Review

Cardiac Surgery-Associated Acute Kidney Injury

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Abstract
Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common and serious postoperative complication of cardiac surgery requiring cardiopulmonary bypass (CPB), and it is the second most common cause of AKI in the intensive care unit. Although the complication has been associated with the use of CPB, the etiology is likely multifactorial and related to intraoperative and early postoperative management including pharmacologic therapy. To date, very little evidence from randomized trials supporting specific interventions to protect from or prevent AKI in broad cardiac surgery populations has been found. The definition of AKI employed by investigators influences not only the incidence of CSA-AKI, but also the identification of risk variables. The advent of novel biomarkers of kidney injury has the potential to facilitate the subclinical diagnosis of CSA-AKI, the assessment of its severity and prognosis, and the early institution of interventions to prevent or reduce kidney damage. Further studies are needed to determine how to optimize cardiac surgical procedures, CPB parameters, and intraoperative and early postoperative blood pressure and renal blood flow to reduce the risk

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of CSA-AKI. No pharmacologic strategy has demonstrated clear efficacy in the prevention of CSA-AKI; however, some agents, such as the natriuretic peptide nesiritide and the dopamine agonist fenoldopam, have shown promising results in renoprotection. It remains unclear whether CSA-AKI patients can benefit from the early institution of such pharmacologic agents or the early initiation of renal replacement therapy.

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Introduction

Cardiac surgery, including coronary artery bypass grafting (CABG) and surgery for valvular disease, represents one of the most common classes of surgical procedures, with over 2 million operations performed per year worldwide. Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common and serious postoperative complication of cardiac surgery that employs cardiopulmonary bypass (CPB), and it is the second most common cause of AKI in the intensive care unit (ICU) [1]. CSA-AKI is characterized by an abrupt deterioration in kidney function following cardiac surgery as evidenced by a reduction in the glomerular filtration rate. Importantly, this deterioration may not be detected in the first 24–48 h using conventional monitoring by serum creatinine (sCr) levels because of the dilutional effects of the CPB pump prime.

CSA-AKI is caused by a variety of factors, including exogenous and endogenous toxins, metabolic abnormalities, ischemia and reperfusion injury, neurohormonal activation, inflammation, and oxidative stress [2]. Postoperative kidney function deterioration has been shown to be an important predictor of morbidity and mortality [3]. In addition, the mortality rate in CSA-AKI when renal replacement therapy (RRT) is required is considerably higher for patients not requiring RRT [4]. To date, there is little evidence from randomized trials in cardiac surgery populations to support specific interventions to prevent AKI [5]. However, the unavailability of direct measures of renal blood flow in the operating room and intensive care makes analyses of interventions difficult.

This review addresses the following aspects of this challenging clinical problem, the AKI that occurs in patients undergoing cardiac surgery:

(1) incidence and mortality of CSA-AKI based on the new consensus diagnostic systems of Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) and Acute Kidney Injury Network (AKIN);

(2) use of biomarkers for the early detection of clinical and subclinical CSA-AKI;

(3) risk factors and risk prediction models of CSA-AKI;

(4) optimal cardiac surgical procedures including conventional versus minimally invasive approaches, on-pump versus off-pump versus mini-pump techniques, and optimal management of cardiac surgical support including duration of CPB, perfusion pressure, hemodilution, blood transfusion, blood sparing techniques, and hypothermia during CPB;

(5) controversial pharmacologic therapies for the prevention and treatment of CSA-AKI including ACE inhibitors, statins, sodium bicarbonate, N-acetylcysteine (NAC), natriuretic peptides, and prophylactic blood purification.

Epidemiology

The definition of AKI used by researchers influences not only the incidence of CSA-AKI reported, but also the identification of risk variables [6]. The lack of a uniform definition for AKI has complicated research in this field and made comparisons of results difficult. Studies

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Table 1. Various studies showing incidence of CSA-AKI based on RIFLE and AKIN criteria

Study	Year published	Patients n	Surgery	Incidence	Diagnosis criteria	In-hospital mortality rates of AKI vs. non-AKI
Karkouti et al. [7]	2009	3,500	CS	three thresholds of AKI: 24, 7, and 3%, respectively	AKIN: 25, 50, and 75% decrease in eGFR within 1 week	three thresholds of AKI: 10, 25, and 39 vs. 1.0%
Bagur et al. [8]	2010	213	TAVI	11.7%	RIFLE: reduction of 25% in eGFR within 48 h	28 vs.7.4%
D'Onofrio et al. [9]	2010	2,488	CS	23.5%	RIFLE: using peak postoperative SCr in the ICU	5.5 vs. 1.5%
Swaminathan et al. [10]	2010	10,275	CABG	10.8%	AKIN: a peak SCr ≥50% above baseline within 5 days postoperatively	n.k.
Englberger et al. [11]	2011	4,836	CS with CPB	diagnosed by AKIN: 26.3%; by RIFLE: 18.9%	defined by RIFLE and AKIN within 7 days postoperatively	RIFLE: 3.8 (R), 18.3 (I), 19.4 (F) vs. 0.53% AKIN: 2.6 (I), 12.3 (II), 44.6 (III) vs. 0.64%
Robert et al. [12]	2010	25,086	CS	diagnosed by AKIN: 30%; by RIFLE: 31%	AKIN and RIFLE	AKIN: 4.1 (I), 14.2 (II), 36.8 (III) vs. 1.3% RIFLE: 3.3 (R), 11.1 (I), 36.4 (F) vs. 1.4%
Brown et al. [13]	2010	4,987	CS	39%	AKIN	HR: 1.54–6.13 (non-AKI HR: 1)
Li et al. [14]	2011	964	elective CABG	19.8% (7.9% in stage 1, 3.5% in stage 2, and 8.4% in stage 3)	AKIN	in-hospital mortality rate [15, 16]: OR 4.07; p < 0.001 (overall in-hospital mortality rate 5.1%)
Parolari et al. [15]	2012	3,219	CS with CPB	8.9%	AKIN	n.k.
Englberger et al. [16]	2012	951	TV	30%	RIFLE class (R, I, or F) within the first 7 days postoperatively	6.5 (R), 17.2 (I), 54.4 (F) vs. 1.5%

