalization and at 1-year follow-up. On subgroup analysis, among patients with estimated glomerular filtration rate (eGFR)  $< 45$  mL/min, the incidence of CI-AKI was significantly higher in the ACEI/ARB group [17.95% (14/78) vs. 6.02% (5/83),  $P = 0.029$ ]. Among patients with eGFR  $\geq 45$  mL/min, the incidence of CI-AKI was comparable in the 2 groups [0.87% (5/572) vs. 2.12% (12/567),  $P = 0.094$ ]. The incidence of MACEs and renal replacement therapy was not comparable in the 2 groups, during hospitalization and at 1-year follow-up. ACEI or ARB treatment can safely be continued after exposure to contrast media, but not in patients with eGFR  $< 45$  mL/min.

**Key Words:** angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin–angiotensin–aldosterone system, contrast-induced acute kidney injury

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## INTRODUCTION

With the increasing use of contrast media in clinical investigations, contrast-induced acute kidney injury (CI-AKI) is a key concern, particularly for patients with coronary artery disease (CAD).<sup>1,2</sup> CI-AKI occurs in 2%–30% of patients exposed to contrast media, leading to an increased risk of severe adverse events such as renal failure, cardiovascular events, stroke, and death.<sup>3</sup> Despite the advances in medicine, CI-AKI has been reported to be the third biggest cause of hospital-acquired acute renal failure in the United States and European countries.<sup>4</sup>

Renin–angiotensin–aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are deemed to be effective against cardiovascular disease and kidney disease.<sup>5,6</sup> However, there is no clear consensus on the effect of ACEIs/ARBs on the occurrence of CI-AKI. Wolak et al<sup>7</sup> found that ACEIs and ARBs can safely be continued after coronary angiography in patients with estimated glomerular filtration rate (eGFR)  $\geq 60$  mL/min. On the contrary, Ma et al<sup>8</sup> found that the incidence of CI-AKI postcoronary artery angiography (CAG)/percutaneous coronary intervention (PCI) in the ACEI/ARB group was significantly higher than that in the no-ACEI/ARB group (26.6% vs. 16.2%,  $P < 0.001$ ). Peng et al<sup>9</sup> also found that ARBs increased the risk of CI-AKI [odds ratio (OR) = 3.31,  $P <$

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Y. W. Lin, H. D. Liu, and D. Q. Yu designed, collected, analyzed and wrote this manuscript. Y. H. Liu, S. H. Dong, J. Yuan, Y. S. Wang and X. Sun assisted in the conduct of study. Y. H. Liu, S. H. Dong, J. Yuan, and X. Sun performed the research. Y. W. Lin, H. D. Liu, and D. Q. Yu was the principal investigator.

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Shenzhen People's Hospital (approval number: SZLY2017025). All participants provided informed consent prior to participation in the study.

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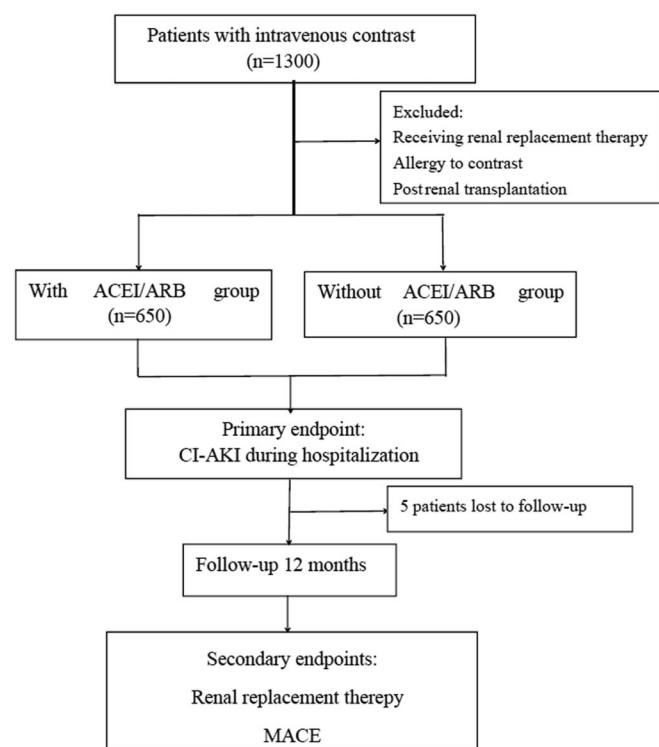
0.0005], but not to be observed for ACEI (OR = 0.86, 95% CI = 0.43–1.72; *P* = 0.664). However, these were single-center studies with a limited sample size. In addition, hydration therapy is now a standard protocol for patients receiving intravenous contrast to reduce the risk of CI-AKI. This may have affected the occurrence of CI-AKI in these patients.

