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Effect of Renin-angiotensin System Inhibitors on Acute Kidney Injury among Patients undergoing Cardiac Surgery: A Review and Meta-analysis

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Keywords

Acute kidney injury; Cardiac surgery; Renin-angiotensin system inhibitors; Angiotensin-converting enzyme inhibitors; Angiotensin II receptor blockers

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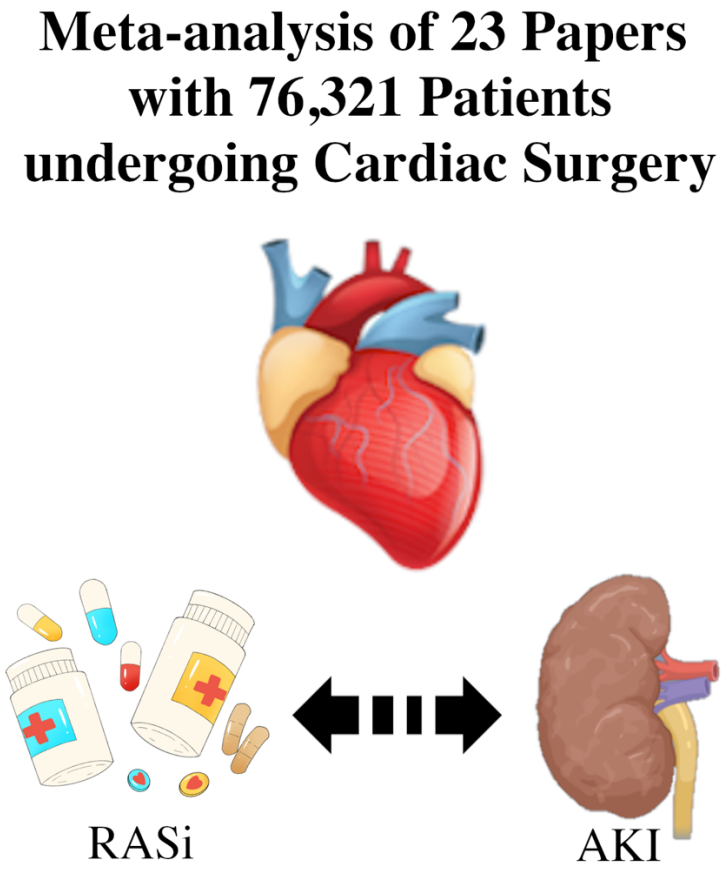
Abstract

Acute kidney injury (AKI) is a frequent complication of cardiac surgery, which can lead to higher mortality and long-term renal function impairment. The effect of perioperative renin-angiotensin system inhibitors (RASi) therapy on AKI incidence in patients undergoing cardiac surgery remains controversial. We reviewed related studies in PubMed, Scopus, and Cochrane Library from inception to February 2020. Two randomized controlled trials (RCTs) and 21 cohort studies were included in the meta-analysis, involving 76,321 participants. The pooled odds ratio and 95% confidence interval were calculated using the DerSimonian and Laird random-effects model. The results showed no significant association between perioperative RASi therapy and postoperative AKI in patients undergoing cardiac surgery. We highlighted the limitations of existing studies and called for well-designed large-scale RCTs to verify the conclusion.

Central Picture



No significant association between RASi and AKI in patients undergoing cardiac surgery

Central Message

Our meta-analysis showed no significant association between perioperative RASi therapy and postoperative AKI in patients undergoing cardiac surgery.

Perspective Statement

The effect of perioperative use of RASi on postoperative AKI in patients undergoing cardiac surgery remains controversial. Our results showed no significant association between RASi and postoperative AKI. These findings suggested that perioperative RASi management strategies did not have a statistically significant effect on the postoperative AKI incidence in patients undergoing cardiac surgery.

Introduction

Acute kidney injury (AKI) is a frequent complication of cardiac surgery, which can lead to higher mortality, long-term renal function impairment, and require more medical resources [1, 2]. Thus, studying the prevention of postoperative AKI in patients undergoing cardiac surgery has important implications for clinical care and resource utilization. Renin-angiotensin System inhibitors (RASi), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are commonly used in patients undergoing cardiac surgery [3]. It is necessary to evaluate whether such common drugs play a protective or harmful role for AKI following cardiac surgery.

