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REVIEW ARTICLE

Kidney Injury Following Cardiac Surgery: A Review of Our Current Understanding

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Abstract
Around one-quarter of all patients undergoing cardiac procedures, particularly those on cardiopulmonary bypass, develop cardiac surgery-associated acute kidney injury (CSA-AKI). This complication increases the risk of several serious morbidities and of mortality, representing a significant burden for both patients and the healthcare system. Patients with diminished kidney function before surgery, such as those with chronic kidney disease, are at heightened risk of developing CSA-AKI and have poorer outcomes than patients without preexisting kidney injury who develop CSA-AKI. Several mechanisms are involved in the development of CSA-AKI; injury is primarily thought to result from an amplification loop of inflammation and cell death, with complement and immune system activation, cardiopulmonary bypass, and ischemia-reperfusion injury all contributing to pathogenesis. At present there are no effective, targeted pharmacological therapies for the prevention or treatment of CSA-AKI, although several preclinical trials have shown promise, and clinical trials are under way. Progress in the understanding of the complex pathophysiology of CSA-AKI is needed to improve the development of successful strategies for its prevention, management, and treatment. In this review, we outline our current understanding of CSA-AKI development and management strategies and discuss potential future therapeutic targets under investigation.

1 Introduction

1.1 What is Cardiac Surgery-Associated Acute Kidney Injury (CSA-AKI)?

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common perioperative complication associated with substantial morbidity and mortality. Patients with CSA-AKI are more likely to experience associated postoperative morbidities such as an increased risk of infection, prolonged stay in the intensive care unit (ICU)—including a prolonged need for mechanical ventilation—and further cardiovascular events (including myocardial infarctions, strokes, and heart failure) than are surgical patients with no postoperative AKI [1–3]. In addition, CSA-AKI is associated with poorer long-term kidney function; patients undergoing cardiac surgery who develop AKI are significantly more likely to experience major adverse kidney events (MAKE) [4, 5]. The umbrella term MAKE includes progression from AKI to chronic kidney disease (CKD) and end-stage kidney disease, as well as an increased risk of mortality in the years following surgery [6]. Although it has been demonstrated that the risk of MAKE – including progression to CKD—rises significantly with the length and severity of CSA-AKI, it is important to highlight that any-stage AKI is associated with an increased risk of MAKE and that permanent injury can occur even when recovery is early [2, 5, 7–14].

Another major clinical consequence, occurring in 2–5% of patients with CSA-AKI, is the need for life-saving kidney replacement therapy (KRT) [15, 16]. The need for prolonged KRT presents its own difficulties, many of which are long term, and is associated with significantly increased healthcare costs [2, 17, 18]. It has also been shown that both operative and long-term mortality risks are increased, in some cases by up to eight times, in patients who develop CSA-AKI compared with those who do not [2, 8, 9, 17, 19–22]. The substantial morbidity and mortality burden, alongside the requirement for longer hospitalization, increased time in the ICU, and greater need for further interventions, emphasizes the lasting impacts of CSA-AKI on both patients and the healthcare system [23].

Although there is some awareness of this complication and its impact, greater understanding of how to identify and manage patients at risk of CSA-AKI, and how to optimally manage patients who do present with CSA-AKI, is needed to reduce the risk of its development and improve outcomes.

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Key Points

Cardiac surgery-associated acute kidney injury is a common postoperative complication associated with considerable morbidity and mortality, and its incidence is increased in patients with impaired preoperative kidney function.

Several mechanistic triggers during cardiac surgery can result in a cycle of uncontrolled complement activation, inflammation, and kidney injury.

Currently, there are no targeted, effective pharmacological interventions for cardiac surgery-associated acute kidney injury. This review discusses the rationale behind several upcoming and ongoing clinical trials.

In this review, we detail the incidence of known risk factors, the underlying pathophysiology of CSA-AKI, and the current and developing management strategies. We also explore the existing evidence supporting the role of inflammation and immunity, particularly the complement system, in this serious post-surgical complication.