CS = Cardiac surgery; TAVI = transcatheter aortic valve implantation; TV = tricuspid valve surgery; eGFR = estimated glomerular filtration rate; HR = adjusted hazard ratio from Cox proportional hazard model; n.k. = not known.

of the epidemiology of CSA-AKI in recent years have been based on the new consensus diagnostic systems of RIFLE and AKIN (table 1). Due to the difference in baseline characteristics and in surgery type, the range of incidence is between 8.9 and 39% [7–16] based on RIFLE or AKIN criteria (table 1). Isolated CABG has the lowest incidence of AKI, followed by valvular surgery and combined CABG with valvular surgery [17]. The development of CSA-AKI leads to the initiation of RRT in 1–5% of cases [18]. Investigators have studied the relative accuracy of the two definition systems in making the clinical diagnosis of CSA-AKI, showing that AKIN applied in cardiac surgery patients without correction of sCr for fluid balance may lead to overdiagnosis of AKI (poor positive predictive value), and modification of RIFLE by staging of all patients with RRT in the failure class F (failure) may improve predictive value. Balancing the limitations of both definition systems of AKI, the application of the RIFLE criteria in patients undergoing cardiac surgery may be preferable [11].

AKI is an independent predictor of mortality after cardiac surgery [7, 19]. Both the AKIN and RIFLE criteria are accurate early predictors of mortality [11, 12]. Applying AKIN and RIFLE criteria, the mortality rate (hospital discharge or 30-day mortality) is between 3.8 and 54.4% in patients who develop CSA-AKI and increases progressively with the degree of renal impairment (table 1). Recent studies reported that even mild increases in sCr levels following cardiac surgery were associated with significant effects on mortality [19, 20]. Furthermore, long-term survival was significantly different by AKI duration [13], and early recovery of renal function was associated with improved long-term survival after CSA-AKI [10].

Biomarkers and Identification of Subclinical CSA-AKI

Changes in sCr occur late in the development of CSA-AKI, typically 48 h after the initiating event [21]. Hemodilution related to the pump prime is a factor in this. The result is that the diagnosis of CSA-AKI may be delayed when in fact serious tubular injury has occurred and may be ongoing. Thus, one of the important reasons that attempts to treat CSA-AKI have been unsuccessful is that the interventions were initiated too late and acute tubular necrosis was already established.

The advent of novel biomarkers of kidney injury have opened a new era of early detection and prognosis prediction for CSA-AKI. The implications are improved monitoring, early institution of treatment measures, and improved patient counseling [22]. The Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study and the Translational Research Investigating Biomarkers Endpoints in Acute Kidney Injury (TRIBE-AKI) study have evaluated the utility of novel biomarkers to refine the diagnosis and prognosis of AKI [23]. Two of the most frequently studied new promising AKI biomarkers to date are neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18).

NGAL has been demonstrated to be a highly sensitive and specific predictor of CSA-AKI [24]. Urinary NGAL was demonstrated as an early biomarker of AKI after CPB, increasing 25-fold within 2 h and declining 6 h after surgery [21]. This promoted the use of urine NGAL as an indicator to forecast subclinical CSA-AKI. A multicenter pooled analysis of prospective studies showed that in the absence of diagnostic increases in sCr, NGAL detected patients with likely subclinical AKI who have an increased risk of adverse outcomes [25]. Accordingly, the role of plasma NGAL to classify AKI severity and predict the need for RRT after cardiac surgery has been suggested [26]. Haase et al. [27] reported that plasma NGAL on arrival in the ICU after cardiac surgery correlated with subsequent AKI duration, severity and length of ICU stay. However, another study found that plasma NGAL was not a useful predictor of AKI within the first 6 h following cardiac surgery, but urinary NGAL was superior to conventional markers and plasma NGAL in the early diagnosis of CSA-AKI [28].

The performance of urine IL-18, as demonstrated by area under the receiver operating characteristics curve, for diagnosis of AKI at 4, 12, and 24 h after CPB was 61, 75, and 73%, respectively [29]. In addition, a prospective, multicenter cohort study involving 1,219 participants confirmed that urine IL-18 and plasma NGAL peaked within 6 h after cardiac surgery, well before the rise in sCr, and these two markers showed graduated relationships with important clinical outcomes, namely longer length of hospital and ICU stay, and higher risk for dialysis or death [30].