Until now, the effect of perioperative RASi therapy on renal function in patients undergoing cardiac surgery remains controversial. Some suggested an increased renin-angiotensin system activity during cardiopulmonary bypass (CPB), which has a prominent role in hypoperfusion-related renal injury, and RASi could improve renal perfusion by blocking the activity [4]. A cohort study by Benedetto et al. [4] showed a reduction in the incidence of postoperative AKI when using ACEIs. However, others suggested that RASi increased the risk of perioperative hypotension, generating a reduction in renal perfusion pressure, a risk factor for renal dysfunction [5]. A meta-analysis conducted by Yacoub et al. [6] found a harmful effect of preoperative RASi therapy on postoperative AKI in patients undergoing cardiothoracic surgery. However, their study was limited by the choice of unadjusted odds ratio (OR) instead of adjusted OR when adjusted OR was available.

A meta-analysis was performed to explore the effect of perioperative RASi on the renal outcomes in patients undergoing cardiac surgery.

Material and Methods

Data Sources and Searches

We searched published studies in PubMed, Scopus, and Cochrane Library from inception to February 2020, using the combination of the following terms: (‘angiotensin-converting enzyme inhibitors’ or’ ACEI’ or’ renin-angiotensin system blockade’) and (‘cardiac surgery’ or’ heart surgery’ or’ coronary artery bypass grafting’ or’ cardiovascular surgery’). We did not use terms related to kidney because we did not want to restrict to the studies that focused on renal function only. References from the retrieved articles were searched manually. Figure 1 depicted the selection process. It should be noted that Benedetto et al. [4, 7] wrote two papers satisfying our criteria in 2008 and 2010, respectively, and the data in these two papers came from the same source, i.e., the data used overlapped to some extent. Thus, we only included one of them [4] in our meta-analysis, considering the renal focus of this paper.

Study Selection

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs) or cohort studies compared the effect of perioperative use of RASi with no RASi undergoing cardiac surgery; (2) studies reported incidence of AKI, or OR with 95% confidence interval (CI) comparing the AKI risk in the treatment group and control group; (3) the follow-up period of renal function was either the in-hospital stay or 30 days.

Data Extraction

A standardized data collection form was used to extract the following information: last name of the first author, publication year, participants, study design, sample size, drug intervention, AKI definition, mean age, country, and publication quality. AKI was defined differently by different authors. The quality of each study was independently evaluated by each investigator using the

Newcastle–Ottawa scale [10] for cohort studies and Cochrane risk of bias tool for RCTs.

Outcome measures

The outcome in the meta-analysis was the incidence of new-onset postoperative AKI.

Statistical Analysis

We conducted a meta-analysis in all included studies. We also performed subgroup analyses on different patterns of RASi therapy and different types of RASi, respectively. The OR was used to evaluate the association of RASi therapy with AKI. They were either directly extracted or calculated from reported AKI incidence. Statistical heterogeneity was evaluated using the Q test, which uses the I^2 statistic to quantify the proportion of the total variation across studies due to heterogeneity rather than chance. The studies included in the meta-analysis were non-identical in terms of AKI definition, drug intervention, and participants. Therefore, we used the DerSimonian and Laird random-effects model for meta-analysis. Publication bias was assessed by Egger's test and funnel plot. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using Review Manager 5.3 software from the Cochrane Collaboration.

Results

We retrieved 23 studies that met our criteria and included them in the meta-analysis. In terms of study design, there were 2 RCTs [11, 12], and the rest were cohort studies. As for the drug intervention, 19 studies focused on the preoperative use of RASi; van Diepen et al. [11] focused on preoperative continuation versus withdrawal; Drenger et al. [13] studied both perioperative therapy (preoperative and postoperative) and postoperative administration; Coca et al. [14] compared not only preoperative continuation with preoperative withdrawal but also preoperative use with no RASi. The type of RASi also varied: 13 studies focused on the use of ACEIs, and

ACEIs/ARBs were administrated in 10 studies. Table 1 described the detailed characteristics of the included studies.