2 CSA-AKI: How Important is This Complication?

2.1 Which Patients are At Risk?

Historically, it has been difficult to assess the true incidence of CSA-AKI because of differing global diagnostic criteria, pooled data combining a variety of cardiac procedures, and minimal data from low-income countries being included in incidence studies [20]. Recently, a large prospective observational study using pooled incidence rates from 30 countries reported that, globally, 25.9% of patients undergoing cardiac surgery subsequently developed CSA-AKI; this is in line with previous estimates from the literature [20, 24, 25]. Cardiac surgery has also been identified as the second most common cause of AKI in the ICU, after sepsis [26, 27]. Secondary analysis of this study demonstrated that around 13% of patients undergoing cardiac surgery developed prolonged AKI (> 7 days to < 3 months duration)—also known as acute kidney disease. These patients were more likely to have had an early occurrence of postoperative AKI than patients who did not develop acute kidney disease [28].

The emergence of CSA-AKI is multifactorial, and a wide range of risk factors and pathophysiological mechanisms contribute to its development and progression. Several patient characteristics known to be risk factors for CSA-AKI include female sex, non-white race, advanced age, preoperative hypertension, and preoperative anemia [2, 15, 29]. A range of procedure-related risk factors also increase the risk posed by surgery performed on cardiopulmonary bypass (CPB), including complex surgeries requiring prolonged CPB and aortic cross clamp durations, hypoperfusion during surgery caused by phases of low flow when on CPB, and direct contact of blood with the CPB circuitry [2, 15, 30].

Impaired preoperative kidney function is an important and often overlooked risk factor; lower preoperative estimated glomerular filtration rate (eGFR) has been demonstrated to be an accurate independent predictor of mortality following cardiac surgery [14, 31]. Existing CKD also increases the risk of CSA-AKI, from ~ 25% in patients without CKD to ~ 50% in those with CKD [25, 32]. This is especially significant as it has been demonstrated that patients with preoperative CKD who develop CSA-AKI have poorer long-term outcomes and a significantly higher risk of dialysis and/or mortality than patients with CSA-AKI who have no previous kidney disease [33].

2.2 How is CSA-AKI Identified in Patients?

It has been suggested that the detection and management of CSA-AKI varies widely because of sub-optimal use of available clinical guidance [14, 34, 35]. Several definitions of AKI are used in clinical practice, and the Kidney Disease: Improving Global Outcomes (KDIGO) definition—noted for its improved diagnostic sensitivity over alternative criteria—is used most routinely [34, 36]. The KDIGO guidelines define serum creatinine (sCr) and urine output thresholds for AKI, with criteria allowing staging from mild to severe (Table 1). Once kidney injury has been identified, its impact is routinely assessed by monitoring eGFR, a surrogate readout for kidney function. Currently, eGFR is calculated using the creatinine-based CKD Epidemiology Collaboration (CKD-EPI) equation for adults, or the CKD in children study (CKiD) equation in pediatric patients [37, 38].

However, reductions in eGFR occur only after significant insult and can return to baseline despite latent injury masked by the renal function reserve (RFR), namely the functional capacity of the kidneys above the resting filtration rate [39–41]. This buffer function acts to protect the kidney from injury during times of stress but can, in effect, mask early injury and delay diagnosis [39]. Therefore, the standard diagnostic tools such as sCr, eGFR, and urine output may lack sensitivity for detecting mild, but nonetheless clinically relevant, kidney damage [42, 43].

Table 1. Kidney Disease: Improving Global Outcomes serum creatinine and urine output criteria for staging of acute kidney injury [Adapted from 40, 44, 45]

AKI stage (severity)	sCr	Urine output
I (mild)	≥0.3 mg/dl increase within 48 h or 1.5–1.9 × baseline for 7 days	<0.5 ml/kg/h for 6–12 h
II (moderate)	2–2.9 × baseline	<0.5 ml/kg/h for 12 h
III (severe)	≥3 × baseline, or increase to ≥4 mg/dl, or initiation of KRT	<0.3 ml/kg/h for 24 h or anuria for 12 h

AKI acute kidney injury; *KRT* kidney replacement therapy; *sCr* serum creatinine.

2.3 How Can Diagnosis of CSA-AKI be Improved?

It has been posited that the extent of previous injury to the kidneys, and the remaining RFR, may have a substantial role in determining the extent of injury following subsequent insults; indeed, patients with higher preoperative RFR have been shown to be somewhat protected against developing severe CSA-AKI [46]. Preexisting CKD leads to a reduced RFR, impairing the ability of the kidney to compensate for subsequent kidney injuries such as CSA-AKI and possibly contributing to the development of undetected, but still impactful, AKI following limited kidney insult [32].