Recently, the TRIBE-AKI consortium has published important related findings. It was found that serum cystatin C (CyC) level was less sensitive for AKI detection than sCr in high-risk adult cardiac surgery patients. Nevertheless, confirmation by CyC level appeared to identify a subset of AKI patients with a substantially higher risk of adverse outcomes [31]. Another finding was that preoperative B-type natriuretic peptide (BNP) was a strong and independent predictor of mild and severe CSA-AKI [32].

Combining the biomarkers enhances the sensitivity of early detection of CSA-AKI compared with individual biomarkers [22]. Based on these recent studies, it is clear that a combination of biomarkers and clinical parameters will emerge as powerful tools for the early prediction and risk stratification of CSA-AKI. The studies also explain how differences in clinical studies, such as different techniques and time points for measurements, cutoffs of serum/plasma or urinary levels, and the definition of AKI employed, explain, at least in part, the differences reported for the diagnosis performance and significance of these biomarkers. Future studies are needed to determine how these biomarkers of AKI can be best utilized to guide risk stratification, therapeutic intervention, and prognostication of CSA-AKI, above and beyond our current clinical measures.

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Risk Factors of CSA-AKI

Risk factors associated with the development of CSA-AKI have been well studied, validated and established. Preoperative risk factors include advanced age, female gender, reduced left ventricular function or congestive heart failure, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, emergent surgery, and elevated sCr [33].

With the application of a chronic kidney disease (CKD) classification, some studies have demonstrated that the degree of preoperative renal dysfunction parallels a proportionally increased risk of CSA-AKI and the requirement of RRT [14]. Preoperatively, one focus is the assessment of the probability of CSA-AKI superimposed on the CKD. Another focus is to avoid subclinical or silent AKI preceding the time of surgery, in which drugs used, especially contrast media, may be a cause. When cardiac catheterization and cardiac surgery have occurred during the same hospitalization, there was an increased risk for postoperative AKI. This is likely due to the necessary time needed for renal cell recovery, prior to the new insults to renal cells from the surgery itself [34]. Also, during the perioperative period, the volume status of the patients is of importance. Of major importance is that low cardiac output, before, during, or after surgery, is directly related to AKI risk, due to hyperactivity of the sympathetic nervous system, with the corresponding activation of the renin-angiotensin-aldosterone (RAA) system, which increases renal vasoconstriction [2].

Other more controversial, but potentially important, modifiable risk factors are those specifically related to the performance of CPB, such as on-pump versus off-pump technique, pulsatile versus nonpulsatile flow, normothermic versus hypothermic CPB, hemodilution during CPB, and the duration of CPB [35]. These factors are addressed in more detail later in this review.

Risk Prediction Model of CSA-AKI

Identification of patients before surgery who are at high risk for developing CSA-AKI should permit the efficient application of prophylactic and therapeutic measures. This should also facilitate a more detailed informed consent. In 1997, Chertow et al. [36] published a landmark study based on a large population database to stratify preoperative renal risk. Since that time, three predictive risk models, that is the Cleveland Clinic score, the Mehta score, and the Simplified Renal Index (SRI) score, have been developed to predict need for RRT (AKI-RRT) after cardiac surgery. However, there is no guideline to recommend the use of a specific prediction model for CSA-AKI.

In 2005, Thakar et al. [37] published the Cleveland Clinic Score with a high level of precision in the calculation of the incidence of AKI-RRT. However, Heise et al. [38] reported the score was not suitable to estimate the real incidence with sufficient precision in their patient population, although it could discriminate between patients with higher or lower risks of AKI-RRT. In 2006, Mehta et al. [39] proposed a bedside tool (Mehta score) for predicting the risk based on 8 preoperative variables in 86,009 patients. In 2007, Wijeysundera et al. [40] established a SRI model (SRI score, Toronto). External validation studies have been performed [41, 42], with findings that the Cleveland scoring system offered the best discriminative value for postoperative RRT. However, before using a model to estimate risk probabilities at a specific center, recalibration may be needed. Parolari et al. [15] proposed that predictive models can be improved by the addition of perioperative management variables.

Other models have been developed to predict AKI not requiring dialysis. However, different definitions of AKI may affect generalization of these risk models. The biomarkers of urine IL-18 and plasma NGAL strongly improved the risk prediction by 25 and 18%, respec-

tively, when added to clinical models using pre- and intraoperative variables [30]. Consensus in definitions of AKI which include biomarkers are needed to develop and validate scores to predict milder and incipient AKI.

Optimizing Cardiac Surgical Procedure and CPB Parameters

The type of cardiac surgical procedure performed, whether or not CPB is employed, and if CPB is used, the specific technical details of the perfusion technique, appear to be directly related to the occurrence of CSA-AKI. To date, there is a paucity of data focusing on the association between specific CPB parameters and risk of CSA-AKI.

Minimally Invasive Cardiac Surgery

Over the last 2 decades, minimally invasive cardiac surgery has emerged as a technical option to reduce postoperative pain and provide faster recovery, especially in high-risk patients. The innovative techniques include small incisions and use of port-access technology [43]. Reports have indicated the noninferiority of this approach to conventional treatment and document trends of lowering stroke rates, minimizing inotropic agents, reducing blood transfusion requirement, shortening ventilation periods, and minimizing kidney injury [44]. Studies in respect to renal outcomes after minimally invasive cardiac surgery have focused on patients undergoing transcatheter aortic valve implantation (TAVI) or minimally invasive mitral valve (MV) surgery.

