Renin-angiotensin system blockers in cardiac surgery

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ABSTRACT
Major complications associated with cardiac surgery are still common and carry great prognostic significance. β-Blockers, statins, antiplatelets, and renin-angiotensin system (RAS) blockers are current medical interventions to prevent cardiovascular complications in cardiac surgery. Renin-angiotensin system blockers include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and antialdosterones. Several lines of evidence support the cardioprotective effects of RAS blockers: they reduce ischemic events and improve outcome in heart failure independently of their effect on heart function and blood pressure. Moreover, early RAS blocker administration has remarkable survival and heart function benefits in patients with acute myocardial infarction. Nevertheless, perioperative studies on the effects of RAS blockers remain few and inconclusive. Results from clinical trials and observational studies are conflicting, and they raise more questions than answers. Further studies are needed to examine whether RAS blockers reduce mortality and major complications in patients undergoing cardiac surgery. In this review, we discuss the use of RAS blockers in the setting of cardiac surgery, underlying the potential benefits in reducing postoperative complications.

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1. Introduction
There has been a decline in overall operative mortality from cardiac surgery due to improvements in both surgical and anesthetic techniques over recent years [1]. Nevertheless, major complications associated with open-heart procedures are still common and include prolonged stay in the intensive care unit (9.2%), stroke (1.63%), renal failure (8%-39%), atrial fibrillation (AF) (24.6%), reoperation (6.3%), and sternal infection (3%) [2-4]. Clinical strategies to prevent these complications are few and unsatisfactory. Current medical treatments to reduce the mortality rate include renin-angiotensin system (RAS) blockers. Several classes of drugs inhibit the RAS and slow the progression of cardiovascular disease. Angiotensin-converting enzyme (ACE) inhibitors decrease the formation of angiotensin II and inhibit the breakdown of bradykinin. The angiotensin receptor blockers (ARBs) bind competitively to and dissociate slowly from angiotensin II type 1 receptors. Antialdosterones competitively inhibit aldosterone-sensitive sodium channels in the cortical collecting tubule of the kidney and cause sodium and free water excretion and potassium retention. However, the critical hemodynamic state after open-heart surgery leads to withdrawal of these drugs because of a high risk of hypotension. Despite this potentially life-threatening side effect, RAS blockers have protective effects in patients with reduced ejection fraction as well as on kidney function. In this review, we will focus on the potential benefits of ACE inhibitors and ARBs in the perioperative period.

1.1. Renin-angiotensin system blockers and vasoplegic syndrome
Patients undergoing cardiac surgery develop a systemic inflammatory reaction as consequence of the institution of the cardiopulmonary bypass (CPB) that could increase postoperative complications [5]. Stress response results in RAS activation, massive release of cytokines, increased production in oxygen free radicals, activation of leukocytes, platelets, and complement system [6-8]. Activation of the RAS occurs after the release of renin by the kidney, an enzyme that catalytically cleavages angiotensinogen to form angiotensin I. Angiotensin I is then converted to angiotensin II by ACE, which is also involved in the inactivation of bradykinin, a potent vasodilator. Angiotensin II increases blood pressure targeting all the organs and systems in vivo including the heart, kidneys, vessels, brain, inflammation, and cell growth [9]. Acute hemodynamic stress during cardiac surgery, such as the induction of anesthesia, leads to RAS activation, which is a primary mechanism for the maintenance of venous return and blood pressure [10]. The reduction in sympathetic tone induced by anesthesia increases vascular capacitance that causes a consequent reduction in the effective intravascular volume. Angiotensin II is a physiological mechanism to counterbalance this phenomenon. Angiotensin II has multiple actions on different vascular beds and organ systems that ultimately elevate extracellular fluid volume and arterial blood pressure (Fig. 1). Angiotensin II causes vasoconstriction of renal and systemic arterioles, which increases total peripheral resistance and blood pressure. Activation of angiotensin II receptors in the brain triggers the sympathetic output to the heart as well as to vasculature, resulting in augmentation of cardiac output and increment of total peripheral resistance. Angiotensin II also promotes the release of arginine vasopressin from the posterior pituitary gland, which results in fluid retention in the renal collecting duct in the kidneys.
Finally, plasma angiotensin II stimulates aldosterone release from the adrenal cortex that increases sodium chloride and fluid reabsorption in the distal nephron [11,12]. Therapy with RAS blockers increases the risk of anesthesia-induced hypotension because of the decrease in vascular resistance [13]. This vasodilatory shock is known as vasoplastic syndrome. In a prospective study of 145 patients undergoing CPB, an ejection fraction less than 35% (odd ratio [OR], 11.9; 95% confidence interval [CI], 2.7-53.1; \( P = .003 \)) and the use of ACE inhibitors (OR, 9.1; 95% CI, 2.1-38.8; \( P = .001 \)) were the 2 independent predictors of vasodilatory shock, a condition that results in an increased inpatient mortality and length of stay (OR, 1.37; 95% CI, 1.04-1.80; \( P = .026 \)) [14]. Severe hypotensive episodes requiring vasoconstrictor treatment occur after induction of general anesthesia in patients chronically treated with ARBs and receiving these drugs the morning before operation in comparison with those in whom ARBs were discontinued the day before operation [15].