Therefore, we conducted a randomized controlled study to evaluate the effect of ACEI/ARB treatment on the incidence of CI-AKI in patients with contrast media exposure at 1-year follow-up.

## METHODS

### Study Population and Design

This multicenter randomized controlled study was conducted in 2 medical centers (Shenzhen People’s Hospital and Guangdong Provincial People’s Hospital) in China. A total of 1300 patients who required contrast media exposure for cardiac catheterization or coronary computed tomography angiography (CCTA) between October 2017 and December 2019 were randomized into 2 groups: with ACEI/ARB group (*n* = 650, ACE/ARB continued throughout the study period) and without ACEI/ARB group (*n* = 650, ACE/ARB stopped 24 hours before the procedure and continued 48 hours after) (Fig. 1). The sample size for each group (*n* ≥ 635) was calculated by Pearson  $\chi^2$  test for comparison of 2 proportions with 1:1 sampling) using PASS 15 software.<sup>10</sup> Written informed consent was obtained from all patients before their enrolment.



**FIGURE 1.** Schematic illustration of the study design and patient-selection criteria.

All patients followed the standard protocol for the preparation for cardiac catheterization or CCTA including hydration treatment 12 hours before and at least 24 hours after, according to the guidelines. This study was approved by the ethics committee of the Shenzhen People’s Hospital and registered in the Chinese Clinical trial Registry (ChiCTR1800015188).

### Inclusion Criteria

The inclusion criteria were: Patients aged >18 years with suspected CAD undergoing cardiac catheterization (CAG or PCI) or CCTA; 2) chronic therapy with ACEI and/or ARB for at least one week.

### Exclusion Criteria

Exclusion criteria were: (1) systolic blood pressure < 90 mm Hg; (2) patients using nonsteroidal anti-inflammatory drugs; (3) contrast media exposure ≤14 days; (4) allergic to contrast media; (5) patients on continuous renal replacement therapy or prior renal transplantation; (6) age >90 years. Patients with acute myocardial infarction (AMI) requiring primary PCI were also excluded.

### Study Endpoints

The primary endpoint was CI-AKI defined as serum creatinine increase ≥ 25% from the baseline or 44 μmol/L ≤ 48 hours. eGFR was calculated by the 4-variable Modification of Diet in Renal Disease (MDRD).<sup>11</sup> The secondary endpoints were major adverse cardiovascular events (MACEs) (defined as the composite of cardiac death, nonfatal myocardial infarction, unstable angina, and heart failure) and the need for renal replacement therapy during hospitalization and at 1-year follow-up. Follow-up data were collected by telephonic interview.

### Statistical Analysis

SPSS 22.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis. Continuous variables are expressed as mean ± SD and between-group differences assessed using Student’s *t* test for normally distributed variables and Kruskal–Wallis test or Mann–Whitney *U* test for abnormally distributed variables. Categorical variables are expressed as frequency (percentage) and between-group differences assessed using  $\chi^2$  or Fisher Exact test. A repeated measures analysis adjusted for the baseline levels was performed to compare creatinine, urea, and eGFR measures before and 24 and 48 hours after catheterization or CCTA between the 2 groups.

## RESULTS

### Baseline Characteristics of the Two Groups

Between October 2017 and September 2019, a total of 1300 patients were included in this study. The baseline characteristics of patients in the ACEI/ARB group and without ACEI/ARB group are compared in Table 1. There was no significant between-group difference with respect to the mean age of patients ( $57.1 \pm 13.9$  years and  $57.1 \pm 12.7$