The incidence of AKI after TAVI (TAVI-AKI) ranges from 1.1 to 28%, depending on the definition of AKI and patient risks. This risk has appeared to be lower than for standard aortic valve replacement. Importantly, the TAVI-AKI mortality was 4 times higher than in TAVI without AKI [45].

Results from the high-risk subgroup of patients in the PARTNER trial, who were still candidates for surgical valve replacement, and who were randomly assigned to undergo either transcatheter or surgical replacement of the aortic valve, indicate that the incidence of AKI and need for RRT were similar in the two groups at both 30 days (2.9 vs. 3.0%; p = 0.95) and 1 year (5.4 vs. 6.5%; p = 0.56) [46]. Causes of TAVI-AKI are related to contrast medium used, hypotension during the procedure, and cholesterol emboli in cases of severe atherosclerosis of the aorta [47].

In 2011, the Valve Academic Research Consortium (VARC), a collaboration of cardiologists and cardiac surgeons in the USA and Europe, introduced the consensus criteria of TAVI-AKI entitled 'modified' RIFLE [48]. A recent meta-analysis of the 3,519 patients who underwent TAVI from 16 studies using the VARC definition showed 7.5% of patients developed AKI stage II–III [49]. Barbash et al. [50] reported a 14.6 and 11.5% incidence of TAVI-AKI according to VARC and RIFLE criteria, respectively. Further studies of TAVI-AKI incidence using this modified classification are needed to facilitate further refinements in this innovative approach to aortic valve replacement.

Minimally invasive MV surgery has become a common technical approach for correction of MV pathology. Murzi et al. [51] showed only a 1% incidence of AKI after video-assisted mini-thoracotomy MV repair, although CPB and cross-clamping times were longer in port-access procedures [52]. This may be related to reduced inflammatory reactions due to less extensive surgical dissection, reduced perioperative bleeding and transfusion requirement and overall less morbidity [53]. Larger studies are needed to confirm the superiority of this approach in regard to reducing the risk of CSA-AKI.

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On-Pump versus Off-Pump Technique

The use of CPB has a critical role in inducing the systemic inflammatory response syndrome (SIRS) leading to CSA-AKI [33]. An important factor is the bio-incompatibility of blood in contact with the artificial surface of the CPB circuit [54]. Modifications that are available to improve biocompatibility include the phosphorylcholine-coated circuit and the Carmeda-coated circuit. Additional factors related to the occurrence of CSA-AKI are aortic cross-clamping and declamping techniques, which are associated with increased risk of systemic embolism. Other surgical factors that are related to inflammation include perfusion pressure, hemodilution, blood transfusion, hypothermia, hemolysis, and embolism [7]. Further prospective studies on larger numbers of patients are needed to determine optimal cardiac surgical techniques to reduce and prevent AKI.

Off-pump coronary artery bypass (OPCAB) has been developed as an attempt to ameliorate perioperative complications related to CPB and aortic manipulation. This technical approach offers more physiologic renal perfusion and less systemic embolization, and induces less SIRS. Studies have pointed to the potential benefits of OPCAB in regard to the reduction of AKI and stroke risks and the reduction of hospital stay and mortality. Nigwekar et al. [55] reported a significant reduction in overall AKI [odds ratio (OR) 0.57, 95% confidence interval (CI) 0.43–0.76] and AKI-RRT (OR 0.55, 95% CI 0.43–0.71) in OPCAB cases compared with on-pump technique. The large randomized controlled ROOBY trial [56] showed no significant difference between off-pump and on-pump CABG with respect to the 30-day composite end point which included AKI-RRT (0.8 vs. 0.9%; p = 0.82). In another large trial, the CORONARY investigators [57] reported a significantly lower rate of AKI at 30 days (28.0 vs. 32.1%; p = 0.01) but no difference in AKI-RRT [1.2 vs. 1.1%, hazard ratio 1.04, 95% CI 0.61–1.76] in OPCAB compared with on-pump. Chawla et al. [58] retrospectively reviewed data from 742,909 nonemergent, isolated CABG cases and suggested that patients with CKD experienced less death or incident RRT when treated with off-pump compared with on-pump CABG. Of note is that no available randomized clinical trial had sufficient power to prove the superiority of off-pump versus on-pump CABG technique in regard to the reduction of CSA-AKI, particularly in CKD patients.

Mini-CPB/Miniaturized Extracorporeal Circuit

Miniaturized CPB systems have been developed to address the limitations of OPCAB in regard to incomplete revascularization due to anatomical constraints [57]. Use of miniaturized extracorporeal circuit (mini-ECC) offers safe, complete beating-heart revascularization. The mini-ECC has a low priming volume and accordingly is designed to reduce hemodilution and inflammation compared with the standard pump-oxygenator systems. Mini-CPB may reduce the risk of CSA-AKI although few studies have focused on the renal benefits. Immer et al. [59] reported a significantly lower serum IL-6 level in the mini-ECC group which correlated with a significantly reduced incidence of AKI. Benedetto et al. [60] reported that the incidence of AKI, as classified by AKIN, in patients undergoing CABG was 40.5% in the standard CPB group compared to 28% in the mini-ECC group (p = 0.03). At this time, there is little data comparing mini-ECC and off-pump technique. Mazzei et al. [61] found no significant difference of overall postoperative complications, including AKI, stroke, shock, sepsis, and myocardial infarction, in CABG cases using mini-ECC versus OPCAB, despite longer CPB time and operative time in the mini-ECC group. Mini-ECC appears to increase graft patency compared with the off-pump technique, but its benefits in regard to renal and other outcomes have not yet been demonstrated.