Study participants

The number of participants ranged from 14 to 10,648; in total, 76,321 patients were included. In terms of surgery type, eight studies focused on coronary artery bypass graft (CABG) surgeries [4, 5, 13, 16, 17, 25, 32, 35]; one focused on aortic surgery [29]; the remaining studies included more than one type of surgeries. Among all of the studies, five mentioned the use of CPB in all patients [4, 13, 28, 31, 36]. Three studies restricted patients to age $\geq$ 18 and one to $\geq$ 65.

Perioperative use of RASi and postoperative AKI

Twenty-three articles were included in this meta-analysis. The random-effects model was used due to high heterogeneity ($I^2 = 82\%$). The pooled OR of postoperative AKI in patients taking RASi perioperatively was 1.02 (95% CI: 0.89-1.17), with the forest plot shown in Figure 2. This result showed no significant association of perioperative use of RASi with increased or decreased risk of postoperative AKI.

Pattern of RASi therapy and postoperative AKI

Subgroup meta-analysis was performed in two different patterns of RASi therapy: preoperative use of RASi versus no RASi, and preoperative continuation versus preoperative discontinuation. Additionally, one study reported postoperative use of RASi versus no RASi. The results might help to decide the initiation or withdrawal of RASi during the procedure of cardiac surgery.

Nineteen studies compared patients taking RASi preoperatively with patients receiving no RASi therapy. The forest plot was shown in Figure 3. A random-effect model was used considering the high heterogeneity ($I^2 = 84\%$), and the pooled OR was 1.02 (95% CI: 0.88-1.18). No significant

association between the preoperative use of RASi and postoperative AKI was found.

For patients chronically taking RASi, two studies compared the continuation of RASi with discontinuation just before cardiac surgery. The meta-analysis of these two studies [11, 14] demonstrated no evidence of increased or decreased risk of AKI when withdrawing RASi before surgery (Figure S1), with the pooled OR being 1.12 (95% CI: 0.94-1.33).

As for the postoperative use of RASi, Drenger et al. [13] defined four groups, where "continuation" meant on ACEIs preoperatively and postoperatively; "withdrawal" denoted taking ACEIs preoperatively but not postoperatively; "addition" represented not on ACEIs preoperatively but had it added postoperatively; "no ACEIs" meant no exposure to ACEIs. When evaluating the effect of ACEIs in the continuation group versus the withdrawal group, the adjusted OR was 0.47 (95% CI: 0.28-0.79), which indicated a possibly improved kidney outcome with the continuation of ACEIs. For the comparison between the addition group and no ACEIs group, the OR was 0.57 (95% CI: 0.24-1.36).

Type of RASi and postoperative AKI

Manning et al. [38] showed that ACEIs and ARBs worked differently and thus, led to different outcomes in their study. To understand the effects of different types of RASi, studies were divided into using ACEIs exclusively and using ACEIs/ARBs. No study solely used ARBs.

The pooled OR of the 13 studies using ACEIs exclusively was 1.10 (95% CI: 0.92-1.32) (Figure S2, provided as online supplementary material). For the ten studies used ACEIs/ARBs, the pooled OR was 0.96 (95% CI: 0.81-1.14) (Figure S3). No significant association was found in both meta-analyses

Publication Bias

The publication bias was examined by the funnel plot (Figure S4) and the Egger's test. The bias

coefficient was -1.19 (95% CI: -3.05-0.67), P = 0.196; thus, no statistically significant publication bias was found.

Sensitivity Analysis

We performed the following sensitivity analysis with different subgroups of studies:

- Since the confounders could bring bias, we restricted to the studies in which the confounders were matched by propensity score matching or adjusted through multivariate regression. The pooled OR was given in Figure S5.
- We separated cohort studies from RCTs and performed the meta-analysis on both subgroups. The results were shown in Figures S6 and S7.
- As CPB appeared to be one of the main reasons that the RAS activities were increased, we analyzed the subgroup of studies that included CPB (Figure S8). We also performed the meta-analysis in the subgroup of studies that only performed CABG (Figure S9).