**TABLE 1.** Baseline Characteristics of Patients in the Two Groups

Characteristics	With ACEI/ARB Group (n=650)	Without ACEI/ARB Group (n=650)	P
Age (y)	57.12 ± 13.95	57.10 ± 12.79	0.978
Male, n (%)	516 (79.38)	519 (79.85)	0.891
Body mass index, kg/m <sup>2</sup>	23.09 ± 3.42	24.45 ± 3.18	0.065
SBP (mm Hg)	132.60 ± 24.27	134.34 ± 23.07	0.187
HR (bpm)	81.72 ± 18.23	81.22 ± 17.15	0.128
Hypertension, n (%)	580 (89.23)	594 (91.38)	0.874
Diabetes mellitus, n (%)	161 (24.77)	148 (22.77)	0.790
Insulin requiring, n (%)	73 (45.34)	70 (47.30)	0.731
Metformin, n (%)	144 (89.44)	134 (90.54)	0.675
Current smoking, n (%)	330 (50.77)	335 (51.54)	0.811
Previous MI, n (%)	31 (4.77)	33 (5.08)	0.792
Previous PCI, n (%)	24 (3.69)	26 (4.00)	0.968
Diagnosis, n (%)			
STEMI, n (%)	40 (6.15)	34 (5.38)	0.154
NSTEMI, n (%)	120 (18.46)	116 (17.85)	0.900
Unstable angina, n (%)	289 (44.46)	294 (45.23)	0.892
Stable angina, n (%)	70 (12.31)	65 (10.0)	0.676
Without significant stenosis, n (%)	131 (20.15)	141 (21.69)	0.889
Hemoglobin (g/L)	137.38 ± 22.79	139.09 ± 19.75	0.148
Albumin (g/L)	31.5 ± 9.3	30.4 ± 10.6	0.765
LDL (mmol/L)	2.83 ± 0.98	2.93 ± 0.98	0.076
HbA1C, %	6.56 ± 3.87	6.67 ± 4.51	0.016
Na <sup>+</sup> (mmol/L)	138.12 ± 4.36	143.42 ± 6.54	0.125
LVEF, %	54.46 ± 10.72	54.80 ± 22.93	0.743
Medical treatment			
Aspirin, n (%)	585 (90.00)	584 (89.85)	0.912
Clopidogrel/ticagrol	545 (83.85)	540 (83.08)	0.930
Statin, n (%)	632(97.23)	635 (97.69)	0.939
Beta-blocker, n (%)	311 (47.85)	300 (46.15)	0.899
Diuretics, n (%)	90 (13.85)	85 (13.77)	0.896
Ca channel blocker, n (%)	125 (19.23)	150 (23.08)	0.565
ACEI, n (%)	281 (43.23)	275 (42.31)	0.776
ARB, n (%)	369 (56.77)	375 (57.69)	0.836
Type of angiography			
Cardiac catheterization, n (%)	551(84.77)	531(81.69)	0.553
CCTA, n (%)	99 (15.23)	119 (18.31)	0.494
No. of patients with PCI, n (%)	335 (52.15)	328 (50.46)	0.757
No. of stents/patient	1.43 ± 0.90	1.40 ± 0.97	0.685
Bleeding complications*	1 (0.15)	1 (0.15)	1.0
TRA/dTRA	638 (98.15)	641 (98.62)	0.911
Volume of contrast media (mL)	92.67 ± 48.34	96.19 ± 42.43	0.165
Hydration			
Intravenous hydration, n (%)	410 (63.08)	405 (62.31)	0.673
Oral hydration, n (%)	240 (39.92)	245 (37.69)	0.673
Daily fluid intake, ml			
24h-post	2242.86 ± 97.59	2295.49 ± 115.01	0.316
48h-post	2554.29 ± 167.22	2687.27 ± 257.45	0.203

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; dTRA, distal transradial approach; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TRA, transradial approach.

\*Bleeding complications were defined as those requiring blood transfusion or causing a decrease in hemoglobin of >3.0g/dL within 72 h after PCI.

years, respectively,  $P = 0.978$ ), hypertension (580, 89.23% and 594, 91.38%, respectively,  $P = 0.874$ ), or baseline creatinine levels ( $96.91 \pm 41.85$  and  $97.27 \pm 45.93$  respectively,

$P = 0.883$ , Table 2). Similarly, there were no significant between-group differences with respect to other demographic characteristics, laboratory parameters, clinical manifestations,