1.2. Angiotensin-converting enzyme inhibitors in cardiac surgery

Angiotensin-converting enzyme inhibitors have the potentiality to benefit coronary artery bypass grafting (CABG) patients because of their vasculoprotective and antiatherogenic properties. They minimize the risk of thrombosis by reducing platelet aggregation and decreasing plasminogen activator 1 as well as tissue plasminogen activator levels [16]. Endothelial function is preserved by preventing bradykinin breakdown and enhancing nitric oxide production. These perseverator mechanisms limit vascular inflammation and oxidative stress, which would otherwise lead to atherosclerotic plaque formation [17]. Increased levels of ACE have been found in atherosclerotic plaques and saphenous vein grafts in CABG patients. The use of ACE inhibitors has been found to reduce restenosis after percutaneous coronary interventions and thus may have a role in decreasing vein graft occlusion after CABG surgery [18]. Experimental studies have demonstrated the benefits of ACE inhibitors during periods of myocardial ischemia. In a porcine model of coronary occlusion followed by cardioplegic arrest on CPB simulating CABG surgery, hearts treated with quinaprilat had reduced infarct size, better recovery of regional wall motion, and preservation of endothelial function [19]. In humans, higher levels of ACE after CABG are associated with higher risk of myocardial infarction [20]. In other experiments using the same porcine model of ischemia-reperfusion on CPB, animals were pretreated with quinapril (20 mg) for 7 days before surgery [21]. Quinapril-treated animals required fewer cardioversions for ventricular arrhythmias and had higher wall motion scores, more complete recovery of endothelial function, and smaller infarcts. These results strongly suggested that pretreatment with ACE inhibitors before CABG may minimize ischemic injury. Starting from these observations, Lazar [22] proposed that use of ACE inhibitors could benefit patients undergoing CABG by minimizing perioperative ischemia and reducing long-term cardiovascular events with a sensible dosing regimen that minimizes hypotension. Studies have also demonstrated positive effects of ACE inhibitors in terms of clinical outcome. The QUO-VADIS study (Effects of quinapril on clinical outcome after coronary artery bypass grafting) evaluated the impact of quinapril in decreasing ischemic including myocardial infarction, revascularization, recurrence of angina, death, ischemic stroke, and transient ischemic attack in 149 patients scheduled for CABG. Ischemic events occurred in 4% of patients in the quinapril group vs 15% in placebo patients (hazard ratio, 0.23; 95% CI, 0.06-0.87; \( P = .02 \)). The QUO-VADIS study did not evaluate the impact of ACE inhibitors on the cardiac remodeling after surgery [23]. The Angiotensin-converting Enzyme Inhibition Post revascularization (APRES) trial by Kjøller-Hansen et al [24] studied 159 patients (130 CABG and 29 PCI) with normal blood pressure and mild to moderate left ventricle dysfunction (left ventricular ejection fraction, 0.30-0.50) to receive either ramipril or placebo shortly after the procedure for a medium follow-up of 33 months. The composite end point of clinical heart failure, acute myocardial infarction, and cardiac death was significantly reduced in the ramipril group (risk reduction, 58%; 95% CI, 7%-80%; \( P = .031 \)). In the APRES study, treatment with ramipril resulted in a reduced rate of cardiac death or hospitalization for acute heart failure up to 4.3 years after randomization (risk reduction, 36%; 95% CI, 13%-99%; \( P = .049 \)) and up to 1.5 years after the end of the study (risk reduction, 26%; 95% CI, 7%-92%; \( P = .037 \)). Furthermore, ramipril reduced left ventricular dilatation, defined as an increase from baseline in left ventricular end-systolic volume index, up to 12 months (9 of 62 vs 19 of 65; \( P = .046 \)) as well as composite event acute myocardial infarction or development of heart failure or left ventricular dilatation (13 of 64 vs 27 of 68; \( P = .015 \)); these events were predictors of the risk for future cardiac death and