Currently, there are no sensitive assays in routine clinical use to detect early kidney damage before changes in markers such as sCr can be detected [47, 48]. Preliminary evidence indicates that changes in the levels of a selection of urinary biomarkers (e.g., NGAL, TIMP-2, and IGFBP7) and plasma biomarkers (e.g., interleukin-8 and tumor necrosis factor-α) may be detectable following early stress and damage, before injury to the kidney is substantial enough to meet the currently defined AKI criteria [47, 49, 50]. Several recent trials—such as PrevAKI1, PrevAKI2, and BigpAK—used the biomarkers urinary TIMP-2 and IGFBP7 to identify patients at high risk of AKI [50–52]. Following these studies, the Acute Disease Quality Initiative Consensus Conference recommended integration of biomarkers into routine clinical practice, with the aim of improving implementation of measures to prevent progressive kidney damage and subsequent AKI [43]. The assessment of CSA-AKI biomarkers specifically in pediatric patients undergoing cardiac surgery identified urinary NGAL, alongside other proteins, including pre-and post-surgical serum FGF23 levels, as markers of post-surgery AKI [53, 54]. Biomarkers with increased sensitivity for kidney injury will further broaden the definition of AKI, allowing identification of subclinical AKI where there is initial stress or damage following surgery [34]. Biomarkers are evaluated for their effectiveness in the prediction, identification, and improved management of patients with AKI. Their use in the preoperative setting needs to be standardized to integrate them into day-to-day practice [43].

Risk following cardiac surgery can be predicted with tools such as the Society of Thoracic Surgeons operative risk calculator. Other scores and tools include the Cleveland Clinic scoring system and the Leicester scoring system [55, 56]. Although these tools are useful for personalized shared decision-making, they do have limitations; for example, the presence of preoperative CKD is a known risk factor for CSA-AKI development but is not recorded in the Society of Thoracic Surgeons operative risk calculator [57, 58]. Additionally, studies to assess the impact of approaches such as real-time AKI risk stratification-biomarker-directed fluid management and the use of the renal angina index to predict severe AKI are ongoing [59, 60]. It is unclear how consistently these tools are used across different countries and regions. Continuing refinement of these tools, as well as initiatives to ensure their consistent adoption in routine clinical practice worldwide, is key [56–58].

3 Mechanism of Injury in CSA-AKI

The pathophysiology of CSA-AKI is multifactorial, which contributes to the difficulty in its identification and management; however, tissue pathologies in CSA-AKI are thought to result in large part from ischemia-reperfusion injury (IRI) [61]. During CPB, the conversion from physiological pulsatile blood flow to laminar flow triggers an intense inflammatory response and reflexive kidney vasoconstriction [62]. Kidney hypoperfusion leads to ischemia, which causes the kidney to be starved of oxygen and adenosine triphosphate, leading to the death of tubular epithelial and endothelial cells [63]. Cellular damage, apoptosis, and/or necrosis occurring during ischemia releases damage-associated molecular patterns (DAMPs), and detection of these by kidney cells and resident immune cells leads to the release of proinflammatory cytokines, alongside activation of complement proteins [64, 65]. At the termination of CPB, reperfusion occurs, which can itself cause substantial damage to the kidney tissue, due in part to infiltration of circulating leukocytes, which migrate to the injury site. Here, they become activated, releasing more proinflammatory cytokines and producing reactive oxygen species, causing further cell death, release of DAMPs, and activation of the complement system, perpetuating and amplifying a cycle of inflammation and injury [66]. Combined, this process of IRI appears to be a major driving force behind CSA-AKI [64].