**TABLE 2.** Comparison of Renal Function Indices in the Two Groups

	With ACEI/ARB Group (n=650)	Without ACEI/ARB Group (n=650)	P
Before contact with contrast			
Creatinine, μmol/L	96.91 ± 41.85	97.27 ± 45.93	0.883
Urea, mmol/L	7.65 ± 9.73	8.15 ± 1.03	0.434
eGFR* (mL/min)	77.74 ± 27.49	77.64 ± 24.24	0.945
cystatin C, mg/L	2.54 ± 1.54	2.44 ± 1.64	0.665
Hs-CRP, mg/L	4.54 ± 3.84	4.34 ± 2.96	0.543
24-post contact with contrast			
Creatinine, μmol/L	94.66 ± 42.96	94.09 ± 56.79	0.839
Urea, mmol/L	8.95 ± 10.01	9.65 ± 10.33	0.771
eGFR* (mL/min)	80.49 ± 28.75	83.10 ± 27.64	0.100
cystatin C, mg/L	3.24 ± 1.31	2.945 ± 1.53	0.766
Hs-CRP, mg/L	5.04 ± 3.13	4.99 ± 2.82	0.675
48-post contact with contrast			
Creatinine, μmol/L	97.82 ± 48.07	97.31 ± 52.40	0.855
Urea, mmol/L	8.55 ± 11.54	8.95 ± 13.21	0.454
eGFR* (mL/min)	79.78 ± 40.64	80.63 ± 31.65	0.675
cystatin C, mg/L	3.99 ± 2.11	3.44 ± 2.54	0.449
Hs-CRP, mg/L	5.44 ± 4.52	5.35 ± 4.44	0.531

Data presented as mean ± SD.

\*eGFR was calculated by the four-variable Modification of Diet in Renal Disease (MDRD).

type of angiography, medical treatment, volume of contrast media, or daily fluid intake.

### Primary and Secondary Endpoints In-Hospital

The occurrence rates of CI-AKI (primary endpoint) in the ACEI/ARB group and the without ACEI/ARB group were 2.92% and 2.62% ( $P = 0.866$ ; Table 3 and Fig. 2), whereas the occurrence rates of MACEs and renal replacement therapy during hospitalization were 8.62% versus

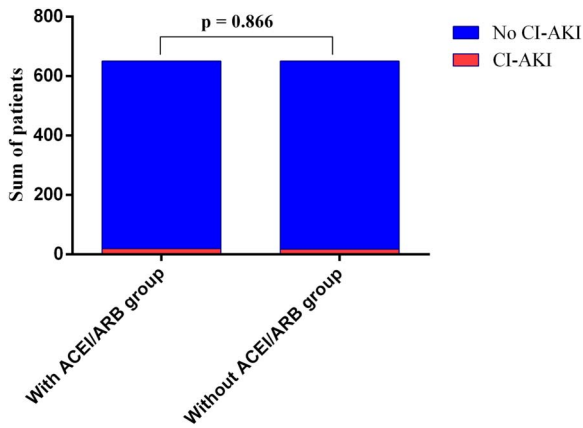
8.92% ( $P = 0.837$ ) and 0% versus 0%, respectively. At one-year follow-up, there were no significant between-group differences with respect to the frequency of MACEs (19.54% vs. 18.92%,  $P = 0.872$ ) or renal replacement therapy (0.31% vs. 0.15%,  $P = 0.795$ ), respectively (Table 3).

We further performed subgroup analysis based on eGFR levels. Among patients with eGFR < 45 mL/min, the occurrence rate of CI-AKI in the ACEI/ARB group [17.95% (14/78)] was significantly higher than that in the

**TABLE 3.** Comparison of Primary and Secondary Outcomes Between the Two Groups

	With ACEI/ARB Group (n = 650)	Without ACEI/ARB Group (n = 650)	P
In-hospital			
CI-AKI, n (%)	19 (2.92)	17 (2.62)	0.866
ACEI	9/281 (3.20)	8/275 (2.91)	0.821
ARB	10/369 (2.71)	9/375 (2.40)	0.874
MACE, n (%)	56 (8.62)	58 (8.92)	0.837
Cardiac death, n (%)	0 (0)	0 (0)	1.0
Nonfatal MI, n (%)	19 (2.92)	18 (2.77)	0.834
Unstable angina, n (%)	22 (3.38)	26 (2.4)	0.787
Heart failure, n (%)	15 (2.31)	14 (2.15)	0.833
Renal replacement therapy	0 (0)	0 (0)	1.0
1-year follow-up			
MACE, n (%)	127 (19.54)	123 (18.92)	0.872
Cardiac death, n (%)	1 (0.15)	0 (0)	0.657
Nonfatal MI, n (%)	34 (5.23)	31 (4.77)	0.821
Unstable angina, n (%)	44 (6.77)	42 (6.46)	0.910
Heart failure to hospitalization, n (%)	46 (7.08)	49 (7.54)	0.901
Renal replacement therapy, n (%)	2 (0.31)	1 (0.15)	0.795

MI, myocardial infarction.