hospitalization with heart failure [24]. In the Heart Outcomes Prevention Evaluation trial, patients with low to moderate risk for future cardiovascular events were randomized to ramipril (10 mg) or placebo for 5 years. Twenty-six percent of patients had already received a CABG. Ramipril significantly decreased the combined incidence of myocardial infarction, stroke, and cardiovascular death by 22%. The beneficial effects of ACE inhibition were evident in multiple subgroups, including men, women, and patients of all ages as well as those with and without evidence of cardiovascular disease, hypertension, or cerebrovascular disease [25]. Similarly, the Multicenter Study of Perioperative Ischemia Research Group found a benefit from continuing ACE inhibitors therapy in CABG. Treatment with ACE inhibitors before and early after surgery was associated with a significantly lower risk of cardiovascular and overall composite events; de novo addition of ACE inhibitors therapy postoperatively was related to a lowering of odds in overall composite outcomes by nearly one half; notably, withdrawal of ACE inhibitors treatment after surgery was associated with significant rise in odds of cardiac and renal ischemic events [26]. A retrospective analysis of 481 patients by Benedetto et al [27] confirmed the beneficial effect of ACE inhibitors in terms of cardiac damage with a significant reduction in the postoperative cardiac troponin I peak concentration in the patients treated with an ACE inhibitor (1.6 ng/mL [1.05-3.4] vs 2.4 ng/mL [1.13-6.10]; \( P = .0006 \)). The positive long-term effects of preoperative ACE inhibitors on cardiovascular outcomes were reported in an observation cohort study of 5946 patients undergoing isolated CABG [28]. Despite positive results of these studies, other reports have shown negative effects related to the use of ACE inhibitors in the perioperative phase of cardiac surgery. The IMAGINE study (Effect of Angiotensin-converting enzyme inhibition in low-risk patient early after coronary artery bypass) [29] evaluated whether early initiation (≤7 days) of an ACE inhibitor reduced cardiovascular events (cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, coronary
revascularization, unstable angina or heart failure requiring hospitalization, documented angina, and stroke) in low-risk patients with left ventricular ejection fraction less than or equal to 40% after CABG. A total of 2553 patients were assigned to receive quinapril or placebo for a maximum of 43 months. The primary composite end point occurred in 13.7% of patients randomized to quinapril vs 12.2% of the placebo group (hazard ratio, 1.15; 95% CI, 0.92-1.42; P = 0.212). Adverse events increased in the quinapril group particularly during the first 3 months. The increase in the primary end point with quinapril was driven by an increased risk of both recurrent and unstable angina (36 vs 21 events; P = 0.060). Patients treated with ACE inhibitors had a significantly higher incidence of hypotension compared with the placebo group (5.5% vs 12%; P < .001). Although authors do not provide the definition of hypotension, this could easily have contributed to the increased incidence of recurrent angina seen in the ACE inhibitor group. Hypotension was not increased in the Heart Outcomes Prevention Evaluation, QUO-VADIS, or APRES trial. This difference raises questions to the methodology used by the authors to institute ACE inhibitors in their study. Notably, this study only included “low-risk” patients undergoing CABG, and the doses of quinapril used in the study led to a higher incidence of hypotension and may therefore have been excessive. The negative results of the IMAGINE study were confirmed in another retrospective analysis by Miceli et al [30] in which preoperative ACE inhibitor use was associated with an increased risk of mortality, use of inotropic support, postoperative renal dysfunction, and new onset of postoperative AF. The overall rate of mortality in the study conducted by Miceli et al was low, at 1%, whereas most studies in which ACE inhibitors confirmed their benefits were conducted on moderate-risk patients [24,26].