All of the subgroup analyses above showed no significant association between perioperative RASi therapy and postoperative AKI.

Quality Assessment

The risk of bias in cohort studies and RCTs were shown in Table 1. The RCTs were at low risk of bias. All observational studies scored four or more stars in the Newcastle–Ottawa scale, while 11 of the 22 studies scored five or more. The common reasons for poor quality included: (1) lack of specific definition of the exposure, i.e., drug intervention; (2) lack of information of the history in renal function insufficiency; and (3) inconsistent assessment of outcomes.

Discussion

The meta-analysis of all included studies showed no significant association between

perioperative RASi therapy and postoperative AKI in patients undergoing cardiac surgery. Furthermore, the subgroup meta-analysis in two different patterns of RASi therapy (preoperative use of RASi versus no RASi, and preoperative continuation versus preoperative discontinuation) also demonstrated no significant association. Overall, there was no evidence of the increased or decreased risk of postoperative AKI when using RASi in patients undergoing cardiac surgery.

This result contradicted with a meta-analysis published in 2013 by Yacoub et al. [6]. There were 18 common studies included in our meta-analysis and [6]. Yacoub et al. found that the preoperative use of RASi was associated with increased odds of postoperative AKI in patients undergoing cardiothoracic surgery. However, their conclusion might be biased due to the choice of unadjusted OR instead of adjusted OR in several included studies [13, 15, 16, 17] while adjusted ORs were available. For example, Rady [15] concluded that preoperative therapy with ACEIs did not influence the AKI incidence based on the regression OR 0.9 (95% CI: 0.7-1.2); Yacoub et al.'s meta-analysis, however, used the unadjusted OR, which was 1.37 (95% CI: 1.08-1.73). One possible explanation of the higher OR before confounder adjustment was that some of the confounders were also risk factors of AKI, like hypertension, diabetes, obesity, and patients with such features were predisposed to AKI.

Another meta-analysis by Cheungpasitporn et al. [18] studied a similar issue in patients undergoing all kinds of operations instead of only cardiac surgery. It showed no significant association between postoperative AKI and preoperative use of RASi in all included studies, while a reduced risk in studies with propensity score analysis.

There were five RCTs reporting lab indices related to renal function. In 1990, an RCT with 18 participants by Colson et al. [19] demonstrated that renal plasma flow and glomerular filtration rate decreased in the controlled group whereas remained unaltered in the treatment group. An RCT in

2001 [21] showed that the administration of RASi helped maintain renal perfusion during surgery. Wagner et al. [22] and Turker et al. [23] showed higher creatinine clearance and lower creatinine under RASi therapy. These results indicated a renoprotective effect of short-term RASi treatment in patients undergoing cardiac surgery. In 1999, Licker et al. [20] performed a case-control study and showed that renal functional and hemodynamic variables did not differ between the controlled and treatment group. Among studies that reported postoperative AKI, some showed a decreased risk of postoperative AKI [4, 12, 15, 17, 24, 25, 26]; some reported the opposite result [5, 14, 16, 27, 28, 29, 30, 31, 32]; and others found no significant association between postoperative AKI and RASi therapy [11, 13, 33, 34, 35, 36, 37].

There were also studies investigating other outcomes of RASi. For example, some research showed that perioperative use of ACEI was associated with protracted vasoplegia before, during, and after CPB [39, 40]. A large multicentre study of 4,224 patients undergoing CABG showed that continuous treatment with ACEI compared with no ACEI was associated with reductions of risks of non-fatal events [13]. The addition of ACEI following surgery was also found to be associated with a significant reduction in both the risk of composite outcome and the risk of a cardiovascular event [13]. A clinical study showed that among patients undergoing transcatheter aortic valve replacement, receiving RASi compared with not receiving was significantly associated with a lower risk of mortality and heart failure readmission [41].