Interaction between the blood and the extra-corporeal circuit during CPB can also contribute to CSA-AKI, likely due to both the nephrotoxic effect of hemolysis and an

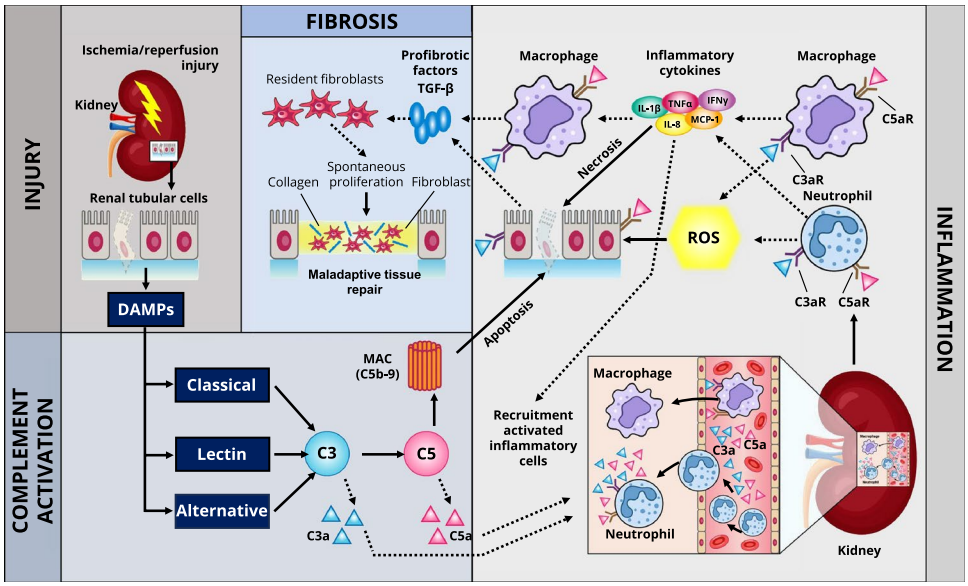

Fig. 1 Pathophysiological mechanisms underlying the development of cardiac surgery-associated acute kidney injury. *DAMPs* damage-associated molecular patterns; *IFN* interferon; *IL* interleukin; *MAC* membrane attack complex; *MCP* monocyte chemoattractant protein; *ROS* reactive oxygen species; *TGF* transforming growth factor; *TNF* tumor necrosis factor. Figure adapted from Danobeitia JS, et al. [64] under CC BY 4.0

uncontrolled activation of circulating complement [67]. Hemolysis results in the generation of free heme, which induces oxidative stress; levels of heme and markers of oxidative stress have been shown to correlate with the risk of CSA-AKI [68]. Laminar blood flow through CPB circuitry further exacerbates hemolysis and damage to the endothelium through shear stress, contributing to kidney injury [69]. The process of CPB has also been shown to contribute to IRI via hemodilution and decreased oxygen tension in the kidneys, suggesting that CPB may contribute to CSA-AKI development via numerous mechanisms [70, 71].

Fluid overload is a risk factor for the development of AKI and is associated with increased severity of AKI and higher mortality rates [72]. The pathophysiological mechanisms underlying this relationship include increased intra-abdominal pressure, venous congestion, and impaired kidney perfusion, all of which contribute to the development of AKI [73].

The relative benefit of off-pump surgeries to avoid CPB is debated: some studies have reported a reduced incidence of CSA-AKI when CPB is avoided, and others have concluded that off-pump surgery does not reduce the need for KRT or mortality [74, 75]. However, in practice, only a small number of cardiac procedures, such as coronary artery bypass graft surgery, can be performed off-pump, and appropriate patient selection for off-pump procedures is crucial, meaning this approach may not be suitable for most patients at risk of CSA-AKI [76].

A schematic detailing the key pathophysiological mechanisms underlying the development of CSA-AKI is presented in Fig. 1.

3.1 CSA-AKI and the Complement System

The complement system is an integral component of the innate immune system, providing defense from microbial invasion, clearance of injured cells, and removal of apoptotic cells [77]. The complement system has also been implicated as a pathophysiological driver of several other conditions as well as CSA-AKI [78–80]. Briefly, the complement system is composed of circulating soluble proteins, membrane-bound receptors, and a variety of regulatory proteins that contribute to signaling via three pathways: classical, lectin, and alternative. All three pathways result in activation of the terminal complement pathway, causing inflammation through release of anaphylatoxins (C3a and C5a), and cell lysis via formation of the membrane attack complex (MAC, C5b-9) (Fig. 2) [77].