Duration Time of CPB

The generation of SIRS and other adverse physiologic processes with CPB exposure explain why the incidence of CSA-AKI correlates with the duration of CPB. A recent meta-

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analysis of 9 studies reported 756 of 12,466 patients (6.06%) who underwent CPB developed AKI by AKIN definition and had longer CPB times. The mean CPB time of patients who developed AKI compared to those who did not develop AKI was significantly longer [4] (23.18 min, 95% CI 16.7–29.66; p < 0.0001). Studies indicate that longer CPB and cross-clamp times are strongly associated with an increased incidence of CSA-AKI. A safe time cutoff has not been determined [4].

Perfusion Pressure during CPB

CPB is associated with significant clinical hemodynamic changes that are related to the unique pressure and flow characteristics of CPB systems. The ultimate goal of CPB, which generally provides nonpulsatile flow, is to maintain regional perfusion at a level that supports optimal cellular and organ function. Generally, in adult cardiac surgery, CPB flow rates of 1.8–2.2 l/min/m^2 are recommended along with a mean perfusion pressure, or mean arterial pressure (MAP), of 50–70 mm Hg [62]. Limited data are available regarding the effect of nonpulsatile flow rate and perfusion pressure on regional renal blood flow and local oxygen delivery rates.

Kidneys are susceptible to ischemic damage because of their unique blood circulation. The renal medulla is perfused at a low oxygen tension, inducing limitation in its functional reserve [2]. Any decrease in renal perfusion can lead to significant cellular injury, depending on its magnitude and duration. Imbalance between renal oxygen delivery and renal oxygen consumption is generally believed to play a pivotal role in CSA-AKI. Renal oxygen delivery is determined by arterial oxygen content and by renal blood flow, which varies during CPB with the nonpulsatile pump flow rate and blood pressure. Given this physiologic situation, it follows that a sufficient perfusion flow rate can ensure adequate renal oxygen delivery, and it may be that MAP itself during CPB is not so important [63]. A study reported by Haase el al. [64] suggested that absolute hypotension alone during CPB was not associated with the development of CSA-AKI, although the role of relative hypotension remained debatable, and in patients with severe anemia, the independent effect of hypotension on AKI was more pronounced [65]. In addition, Kanji et al. [66] proposed a Δ MAP (preoperative MAP minus intraoperative MAP) ≥26 mm Hg was independently associated with development of early CSA-AKI in high-risk patients.

Pulsatile versus Nonpulsatile CPB Flow

Maintaining pulsatile perfusion during CPB is believed to attenuate organ injury by lowering peripheral vascular resistance, maintaining better microcirculation and tissue metabolism, and decreasing tissue edema [67]. However, no difference was found in total renal cortical flow or in flow distribution using pulsatile or nonpulsatile perfusion [68]. Studies comparing the effect of pulsatile and nonpulsatile CPB flow on renal outcome had inconsistent results. A recent study that included 1,959 consecutive patients showed that pulsatile perfusion did not influence perioperative renal function and mortality, but resulted in shorter hospital stay, especially in critically ill patients [69]. Another group of investigators demonstrated that patients who underwent myocardial revascularization had significantly better perioperative renal function when pulsatile CPB was employed [70]. In another study, Adademir et al. [71] found the difference in the urinary NGAL level between pulsatile and nonpulsatile flow group was associated with prolonged cross-clamp time. These results suggest that the benefits of pulsatile perfusion would be most prominent in critically ill patients, or in patients with a prolonged operation. However, there is insufficient evidence to recommend the routine use of pulsatile CPB flow to reduce the incidence of AKI.

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Hemodilution during CPB

During CPB, hemodilution decreases blood viscosity, improving regional blood flow in the setting of hypoperfusion and hypothermia, and minimizes the need for blood transfusion. Increases in regional blood flow are expected to compensate for the decreased oxygen-carrying capacity of the blood. The impairment of oxygen delivery to the hypoxic kidney medulla or the increase in systemic inflammatory mediators caused by ischemia is thought to play an important role in the pathogenesis of kidney injury [33, 35]. In a retrospective study of 1,760 CPB surgery patients, it was found that intraoperative hematocrit <24% was significantly associated with an increased risk of CSA-AKI [72]. Karkouti et al. [73] showed that moderate hemodilution (hematocrit concentration 21–25%) was associated with the lowest risk of AKI-RRT, and the risk increased as the nadir hematocrit concentration deviated from this range in either direction. In a recent prospective study, postoperative kidney injury and tissue hypoxemia (lactate) markers were higher in the low-hematocrit group (<24%) [74]. These studies suggest that a hematocrit level of <24% is associated with an increased risk of CSA-AKI. The need for randomized controlled studies remains.