Limitations

There were several limitations to our study. First, the heterogeneity in our study was relatively high. The heterogeneity might arise from the study populations and different drug management practices. We tried to decrease the heterogeneity by classifying the studies for subgroup analysis. Unfortunately, the heterogeneity remained relatively high in all of the subgroup analyses.

Second, most included studies were cohort studies, and only two were RCTs, which were limited by their study designs. Van et al. [11] performed an RCT among 121 patients, and the number of patients who developed AKI was one in both treatment and control groups, which was quite small. In the other RCT [12], the definition of AKI was serum creatinine >2.5 mg/L, which was less commonly used.

Third, the language included in the study was limited to English, and we did not identify unpublished studies. Thus, the studies included might be incomplete.

Conclusion

In conclusion, our results showed no significant association between perioperative RASi therapy and postoperative AKI, which was different from a previous meta-analysis on the same topic. The difference was largely due to our choice of adjusted OR rather than the unadjusted OR used in the previous meta-analysis. Our findings suggested that perioperative RASi management strategies did not have a statistically significant effect on the postoperative AKI incidence in patients undergoing cardiac surgery. Due to the limitations of existing studies, well-designed large-scale RCTs are needed to verify the conclusion.

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Figure Legend

Figure 1: Flow diagram of study selection. AKI = acute kidney injury

Figure 2: Forest plot of all the included studies comparing the risk of postoperative AKI in patients with and without perioperative use of RASi, using a random-effect model. A diamond data marker represents the overall odds ratio and 95% CI for the outcome. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure 3: Forest plot of all the included studies comparing the risk of postoperative AKI in patients with and without preoperative use of RASi, using a random-effect model. A diamond data marker represents the overall odds ratio and 95% CI for the outcome. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure 4: Graphical abstract of the meta-analysis. No significant association between perioperative RASi therapy and postoperative AKI in patients undergoing cardiac surgery was observed with OR being 1.02 (95% CI: 0.89-1.17). RASi = renin-angiotensin system inhibitors; OR = odds ratio

Figure S1: Forest plot of all the included studies comparing the risk of postoperative AKI in patients with the preoperative continuation of RASi and with preoperative withdrawal, using a random-effect model. A diamond data marker represents the overall odds ratio and 95% CI for the outcome. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure S2: Forest plot of all the included studies comparing the risk of postoperative AKI in patients with ACEIs therapy and not with, using a random-effect model. AKI = acute kidney injury; IV =

inverse-variance; ACEIs = angiotensin-converting enzyme inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure S3: Forest plot of all the included studies comparing the risk of postoperative AKI in patients with ACEIs/ARBs therapy and not with, using a random-effect model. AKI = acute kidney injury; IV = inverse-variance; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure S4: Funnel plot of publication bias

Figure S5: Forest plot of all the matched or adjusted studies comparing the risk of postoperative AKI in patients with perioperative RASi therapy and not with, using a random-effect model. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure S6: Forest plot of all the observational studies comparing the risk of postoperative AKI in patients with perioperative RASi therapy and not with, using a random-effect model. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure S7: Forest plot of all the randomized controlled trials comparing the risk of postoperative AKI in patients with perioperative RASi therapy and not with, using a random-effect model. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure S8: Forest plot of all the studies where the surgery uses cardiopulmonary bypass comparing the risk of postoperative AKI in patients with perioperative RASi therapy and not with, using a random-effect model. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin

system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom

Figure S9: Forest plot of all the studies where the surgery is isolated CABG comparing the risk of postoperative AKI in patients with perioperative RASi therapy and not with, using a random-effect model. AKI = acute kidney injury; IV = inverse-variance; RASi = renin-angiotensin system inhibitors; SE = standard error; CI = confidence interval; df = degrees of freedom; CABG = coronary artery bypass graft