Several studies have demonstrated the role of complement in IRI, particularly components of the terminal complement cascade. Anaphylatoxins, such as C3a and C5a, are proinflammatory mediators, acting as both chemo-attractants for and activators of leukocytes; they are also detectable by non-immune cells, which express their receptors [81]. Mouse models have demonstrated that deletions in terminal complement components, or their receptors, are protective against kidney damage in the context of IRI [82, 83]. The role of complement in kidney IRI has been well reviewed previously, and—although all complement pathways are involved to some extent—injury seems primarily mediated by terminal complement, namely generation of C5a, MAC formation, and cell lysis [64].

Increasing evidence indicates that the complement system is also activated throughout and after CPB. First, activation markers of both the classical and the alternative complement pathways have been shown to increase during CPB

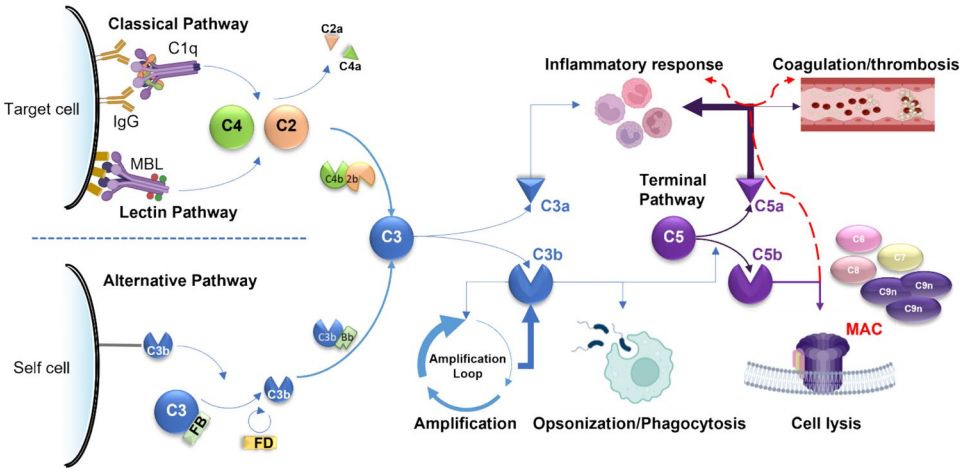

Fig. 2 The complement system. Adapted from assets used in Meri et al. [78]. *Bb* complement fragment Bb, *FB* complement factor B, complement factor D, *IgG* immunoglobulin G, *MAC* membrane attack complex, *MBL* mannose binding lectin

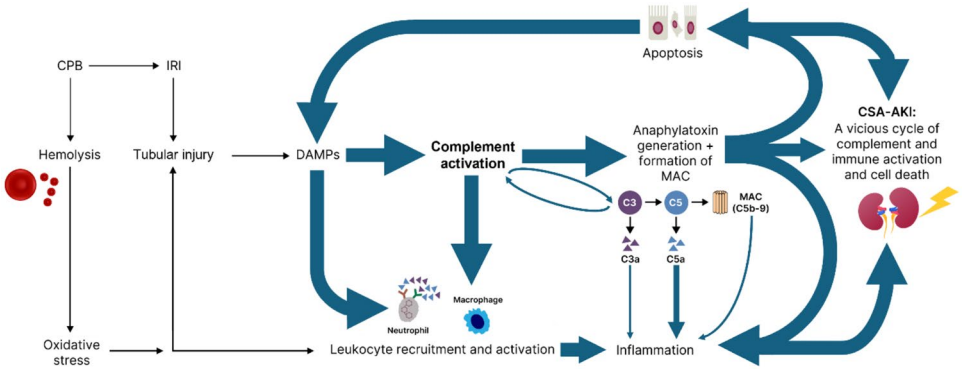

Fig. 3 Complement activation in cardiac surgery-associated acute kidney injury (CSA-AKI). *CPB* cardiopulmonary bypass, *DAMPs* damage-associated molecular patterns, *IRI* ischemia–reperfusion injury, *MAC* membrane attack complex

[84]. Activation of these pathways results in terminal complement activation, which can cause secondary damage to kidney cells through a variety of mechanisms, including kidney cell lysis [77]. It is noteworthy that, although complement activation can cause hemolysis, the presence of free heme triggered by CPB can in turn activate the complement system, highlighting a possible feedback loop of worsening activation and damage [80]. It has also been demonstrated that alternative pathway activation during tubular necrosis leads to localized deposition of C3d in the kidney tubules and increased levels of the complement fragment Ba in the urine of patients with AKI; C3d and Ba levels both correlate with increases in sCr [85, 86]. These data indicate a role for complement activation in the mechanism of ischemic injury and direct cellular damage in the kidneys, following cardiac surgery requiring CPB (Fig. 3).