**FIGURE 2.** Occurrence of CI-AKI in the 2 groups (2.92% vs. 2.62%,  $P = 0.866$ ).

without ACEI/ARB group [6.02% (5/83),  $P = 0.029$ ]. However, among patients with  $eGFR \geq 45$  mL/min, there was no significant difference in the occurrence rate of CI-AKI [0.87% (5/572) versus 2.12% (12/567),  $P = 0.094$ ], respectively (Fig. 3).

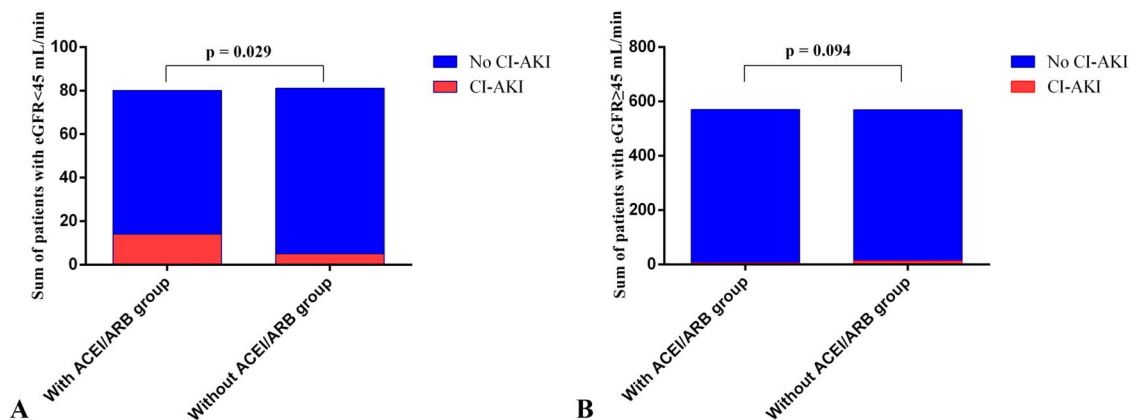
We also further performed subgroup analysis based on AMI or with PCI. The incidences of CI-AKI were similar between groups in patients with AMI [9.38% (15/160) versus 8.00% (12/150);  $P = 0.691$ ] or with PCI [5.07% (17/335) versus 4.57% (15/328);  $P = 0.857$ ], respectively (Fig. 4).

### DISCUSSION

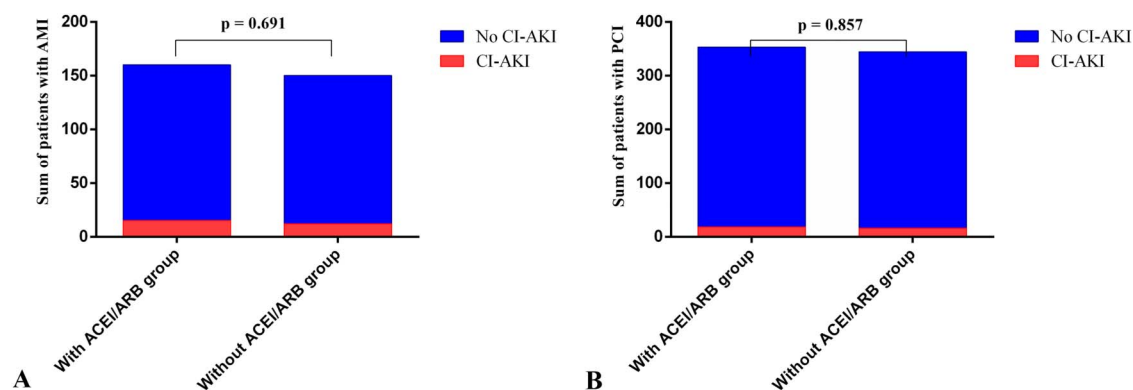
The multicenter randomized controlled study was conducted to evaluate the safety of ACEI/ARB in patients with contrast exposure at 1-year follow-up. The major findings were as follows: (1) ACEI/ARB use was not associated with increased incidence of CI-AKI, composite frequency of MACE, or the requirement for renal replacement therapy. (2) ACEI/ARB should be avoided in patients with  $eGFR < 45$  mL/min.