402 Table 1: Main characteristics of the studies included in this meta-analysis

Author, year	Participants	Study design	Size	Drug intervention	AKI definition	Mean age	Country	Quality
Argalious, 2010 [28]	Patients underwent CABG using CPB or valve surgery	Cohort study	10648	On ACEIs before surgery	RIFLE classification criteria	Not mentioned	USA	Selection: 2, Comparability: 0, Outcome: 2
Arora, 2008 [27]	Adult patients underwent cardiac surgery	Cohort study	1358	Long-term use of ACEIs/ARBs	Modified RIFLE classification criteria	Intervention: 66 Control: 66	USA	Selection: 1, Comparability: 1, Outcome: 2
Bandeali, 2012 [16]	Patients undergoing isolated CABG	Cohort study	8889	Taking ACEIs until the surgery day	SCr >2 mg/dL or an increase of 50% from baseline	Intervention: 64 Control: 64	USA	Selection: 2, Comparability: 2, Outcome: 2
Barodka, 2011 [24]	Patients underwent cardiac surgery ≥65 years, no preexisting renal failure	Cohort study	346	Chronic use of ACEIs/ARBs preoperatively	Increase in SCr >2 mg/dL, doubling of preoperative SCr level or new requirement for dialysis	Intervention: 74 Control: 75	USA	Selection: 2, Comparability: 1, Outcome: 2
Benedetto, 2008 [4]	Patients underwent CABG on CPB, exclude patients with preoperative end-stage renal failure	Cohort study	536	Two or more weeks of ACEIs therapy until the day of operation	50% or more decrease in the GFR	Intervention: 68 Control: 61	Italy	Selection: 3, Comparability: 1, Outcome: 1
Cittanova, 2001 [29]	Patients admitted for aortic surgery	Cohort study	249	Chronic use of ACEIs, ACEIs is withdrawn the day before surgery and restarted the day after surgery	A 20% decrease in GFR between day 0 (before surgery) and day 7 (after surgery).	Not mentioned	France	Selection: 2, Comparability: 0, Outcome: 2

Drenger, 2012 [13]	Patients undergoing CABG with CPB	Cohort study	3638	On ACEIs preoperatively and postoperatively versus no ACEIs; On ACEIs postoperatively versus no ACEIs	A postoperative SCr of at least 177 μmol/L accompanied by an increase of at least 62 μmol/L from baseline	Not mentioned	Worldwide	Selection: 3, Comparability: 0, Outcome: 2
Coca, 2013 [14]	Adults undergoing CABG and/or valve surgery	Cohort study	1594	No preoperative use of ACEIs/ARBs vs. on them within 30 days until the surgery morning vs. on them but held on surgery morning	At least a change in SCr of 50% or 0.3 mg/dL from baseline (preoperative) to peak level (postoperative)	Continued: 70 Held: 71 None: 73	USA	Selection: 2, Comparability: 1, Outcome: 2
Dag, 2013 [33]	Patients undergoing cardiac surgery	Cohort study	366	On ACEIs for more than two weeks before surgery	(1)Decrease ≥50% in GFR and creatinine clearance of 80 mL/dk/1.73 m^2 (2)Blood urea nitrogen >50 mg/dL &SCr >1.4mg/dL(3)Postoperative renal failure requiring dialysis	Intervention: 59 Control: 60	Turkey	Selection: 2, Comparability: 1, Outcome: 2
Karkouti, 2009 [34]	Patients undergoing cardiac surgery with CPB	Cohort study	3460	Use of ACEIs/ARBs therapy before surgery	≥25% decrease in GFR within one week after surgery or dialysis during the postoperative hospital stay	Not mentioned	Canada	Selection: 2, Comparability: 0, Outcome: 2