4 Current Management and Future Targets

Current management of CSA-AKI focuses on risk reduction and prevention, because effective pharmacological therapies for the treatment of emergent CSA-AKI are lacking. Several proposed treatments, such as fenoldopam (arterial vasodilator), levosimendan (inotrope), and spironolactone (aldosterone antagonist), have failed to demonstrate any significant efficacy in reducing AKI development and/or any substantial effect on patient outcomes following cardiac surgery [2, 87–91]. Although severe AKI is often managed with KRT, the optimal timing of such treatments is still debated, and more targeted management options for CSA-AKI, especially those that can be administered earlier in the disease course, are still required [92]. Specifically in pediatric patients, a meta-analysis published in 2021 assessed data from a total of 2339 patients undergoing cardiac surgery from 20 randomized controlled trials (RCTs) and found that the effectiveness of most strategies currently employed to prevent CSA-AKI in children are not supported by current clinical data; there is some limited support for the use of dexmedetomidine and remote ischemic preconditioning (RIPC) [93].

Currently, the KDIGO guidelines recommend a perioperative bundle of care in patients at high risk to prevent and reduce the severity of AKI following major surgical procedures. This bundle includes optimization of perfusion, pressure and fluid management, halting nephrotoxic medication, avoiding contrast agents, and close monitoring

of postoperative kidney function [2, 52, 94]. However, only around 5% of patients receive the full bundle of care in clinical practice, despite evidence from the PrevAKI trials demonstrating that biomarker-guided use of the KDIGO bundle of interventions was more effective in reducing the severity of CSA-AKI than standard ICU care [52, 95]. Although the severity of CSA-AKI correlates with the severity of patient outcomes, any occurrence of post-surgical AKI—including mild or transient injury—confers an increased risk of MAKE, highlighting the importance of wider implementation of preventive strategies [5].

Two organizations, Enhanced Recovery After Surgery and the PeriOperative Quality Initiative, have collaborated to develop expert-led guidance for the treatment of cardiac surgery patients. The outcome of this collaboration was an established protocol for the perioperative care of cardiac patients, with a recommendation for multidisciplinary team involvement throughout to improve patient outcomes, including in reducing the incidence of CSA-AKI [96]. This multi-modal approach aims to allow specialist management of each aspect of patient health; for example, ongoing discussions between clinical specialists such as surgeons, intensivists (preferably with critical care nephrology expertise), and perfusionists when managing cardiac surgery patients may aid in the recognition of individuals at high risk of CSA-AKI, support earlier diagnosis of postoperative kidney injury, and reduce delays in the implementation of appropriate management approaches. This may ultimately lead to a reduction in the risk of CSA-AKI and the associated morbidity and mortality [97].

Outside the preventive KDIGO bundle of care, there are currently two non-pharmacological, surgical measures that may reduce the risk of mild CSA-AKI. First, the Enhanced Recovery After Surgery and PeriOperative Quality Initiative consensus report strongly recommends goal-directed perfusion as standard of care—whereby oxygen delivery is maintained above a critical level throughout surgery, although its effectiveness in moderate and severe cases of CSA-AKI remains to be demonstrated [96, 98, 99] and a meta-analysis of two RCTs found a very low level of evidence for its use [99]. Second, several studies have explored the efficacy of RIPC for reducing the emergence of CSA-AKI, as discussed. Induction of RIPC consists of repeated, short instances of ischemia–reperfusion induced in a remote location (often a distant limb) to promote protection against subsequent IRI [100]. A meta-analysis of 21 RCTs supported the use of RIPC in reducing the incidence of CSA-AKI, the requirement for ventilation, and the need for ICU admission, particularly in younger patients undergoing less complex surgeries [101]. However, this meta-analysis did not account for method of anesthesia, despite previous evidence demonstrating that the effect of RIPC was eliminated with the administration of propofol [102]. A further meta-analysis of 31 RCTs found a moderate level of evidence for the use of RIPC [99]. Despite this, the use of RIPC is likely to reduce the risk of CSA-AKI, kidney injury markers, and the need for KRT in high-risk patients not anesthetized with propofol [103].