Blood Transfusion

Although the transfusion of red blood cells (RBCs) is intended to improve organ function by increasing oxygen delivery, there is increasing evidence that transfused RBCs may actually cause organ injury in susceptible patients, probably because of the changes that occur during storage, especially with a duration of >14 days [75]. Stored RBCs become less deformable, undergo ATP and 2,3-diphosphoglycerate depletion, lose their ability to generate nitric oxide (NO), have increased adhesiveness to vascular endothelium, release procoagulant phospholipids, and accumulate proinflammatory molecules, as well as free iron and hemoglobin. The result is that transfusion of stored RBCs may actually impair tissue oxygen delivery, promote a proinflammatory state, increase tissue oxidative stress, and activate the coagulation cascade [7]. Studies have demonstrated that in patients undergoing cardiac surgery, especially those with preoperative lung disease, these changes can lead to organ dysfunction and particularly kidney injury [7]. A recent study of 920 on-pump cardiac surgery patients showed that a hemoglobin level of >8 g/dl and volume of RBC transfusion were independent risk factors for AKI defined by RIFFLE criteria [65]. In the light of these studies, the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists recommend using evidence-based blood conservation techniques including drugs that increase preoperative blood volume (e.g. erythropoietin) or decrease postoperative bleeding, devices that conserve blood (e.g. intraoperative cell salvage and blood sparing interventions), and interventions that protect the patient's own blood from the stress of operation (e.g. autologous pre-donation and normovolemic hemodilution) [76]. They state that with hemoglobin levels <6 g/dl, RBC transfusion is reasonable, also in most postoperative patients whose hemoglobin is <7 g/dl, but no high-level evidence supports this recommendation [77].

Cell Salvage Techniques

Intraoperative cell salvage techniques have become popular in major surgery as a means of retransfusing shed blood to decrease the need for allogeneic transfusion. In cardiac surgery, blood can be returned to the patient directly from the cardiotomy suction through the bypass circuit or after washing noncellular matter by the use of a cell-saving device [78]. The cardiotomy suction reservoir has been found to be a major collection chamber for particulate and gaseous microemboli, as well as a source of hemolysis, cellular aggregation, and platelet damage. Cardiotomy suction blood is known to be saturated with fat released from the subcutaneous tissue. Accordingly, cell salvage during CPB is an attractive alternative to cardiotomy suction. It allows for the conservation of RBCs while reducing the transfusion of fat micro-

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emboli. During blood processing, only RBCs are retained while the plasma, platelets, heparin, plasma-free hemoglobin (PfHb), and inflammatory mediators are discarded with the wash solution. The resulting RBCs are finally suspended at a hematocrit of 50–70% in normal saline and reinfused [79]. As of now, there are no data regarding the impact of such blood-sparing techniques on renal outcomes. A recent Cochrane review concluded that cell salvage techniques in major cardiac surgery had some effectiveness in decreasing blood transfusions; however, the studies were nonrandomized and unblinded [80].

Recent guidelines regarding blood conservation in cardiac surgery do not recommend the direct reinfusion of shed postoperative mediastinal blood as a means of blood conservation. There is little evidence to suggest that directly reinfusing unwashed blood through a cardiotomy reservoir confers any benefit and may increase the risk of sternal and mediastinal infections [77].

Hypothermia during CPB

Most cardiac surgical procedures utilizing CPB are performed with mild to moderate systemic hypothermia (typically a nasopharyngeal temperature of 25–32°C). Some cardiac surgeries may be performed under normothermic conditions. More challenging operations may require deep hypothermia (15–22°C) to allow periods of low blood flow or deep hypothermic circulatory arrest. Some studies have demonstrated that the use of normothermia may yield comparable outcomes in cardiac surgery, while others have shown a causative role of hypothermia in the induction of kidney injury.

A possible reason for this discrepancy is the type of temperature recorded. Monitoring nasopharyngeal, bladder or rectal temperature has a limited pathophysiological significance, since such measurements are dependent on parameters such as body habitus, percent of body fat, and ambient temperature, and may not provide a good estimation of the temperature of the blood which directly interacts with organs. Nussmeier et al. [81] found that the arterial temperature rather than core temperature provided a good approximation of jugular bulb temperature.

Another possible explanation for the contradictory results is that rewarming, and the rate of rewarming, rather than the degree of temperature achieved may also be involved in the pathogenesis of organ damage, related to ischemia-reperfusion injury. In a recent randomized trial, 223 patients undergoing routine CABG were cooled to 32°C and randomly assigned to rewarming to 34 or 37°C. Those who were rewarmed to 37°C had a higher incidence of AKI, suggesting that rewarming, rather than cooling, is the process responsible for renal injury [82]. Based on such data, it may be that rewarming speed is a critical factor regarding appropriate balance of oxygen supply and demand in cardiac surgery with hypothermia. This is also confirmed by an experimental model in which during restoration of normothermia, underperfusion of the superficial kidney cortex occurs with potential damage to these nephrons during the increased metabolic demands of rewarming. Moreover, the high perfusion of the kidney could amplify the deleterious effect of rewarming.