Kincaid, 2005 [30]	Patients undergwent CABG and/or valve surgery	Cohort study	1209	On ACEIs before surgery and continued to the day of surgery	More than 25% increase in SCr, SCr > 2.0 mg/dL within 72 h after surgery	Intervention: 62 Control: 69	USA	Selection: 2, Comparability: 0, Outcome: 2
Metz, 2009 [31]	Patients underwent cardiac surgery on CPB, exclude ESRD patients	Cohort study	2556	preoperative use of ACEIs	More than 50% postoperative increase in SCr from baseline	Not mentioned	USA	Selection: 2, Comparability: 0, Outcome: 2
Miceli, 2009 [32]	Patients underwent isolated CABG, exclude patients with preoperative cardiogenic shock	Cohort study	6104	Preoperative use of ACEIs within 24h before surgery	An SCr 200 μmol/l plus an increase of at least 1.5 times preoperative baseline concentrations	Intervention: 65 Control: 65	UK	Selection: 4, Comparability: 2, Outcome: 3
Ouzounian, 2012 [35]	Patients undergoing isolated CABG	Cohort study	5946	Preoperative use of ACEIs/ARBs	Creatinine exceeding 176 μmol/L and showing more than a 50% increase from its preoperative level	Intervention: 65 Control: 65	Canada	Selection: 2, Comparability: 0, Outcome: 2
Pretorius, 2012 [12]	Patients underwent elective CABG and/or valve surgery	RCT	458	7 to 4 days before surgery, patients were randomized to treatment with placebo, ramipril	Scr more than 2.5mg/dL	Intervention: 59 Control: 60	USA	Low-risk
Provenchere, 2003 [36]	Patients underwent CABG or valve surgery with CPB	Cohort study	649	Preoperative use of ACEIs	More than 30% increase in SCr within seven days after surgery	Not mentioned	France	Selection: 2, Comparability: 0, Outcome: 2
Radaelli, 2011 [5]	Patients undergoing isolated CABG	Cohort study	3139	On ACEIs/ARBs for > 2 weeks and within 24 h before surgery	Increase in SCr of >0.5 mg/dL or more than 50% from baseline	Intervention: 61 Control: 61	Brazil	Selection: 2, Comparability: 0, Outcome: 2

Rader, 2010 [37]	Patients undergoing CABG and/or valve surgery	Cohort study	6744	ACEIs/ARBs use within 30 days with the last dose given within in 24 h before surgery	SCr >2 mg/dL	Intervention: 66 Control: 66	USA	Selection: 2, Comparability: 2, Outcome: 2
Rady, 1998 [15]	All admissions to an ICU after cardiac surgery.	Cohort study	11330	More than two weeks of treatment with ACEIs on a standard dosage schedule before the date of surgery	Postoperative SCr larger than 3.8 mg/dL, doubling of SCr if the preoperative value was >1.9 mg/ dL or requirement for renal replacement therapy	Intervention: 64 Control: 63	USA	Selection: 2, Comparability: 0, Outcome: 2
Seese, 2019 [25]	Patients undergoing isolated CABG	Cohort study	5270	Preoperative exposu re to ACEIs within 48-hours of CABG	RIFLE classification criteria	Intervention: 66 Control: 66	USA	Selection: 3, Comparability: 1, Outcome: 2
Shi, 2013 [26]	Patients undergoing cardiac surgery	Cohort study	1239	On ACEIs/ARBs for ≥2 weeks before surgery	Increase in SCr of > 0.3 mg/dL or >50% from baseline within 48 h after surgery	Intervention: 63 Control: 62	China	Selection: 3, Comparability: 0, Outcome: 2
Van, 2018 [11]	Patients under nonemergent cardiac surgery, age >18, treated with ACEIs/ARBs for >7 days	RCT	121	ACEIs/ARBs continuation or discontinuation 2 days before surgery	A doubling of SCr or a >50% decline in GFR	Intervention: 67 Control: 64	Cana da	Low-risk
Yoo, 2010 [17]	Patients undergoing isolated off-pump CABG	Cohort study	472	On ACEIs/ARBs for at least 2 weeks and continue to the surgery day	Increase in SCr of 0.3 mg/dL or 50% from baseline	Not mentioned	Japan	Selection: 2, Comparability: 2, Outcome: 2

403 ACEIs = angiotensin-converting enzyme inhibitors; ARBs = ngiotensin II receptor blockers; CABG = coronary artery

404 bypass graft; CPB = cardiopulmonary bypass; GFR = glomerular filtration rate; RCT = randomized controlled trials;

RIFLE = risk, injury, failure, loss, ESRD; SCr = Serum creatinine