Although several clinical trials have evaluated pharmacological interventions for the prevention of CSA-AKI, most of these have failed to meet their primary endpoints. Despite promising tolerability and demonstrable renoprotective effects observed in a phase Ib study using recombinant alpha-1-microglobulin (RMC-035) to target free heme [104], the subsequent phase II trial (NCT05126303) was terminated prematurely because of early futility. Further, a phase III trial of a p53-mediated cell death inhibitor (QPI-1002) was terminated because of low efficacy (NCT03510897). Lastly, although prophylactic delivery of recombinant human erythropoietin was initially shown to reduce the incidence of postoperative AKI in one RCT [105], later meta-analyses revealed that, although it was efficacious if given before anesthesia, the effect was limited to low-risk patients and therefore had no effect on the overall incidence of CSA-AKI [106, 107]. These trials demonstrate a continuing pattern of pharmacological therapies that either fail to target the root causes of CSA-AKI or neglect to show benefit in the most high-risk populations, including patients with preexisting CKD.

Despite many trials failing to meet their primary endpoints, several ongoing studies are evaluating pharmacological agents for the prevention of CSA-AKI. One pilot trial is using low-dose lithium, a well-tolerated glycogen synthase kinase-3β inhibitor, within the perioperative period to prevent kidney injury in patients at high risk of AKI (NCT03056248). Upregulation of glycogen synthase kinase-3β has been observed following kidney injury, and this trial aims to dampen immune-mediated injury by inhibiting upstream triggers [108]. Another recent phase III trial, investigating the renoprotective effect of ilofotase alfa (human recombinant alkaline phosphatase) in patients with sepsis-associated AKI, was terminated early because of futility in the primary endpoint [109]. However, the observation of a reduction in the occurrence of MAKE led to the initiation of a phase II trial of ilofotase alfa in patients undergoing cardiac surgery (NCT06168799). A further trial, studying the effects of LSALT peptide in patients undergoing cardiac surgery with CPB, is currently recruiting (NCT05879432); the LSALT peptide is an inhibitor of dipeptidase-1, an endothelial adhesion molecule involved in the recruitment of innate immune cells.

More recently, positive results from the PROTECTION study (NCT03709264) have demonstrated the benefits of intravenous amino acid administration in protecting adult patients from the development of CSA-AKI. The trial found that, in patients scheduled to undergo cardiac surgery, amino

acid infusions given for up to 3 days were well tolerated and associated with a significant reduction in the risk of developing any-stage CSA-AKI compared with placebo (relative risk 0.85; 95% confidence interval 0.77–0.94; $p = 0.002$) [110]. This study was limited to using only sCr to diagnose AKI, and most patients had less severe injury than is highlighted in our review. However, the promising benefits observed in this study raise the possibility that amino acid depletion during cardiac surgery may also play a pathogenic role in the development of CSA-AKI [110, 111].

It is also important to note that the clearance and distribution of drugs is altered in patients with kidney impairment, so calculations such as CKD-EPI and CKiD should be used to aid rational dose adjustments in patients with preexisting kidney damage; consideration of differences in drug metabolism and pharmacokinetics in this population may help further improve the design of upcoming clinical trials [112]. Further understanding of the pathophysiological mechanisms underpinning CSA-AKI development, and treatments targeting these, are clearly required, and the results of the ongoing trials will be of great interest to the field.