1.3. Angiotensin receptor blockers in cardiac surgery

Angiotensin receptor blockers have very similar effects to ACE inhibitors and are used for the same indications. Their mechanism of action, however, is very different from ACE inhibitors. Angiotensin receptor blockers are receptor antagonists that block AT1 receptors on blood vessels and other tissues. These receptors stimulate vascular smooth muscle contraction and changes of cellular metabolism. Because ARBs do not inhibit ACE, they do not cause an increase in bradykinin, which contributes to the vasoconstriction produced by ACE inhibitors and also to some of the side effects of ACE inhibitors (cough and angioedema) [31]. Experimental evidence suggests a potential benefit of ARBs in cardiac surgery. Angiotensin receptor blockers can prevent left ventricular remodeling and improve operative results of left ventricular restoration [32]. Attention of transforming growth factor β signaling by ARBs may represent a mechanistically based strategy to modulate the pathologic progression of mitral valve prolapse and to improve the results of valve reconstructive surgery [33]. Angiotensin receptor blockers reduce the serum levels of cytokines in patients awaiting heart bypass surgery [34] and slow the endothelial damage of the radial artery after CABG [35]. Despite this experimental evidence, few studies tested the use of ARBs in cardiac surgery. A recently published meta-analysis of 54,528 cardiac surgery patients suggested that preoperative use of ARBs or ACE inhibitors was not associated with a significant reduction of early all-cause mortality, myocardial infarction, or stroke [36].

1.4. Renin-angiotensin system blockers, cardiac surgery, and acute kidney injury

Incidence of acute kidney injury (AKI) after cardiac surgery is between 8.9% and 39% based on risk, injury, failure, loss, end-stage renal disease (RIFLE) or Acute Kidney Injury Network (AKIN) criteria [37-40].