ACEI/ARBs are commonly used in patients with cardiovascular diseases such as hypertension, diabetes mellitus, heart failure, or chronic kidney disease to prevent end organ damage, unless contraindicated.<sup>12,13</sup> These drugs have been shown to improve the long-term prognosis of patients with cardiovascular and renal diseases. However, the effect of ACEI/ARBs on CI-AKI is not clear. In the study by Rim et al,<sup>14</sup> 64% of patients undergoing coronary angiography were treated with ACEI/ARB, which significantly increased the incidence of CI-AKI after propensity score matching (11.4% vs. 6.3%,  $P < 0.001$ ). Bainey et al<sup>15</sup> randomly divided 208 patients with renal insufficiency requiring contrast media into 2 groups: continuing ACEI/ARB or stopping ACEI/ARB 24 hours before surgery. The incidence of CI-AKI (18.5% vs. 10.9%) and renal replacement therapy (3.9% vs. 0%) was obviously higher in the continuing ACEI/ARB group. RAAS inhibitors cause a decrease in eGFR and an increase in SCr, promoting CI-AKI.<sup>16</sup> However, Wolak et al<sup>7</sup> and Kevin et al<sup>15</sup> found no significant difference between ACEI/ARB use and contrast contact in patients with  $eGFR \geq 60$  mL/min or moderate renal insufficiency. Similar conclusions were drawn by a meta-analysis of RCTs (pooled OR = 1.22,  $P = 0.63$ ) in patients with normal or mild-to-moderate renal insufficiency.<sup>17</sup> Our results also suggest that ACEIs and ARBs can be safely continued after angiography in patients exposed to contrast media with suspected CAD. The following factors may explain these results. First, these studies included patients with normal or mild-to-moderate renal dysfunction. In our RCT, patients with  $eGFR < 45$  mL/min accounted for only 10.08% of all patients. Second, each included patient received rigorous standardized hydration treatment. The increasing awareness of hydration treatment and the improvement in surgical techniques of PCI, have caused a dramatic decline in the occurrence of CI-AKI.

ACEI/ARBs should be avoided in patients with  $eGFR < 45$  mL/min because the incidence of CI-AKI was significantly higher in this subgroup [17.95% vs. 6.02%;  $P = 0.029$ ]. It is generally believed that abnormal



**FIGURE 3.** Influence of RAAS inhibitors on CI-AKI after coronary angiography in patients with different eGFR grade during hospitalization. A, Patients with  $eGFR < 45$  mL/min: the incidence of CI-AKI was significantly higher in the with ACEI/ARB group [17.95% (14/78) versus 6.02% (5/83);  $P = 0.029$ ]. B, Patients with  $eGFR \geq 45$  mL/min: the incidence of CI-AKI in the with and without ACEI/ARB groups was 0.87% (5/572) versus 2.12% (12/567), respectively;  $P = 0.094$ .



**FIGURE 4.** Influence of RAAS inhibitors on CI-AKI after coronary angiography in patients with AMI or with PCI during hospitalization. A, Patients with AMI: The incidence of CI-AKI was no difference between groups [9.38% (15/160) versus 8.00% (12/150);  $P = 0.691$ ]. B, Patients without PCI: The incidence of CI-AKI was no difference between groups [5.07% (17/335) vs. 4.57% (15/328);  $P = 0.857$ ].

hemodynamics is the main pathological basis of CI-AKI caused by ACEI/ARBs. Their stronger effect of selectively expanding glomerular outlet arterioles leads to lower renal perfusion and lower glomerular filtration rate. Accordingly, CI-AKI is more likely to occur after exposure to contrast agents.<sup>18</sup> In addition, recent studies have also indicated the existence of an angiotensin-converting enzyme-angiotensin II-angiotensin II receptor 1 axis in the RAAS system.<sup>19</sup> Angiotensin II induces the formation of transforming growth factor-beta 1 to promote regeneration and repair after renal injury and the inhibition of angiotensin II activity by ACEI/ARB may be involved in the occurrence and development of CI-AKI.<sup>20,21</sup> Therefore, the continued use of ACEI/ARB after contrast agent exposure aggravates the occurrence of CI-AKI and worsens the prognosis of patients with severe renal insufficiency. Several studies have confirmed the harmful effects of angiotensin II blockade on patients exposed to contrast agents, mostly in patients with impaired renal function and the elderly.<sup>22</sup>

Some limitations of our study should be acknowledged. First, since most RAAS inhibitors have a half-life of more than 24 hours, ACEI/ARBs should be stopped at least 48 hours before contrast media exposure. Second, a larger sample of patients with severe renal dysfunction should be included in next study. In addition, future RCT studies should separately assess the effect of ACEIs and ARBs on CI-AKI.

### CONCLUSIONS

Our results suggest that ACEIs and ARBs can safely be continued after contrast media exposure during CAG/PCI or CCTA in patients with suspected CAD, but not in patients with eGFR < 45 mL/min.

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