4.1 Targeting Complement-Mediated Kidney Injury

Inhibition of the terminal complement component C5 with the monoclonal antibody pexelizumab was demonstrated to be safe in patients undergoing cardiac surgery and was associated with reduced mortality rates in early clinical trials [113, 114]. Unfortunately, these promising findings were not fully validated in later cohorts, and results failed to meet statistical significance [115]. However, following this initial proof of concept, a randomized, double-blind, placebo-controlled, global phase III study of ravulizumab in adults with CKD undergoing surgery with CPB was designed and is currently recruiting (ARTEMIS, NCT05746559). Ravulizumab is a humanized monoclonal antibody against complement C5 that inhibits C5 cleavage to C5a and C5b and thus prevents formation of the MAC [116, 117]. Complement C5 inhibition has been safely and effectively used in the treatment of patients with complement-mediated illnesses—such as atypical hemolytic uremic syndrome, generalized myasthenia gravis, and paroxysmal nocturnal hemoglobinuria—for almost 20 years [118, 119]. Furthermore, recent results from phase II and phase III studies have confirmed that ravulizumab is also well tolerated; long-term follow-up data from the ravulizumab 301 study demonstrated positive efficacy and tolerability following up to 6 years of treatment in patients with paroxysmal nocturnal hemoglobinuria [117, 120–122]. One major risk of complement inhibition is increased susceptibility to infection with encapsulated bacteria, especially *Neisseria meningitidis*. Vaccination (and additional antibiotic prophylaxis as appropriate) is a requirement for all patients using complement inhibitors. The risk of such infections is elevated following complement inhibition, but recent real-world data have shown that this can be successfully mitigated at the population level and should not be a barrier to treatment [123].

The ARTEMIS study will assess the occurrence of MAKE in participants with stage 3 or 4 CKD following non-emergent cardiac surgery with and without inhibition of the terminal complement pathway. The results of ARTEMIS will indicate whether complement activation during and after surgery is a key driving force in CSA-AKI, as suggested by the available preclinical and patient-level data [86, 124]. Beyond the potential kidney-specific benefits, recent evidence also suggests that complement inhibition may have an additional therapeutic effect during cardiac surgery: a positive correlation has been observed between serum levels of both MAC components and anaphylatoxins with blood loss following surgery with CPB [84]. Therefore, in addition to providing renoprotection via complement inhibition, blood loss—another factor known to directly influence patient outcomes following surgery—may also be reduced.

5 Conclusion

CSA-AKI is an underappreciated perioperative complication that significantly increases morbidity and mortality in patients undergoing cardiac surgery, particularly in high-risk populations such as those with preexisting CKD. The pathophysiology of CSA-AKI is multifactorial, encompassing patients' preoperative clinical characteristics, surgical factors, and postoperative management. Substantial evidence indicates that activation of immune and inflammatory cascades is key to the pathophysiology of CSA-AKI, likely beginning with contact-mediated complement activation, alongside IRI. This creates a feedback loop whereby complement-mediated kidney injury causes the release of pro-inflammatory mediators, propagating further activation of complement in the kidneys and perpetuating kidney damage. The KDIGO bundle has been suggested to be efficacious in reducing the overall incidence and severity of CSA-AKI, including in patients at high risk for postoperative AKI. However, implementation of the full bundle is not recommended in all patients, and it is uncommon for patients to receive the complete bundle of interventions. It also remains unclear whether all components of the bundle are equally as effective (or necessary) to control the risk of developing CSA-AKI; adequately powered global trials to interrogate this further are ongoing [125]. Patients with preexisting CKD are at a significantly increased risk of developing CSA-AKI and suffer more severely in both the short and the long term, highlighting an unmet need for thorough assessment of kidney function before surgery. It also emphasizes the need for more effective therapeutic options for reducing the

risk of CSA-AKI development and for the treatment of CSA-AKI in patients who develop this complication. Although there are some promising preclinical studies and therapeutics in development, further research is required to improve our understanding of the pathophysiology of CSA-AKI and allow the development of more effective and targeted strategies for the prevention, management, and treatment of this complex post-surgical complication.

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Declarations

Conflict of interest Dr Kamla is the site investigator for the ARTEMIS trial at the University Hospital LMU Munich. Dr Meersch-Dini has received lecture fees from Fresenius Medical Care and Baxter and an unrestricted research grant from Baxter. Dr Palma has received honoraria from Alexion, AstraZeneca Rare Disease Brazil, and consultancy fees from Novartis and Apellis.

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Informed consent Not applicable.

Data availability Not applicable.

Compliance with ethical standards Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

Ethics statement This is a review article, with no new experimental data generated in either humans or animal models. Therefore, no ethical approval was required.

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