The primary mechanism proposed for the development of AKI is perioperative hypotension and resulting vasoconstrictor therapy leading to impaired kidney perfusion. Angiotensin II preferentially constricts efferent arterioles in glomeruli. Therefore, RAS blockers cause efferent arteriolar dilatation. In circumstances in which maintenance of glomerular filtration requires efferent arteriolar constriction, RAS blockers may cause AKI. The association between postsurgical AKI and the use of ACE inhibitors has been investigated in 3 studies with contrasting results [30,41,42]. Benedetto et al [42] evaluated the effect of preoperative ACE inhibitors on the occurrence of postoperative AKI in a propensity score-based analysis of 536 patients undergoing on-pump CABG. The incidence of AKI was 6.4% in patients who received preoperative ACE inhibitors and 12.2% in patients who did not (P = 0.02). The incidence of AKI requiring dialysis was 2.4% in the treatment group and 6.3% in controls (P = 0.03). After adjusting for propensity score and covariates, administration of preoperative ACE inhibitors was found to reduce the incidence of postoperative AKI (OR, 0.48; 95% CI, 0.23-0.77; P = .04). Despite these positive findings, Miceli et al [30] and Bandeali et al [41] observed an increased incidence of AKI in patients treated with ACE inhibitors in large cohort studies of patients having CABG. Other studies on the incidence of AKI in the postcardiac surgery setting have been conducted on patients treated with ACE inhibitors or ARBs. Yoo et al [43] evaluated the effects of RAS inhibitors on postoperative renal function in patients undergoing isolated off-pump CABG. The incidence of postoperative AKI was similar between patients treated with RAS inhibitors and those not treated (19.9% vs 20.9%; P = .815). The highest postoperative serum creatinine levels were similar between the groups (1.2 ± 0.4 mg/dL vs 1.2 ± 0.5 mg/dL; P = .078). In a multivariate logistic regression using propensity scores, preoperative treatment with RAS inhibition was not a risk factor of postoperative AKI (OR, 0.841; 95% CI, 0.503-1.407; P = .509). Diabetes, preoperative creatinine levels, and perioperative transfusion were independently associated with postoperative AKI [43]. Shi et al [44] observed similar positive results; in their analysis, preoperative RAS inhibitor therapy was associated with a reduction in the incidence of AKI (27.2% vs 34.0%; P < .001). After adjusted propensity scores and multivariable logistic regression, preoperative RAS inhibitors were found to have protective effects against AKI (OR, 0.764; 95% CI, 0.670-0.873; P < .001), sepsis (OR, 0.515; 95% CI, 0.348-0.761; P < .001), and operative mortality (OR, 0.539; 95% CI, 0.348-0.758; P = .001) [44]. Positive association between RAS inhibition and AKI was not confirmed in other observational studies. Arora et al [45] found a significant association between preoperative use of RAS blockers and the development of AKI, as defined by RIFLE criteria, using logistic, propensity score, and bivariate models. In a retrospective analysis of 346 patients who were 65 years or older and underwent elective cardiac surgery, preoperative RAS inhibitors significantly and independently reduced the incidence of postoperative AKI compared with those not taking them: 1.6% vs 7.6%, yielding an odds ratio of 0.19 (95% CI, 0.04-0.84; P = .029) [46]. Large meta-analysis suggests that RAS blockers are associated with an increased incidence of AKI [47] (Table 1).

Renin-angiotensin system blockers preoperatively might increase the risk of kidney injury by decreasing systemic vascular resistance intraoperatively and in the early postoperative period. As a result, hypotension, increased requirement for vasopressors, and decreased kidney function could occur [14]. The study by Coca et al [48] confirmed this hypothesis, as the postoperative increase of serum creatinine was not associated with a rise in urinary biomarkers of tubular damage, suggesting that AKI in those continued on RAS blockers is primarily due to hemodynamic changes that lead to glomerular hypofiltration. Stopping RAS blockers 48 to 72 hours before surgery could avoid the risk of vasoplegia and might help reduce the incidence of AKI. However, lack of randomized controlled trials makes it impossible to draw definite conclusions on the relation between RAS inhibitors and AKI. All studies show a great variability in terms of patients included in the analyses and type of surgical procedure. Moreover, studies on AKI use different criteria to define renal damage with possible overdiagnosis of acute renal failure after cardiac surgery.

1.5. Renin-angiotensin system blockers and postcardiac surgery AF

Postoperative AF is one of the most common complications after cardiac surgery. It predisposes patients to a significantly increased risk
of mortality and morbidities including stroke, hemodynamic compromise, and ventricular arrhythmia. Increased expression of ACE in the atrial tissue of patients with AF and increased angiotensin II concentrations in animal models of AF suggest that RAS may play a role in the pathogenesis of postoperative AF [49]. Renin-angiotensin system inhibition can prevent AF through 3 mechanisms:

1) Improvement of left ventricular hemodynamic and reduction of atrial stretch: Hemodynamic effects of RAS blockers include systemic-arteriolar dilatation and increased large artery compliance that decreases systolic blood pressure. Renin-angiotensin system inhibition reduces afterload and systolic wall stress, improving cardiac function, atrial overload, and wall stress.

2) Suppression of angiotensin II–induced fibrosis: Angiotensin II regulates cardiac fibroblast proliferation [50]. Angiotensin II binding to AT1 receptors stimulates fibrous tissue formation by promoting transforming growth factor β1 synthesis. Selective cardiac overexpression in transgenic mice causes atrial but not ventricular fibrosis, with predisposition to AF. Cardiac specific ACE overexpression produces atrial enlargement and AF, consistent with an angiotensin II/fibrosis/AI link [51,52].

3) Modulation of ion-channel function: Direct cellular electrophysiological effects of angiotensin II are controversial. L and T-type Ca2+–current (I_{Ca,L}, I_{Ca,T}) regulation by angiotensin II has been reported. Intracellular angiotensin II reduced I_{Ca,L} in rat ventricular cells, whereas the opposite was observed in hamsters [53]. Angiotensin II increases I_{Ca,T} through PKC-dependent pathways. I_{Ca,T} is increased by angiotensin II stimulation. As I_{Ca,T} blockade prevents AF substrate development, RAS inhibition might be beneficial by preventing angiotensin II–mediated I_{Ca,T} increases [54,55]. However, the lack of ACE inhibition benefit against 1-week atrial tachycardia remodeling, in contrast to the clear benefit from the I_{Ca,T} inhibitor mibefradil in the same model, argues against an I_{Ca,T} inhibition–mediated mechanism for ACE inhibitor benefit [56].

Modulation of K+ currents has also been reported [57]. The increase in angiotensin II concentrations after CABG [58] may cause electrophysiological and structural remodeling, which may trigger postoperative AF. Inflammation, which commonly accompanies cardiac surgery, may also cause electrophysiological and structural remodeling and may induce postoperative AF. Another important determinant of the occurrence of postoperative AF is adrenergic hyperactivity [59].

Because inflammation, sympathetic hyperactivity, and RAS activity are associated with postoperative AF, inhibition of these factors should decrease the incidence of postoperative AF. In addition to their angiotensin II blocker effects, ARBs also have anti-inflammatory and antiadrenergic activity, and therefore, they may lower the rate of postoperative AF [60,61]. Based on this evidence, various studies have investigated the effect of RAS inhibitors on the development of postoperative AF, yielding discordant results. Ozaydin et al [62] randomized patients undergoing cardiac surgery and treated with ACE inhibitor to candesartan or placebo. Those treatment groups were compared with a nonrandomized control group. Results showed a significant relative risk reduction of 72% (ACE inhibitor plus candesartan) and 66% (ACE inhibitor and placebo) of postoperative AF. Addition of candesartan to ACE inhibitor did not further reduce postoperative AF [62]. Chin et al [63] found that preoperative use of ACE inhibitors or ARBs, ACE inhibitors alone, and ARBs alone did not exert any beneficial effect on the occurrence of AF in patients undergoing isolated off-pump CABG. Interestingly, preoperative ACE inhibitor or ARBs use was instead associated with an increased incidence of AF. The authors found that RAS blockers give an increased risk of hypotension with a consequent use of inotropes, which can trigger arrhythmias [63]. The Atrial Fibrillation Suppression Trial II and III investigated preoperative ACE inhibitors and their association with postoperative AF. In the original trials, patients were randomized to amiodarone or atrial pacing in a factorial design, and patients’ ACE inhibitor use was associated with a nonsignificant OR of 0.72 (95% CI, 0.42–1.20). However, a post hoc power analysis suggested that the study fell 260 patients short to detect a significant difference for the observed treatment effect [64]. In a retrospective analysis of 8889 patients who underwent isolated CABG, preoperative use of ACE inhibitors was significantly associated with an increased incidence of AF (OR, 1.15; 95% CI, 1.05–1.27) frequently associated with hypotension and postoperative vasoplegic syndrome [41].

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Drugs</th>
<th>End point</th>
<th>AKI definition</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Benedetto et al [42]</td>
<td>Propensity score–based analysis</td>
<td>536</td>
<td>ACE-Inhibitors</td>
<td>AKI</td>
<td>≥50% increase in GFR from preoperative levels</td>
<td>ACE inhibitors reduced incidence of AKI (OR, 0.48; 95% CI, 0.23–0.77; P = .04)</td>
</tr>
<tr>
<td>Barodka et al [46]</td>
<td>Retrospective cohort study</td>
<td>346</td>
<td>ACE inhibitors and ARBs</td>
<td>Mortality, AKI</td>
<td>Creatinine ≥2 mg/dL, doubling of preoperative creatinine</td>
<td>RAS blockers reduced incidence of AKI (OR, 0.19; 95% CI, 0.04–0.84; P = .029)</td>
</tr>
<tr>
<td>Yoo et al [43]</td>
<td>Retrospective cohort study</td>
<td>472</td>
<td>ACE inhibitors and ARBs</td>
<td>Mortality, AKI</td>
<td>AKIN criteria</td>
<td>RAS blockers did not increased risk of AKI (OR, 0.335; 95% CI 0.114–1.097; P = .090)</td>
</tr>
<tr>
<td>Arora et al [45]</td>
<td>Retrospective cohort study</td>
<td>1358</td>
<td>ACE inhibitors and ARBs</td>
<td>Mortality, AKI</td>
<td>RIFLE criteria</td>
<td>ACE inhibitors and ARBs increased the risk for AKI by 27.6%</td>
</tr>
<tr>
<td>Miceli et al [30]</td>
<td>Propensity-matched cohort</td>
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<td>ACE inhibitors and ARBs</td>
<td>Mortality, AKI</td>
<td>Creatinine level ≥2 mg/dL or an increase of 1.5 times preoperative concentrations AKIN criteria</td>
<td>ACE inhibitors increased the risk of AKI (OR, 1.7; 95% CI, 1.22–2.38; P = .0002) and mortality (OR, 2.83; 95% CI, 1.03–7.8; P = .04)</td>
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<tr>
<td>Shi et al [44]</td>
<td>Retrospective cohort study</td>
<td>2322</td>
<td>ACE inhibitors and ARBs</td>
<td>Mortality, AKI</td>
<td>Creatinine level ≥2 mg/dL or an increase of 1.5 times preoperative concentrations AKIN criteria</td>
<td>RAS inhibitors reduced incidence of AKI (OR, 0.764; 95% CI, 0.670–0.873; P &lt; .001) and operative mortality (OR, 0.539; 95% CI, 0.348–0.758; P &lt; .001)</td>
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<tr>
<td>Bandeali et al [41]</td>
<td>Retrospective cohort study</td>
<td>8889</td>
<td>ACE inhibitors and ARBs</td>
<td>Mortality, AKI</td>
<td>Creatinine level ≥2 mg/dL or an increase of 1.5 times preoperative concentrations Increase in creatinine of 50% or 0.3 mg/dL from baseline. Structural AKI was defined by values of NGAL, IL-18, KIM-1 and L-FABP in the upper quintile of peak concentration.</td>
<td>ACE inhibitors increased the risk of AKI (OR, 1.18; 95% CI, 1.03–1.36; P = .016) and mortality (OR, 0.79; 95% CI, 0.63–1.02; P = .08)</td>
</tr>
<tr>
<td>Coca et al [48]</td>
<td>Prospective cohort study</td>
<td>1594</td>
<td>ACE inhibitors and ARBs</td>
<td>Functional and structural AKI</td>
<td></td>
<td>Preoperative use of RAS inhibitors was associated with beneficial but functional structural AKI</td>
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GFR indicates glomerular filtration rate; NGAL, neutrophil gelatinase–associated lipocalin; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; L-FABP, liver fatty acid binding protein.
2. Conclusions

Despite their widespread use in clinical practice, literature relating to the use of RAS blockers in cardiac surgery is contradictory. Most of the studies report conflicting results without a convincing consensus on their utility. The heterogeneous results obtained are related to the different risk profile of patients. Renin-angiotensin system blockers should be avoided in patients at high risk for vasopressive damage, worsening of renal function, and deterioration of left ventricular ejection fraction. In patients with critical perioperative state, RAS blockers should be discontinued and reintroduced as soon as possible according to the hemodynamic profile of the patient because of their important prognostic role in long-term follow-up.

References