Hemolysis during CPB

Hemolysis is a common consequence of CPB. Many factors are involved in RBC disruption, such as mechanical forces generated by blood pump and suction system [83], deposition of C5b-9 complex on the surface of RBCs, and contact with artificial materials. There are conflicting data concerning the superiority of rollers versus centrifugal pumps with regard to hemolysis. In general, nonocclusive roller pumps cause similar or lower hemolysis than that seen with centrifugal pumps, but with a roller pump with a standard occlusion setting, hemolysis is the same or higher than that with a centrifugal pump [83].

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In the setting of CPB, studies have shown an increase in PfHb [84], noting that it is an independent predictor of CSA-AKI. The mechanisms of kidney damage through RBC destruction are multifactorial. Loss in RBC mass, impaired endothelial function, oxidative damage, and cytotoxic tubular damage are factors involved. Many of the clinical sequelae of intravascular hemolysis are explained by hemoglobin-mediated NO scavenging. In fact, when scavenger systems are saturated, PfHb binds to NO derived from the endothelium in a rapid and irreversible way, resulting in NO depletion, consequently increasing vascular resistance, thrombin formation, fibrin deposition, and platelet activation. Moreover, PfHb dissociates from its usual tetrameric globin structure into dimeric hemoglobin which is easily filter by the glomerulus and incorporated into proximal tubular cells. Intratubular casts formed from the interaction of heme proteins with Tamm-Horsfall protein can also contribute to tubular damage [85].

In addition to the complete destruction of the RBC with resultant immediate hemolysis, RBCs passing through a CPB circuit can be damaged on a sublethal level, resulting in decreased deformability and increasing aggregability. This sublethal modification can lead to a shorter life span of the RBC and alteration in its rheological properties so that the ability to enter in small vessels and the surface contact with vessel walls is reduced. This compromises oxygen delivery to cells and contributes to organ ischemia [83].

Mechanical damage of RBCs can be related to shear stress, blood-air and blood-endothelial interface, and positive and negative pressures. In this regard, all the components of a CPB system can potentially be responsible for the damage of RBCs. The following factors may be responsible for mechanical damage to RBCs during CPB: the modification of flow from laminar to turbulent when the flow overcomes its size capacity in connectors, the flow characteristics of arterial and venous cannula, the air interface in the reservoir, the occlusive setting of the pump, and the shear stress together with heat generation when flow and rotation are not properly set in the pump. However, if the CPB system is set properly, the pump function of the CPB system should not be considered an important factor in hemolysis [83].

Conversely, the cardiotomy suction component of a CPB system is the major source of hemolysis because of the amount of air that is aspirated together with the blood [79]. Beside the intensity of mechanical shear stress, RBCs can also have different susceptibilities to this stress, such as pediatric RBCs or RBCs exposed to hypothermia or hemodilution solutions which do not have plasma proteins.

Considering the clinical consequences of both hemolysis and sublethal damage of RBCs, all efforts should be made to minimize RBC damage during CPB. Possible strategies to reduce hemolysis and its clinical consequences include: application of a separate cardiotomy reservoir to eliminate damaged RBCs and PfHb [79], administration of haptoglobin or NO donors such as sodium nitroprusside compensating for the decrease of endogenous NO caused by the binding with PfHb [83], and usage of super high-flux 100,000-Da hemofilter to remove PfHb as efficiently as washing and centrifugation [86].

Embolism during CPB

Macroscopic and microscopic emboli, both gaseous and particulate, are generated during CPB and may result in significant end-organ injury. The importance of embolism during CPB is confirmed by the fact that postmortem studies have documented atheroemboli in the brain, heart, gastrointestinal tract, kidney, and lower extremity tissues of patients who had undergone CPB [87].

Supporting this finding, the presence of an atherosclerotic ascending aorta has been found to be an independent predictor of postoperative stroke and renal dysfunction. Sreeram et al. [88] found that postsurgical increase of creatinine was correlated with the number of cerebral emboli assessed by transcranial Doppler. Pulses of embolic signals were obtained

during cannulation, aortic clamping, and aortic clamp release suggesting their possible atherosclerotic aortic origin. Considering that atheromatous emboli are dislodged mainly from the aorta during its instrumentation and manipulation, the use of ultrasonic epiaortic echocardiography to identify optimal sites for cannulation and clamping should be advantageous in patients likely to have aortic atherosclerosis. In the presence of extensive aortic or iliofemoral disease, arterial perfusion through the axillary artery provides adequate antegrade aortic flow and represents a valid alternative to aortic cannulation with fewer atheroembolic complications [89]. Some studies support the use of intra-aortic filtration (EMBOL-X® System), a grid designed to capture ascending aorta emboli, before aortic declamping and aortic cross-clamping. The system is designed to protect against embolism during cardiac surgery, reducing postoperative morbidity, in particular neurological and renal complications, as well as decreasing the hospital stay and mortality. Studies with larger samples are necessary in order to identify patients who would most benefit from the use of intra-aortic filters [90]. In regard to reduction of fat microembolism by use of a cell saver, the use of this technology is attractive but has not been proven as a method to prevent or reduce neurocognitive impairment or renal dysfunction.

Renoprotective Pharmacological Agents

Several drugs have been evaluated for their renoprotective effects in patients undergoing cardiac surgery with inconsistent results. Furthermore, data regarding some agents, including furosemide and dopamine, have suggested harmful effects. In this review, we will summarize some opinions about controversial drugs or promising agents (table 2).

Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers
It is common for patients undergoing cardiac surgery to be receiving long-term treatment with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB). Whether long-term use of ACEIs or ARBs is associated with an increased incidence of CSA-AKI has not been proven, and whether or not to discontinue their preoperative use is still controversial. Some studies have shown that preoperative use of ACEIs/ARBs is associated with a higher risk for AKI postoperatively and that stopping ACEIs/ARBs before cardiac surgery may reduce the incidence of AKI [91]. However, other studies have found that preoperative ACEIs reduce or do not increase the incidence of postoperative AKI [92]. A risk/benefit analysis and appropriately sized randomized control trials are needed to produce clear clinical guidelines.

Sodium Bicarbonate
Urinary alkalinization may protect from renal injury induced by oxidant substances, iron-mediated free radical pathways, complement activation, and tubular hemoglobin cast formation and hemoglobin-induced pigment nephropathy [93]. Haase et al. [94] designed a double-blind, randomized controlled trial and found that sodium bicarbonate treatment was associated with an absolute risk reduction for AKI of 20% and with a significant attenuation in the postoperative increase of plasma urea, urinary NGAL and urinary NGAL/urinary creatinine ratio. But another prospective observational cohort study in a large population of cardiac surgical patients concluded that routine perioperative administration of sodium bicarbonate failed to improve postoperative renal function [95]. Considering sodium bicarbonate is safe, easy to administer, and inexpensive, it would be reasonable to regard it as a prophylactic measure option for patients at high risk for CSA-AKI.

Table 2. Potential CSA-AKI prophylactic pharmacological agents

Agents [reference]	Intervention	Control	Baseline renal function[1]	Renal outcomes
Sodium bicarbonate [94]	24 h of intravenous infusion of sodium bicarbonate 4 mmol/kg	24 h of intravenous infusion of sodium chloride 4 mmol/kg	91.9±27.3 µmol/l /n.k.	16/50 developed AKI vs. 26/50 of controls (OR 0.43, 95% CI 0.19–0.98; p = 0.043); the increase in sCr, Bun, urinary NGAL and urinary NGAL/urinary creatinine was less (p = 0.014, 0.047, 0.009, and 0.004, respectively)
Fenoldopam [100]	intravenous infusion of fenoldopam (0.1 mg/kg/min) from start of CPB to 12 h	placebo	1.39±1.65 mg/dl/ 80±41 ml/min	urine output did not differ between groups; AKI: 0 vs. 10% of controls
Human atrial natriuretic peptide (hANP) [107]	hANP at 0.02 mg/kg/min from start of CPB	placebo	without renal impairment: sCr <1.3 mg/dl and a Ccr ≥80 ml/min	maximum sCr level (0.97±0.02 vs. 1.14±0.03 mg/dl) and percent increase of sCr (15.7±25.1 vs. 41.5±80.1%) were significantly lower in the hANP group (p < 0.0001); sCr increase of ≥0.3 mg/dl was 15.9 vs. 36.4% in the placebo group (p < 0.0001)
Nesiritide [111]	a fixed dose of intravenous nesiritide 0.01 µg/kg/min for a minimum of 24 h, started after induction of anesthesia	placebo	1.07±0.40 mg/dl/ 82.0±30.3 ml/min	attenuated peak increase in sCr (0.15±0.29 vs. 0.34±0.48 mg/dl; p < 0.001) and a smaller fall in GFR (−10.8±19.3 vs. −17.2±21.9 ml/min/1.73 m^2; p = 0.001); a greater urine output (2,926±1,179 vs. 2,350±1,066 ml; p < 0.001) during the initial 24 h

n.k. = Not known; Ccr = creatinine clearance; Bun = blood urea nitrogen; hANP = human atrial natriuretic peptide; GFR = glomerular filtration rate. [1] sCr ± SD/creatinine clearance ± SD.

Statins

Besides their lipid-decreasing properties, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) reduce endothelin secretion, have antioxidant effects, and have anti-inflammatory properties that may confer protection against CSA-AKI. The pleiotropic effects of statins provide biologically plausible mechanisms for their potential renoprotective effects in cardiac surgical patients. Some studies have found that statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome [96]. Furthermore, early postoperative statin use has been found to be associated with a lower incidence of AKI [97]. However, other relatively large cohort investigations or double-blind randomized controlled trials have failed to validate statin treatment as a means to reduce the incidence of CSA-AKI, AKI-RRT or hospital mortality [98, 99]. Appropriate sample size trials are needed to evaluate the effect of statins on the incidence of AKI following cardiac surgery.

Fenoldopam

Fenoldopam, a derivative of benzazepine, was the first selective agonist of dopamine-1 (DA1) receptors authorized for clinical use. Fenoldopam causes relaxation of smooth muscle, vasodilatation and inhibition of tubular reabsorption of sodium in the kidney. It would be expected to protect renal function through its selective renal vasodilatory and natriuretic effects. Intravenous fenoldopam significantly increased renal blood flow and decreased vascular resistance in healthy volunteers and hypertensive patients. In the setting of cardiac surgery, fenoldopam has shown beneficial effects in terms of renal protection when administered for at least 24 h and at rates of >0.1 mg/kg/min [100]. Recently, a meta-analysis

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including a total of 440 patients from 6 randomized placebo-controlled trials showed that fenoldopam consistently and significantly reduced the risk of AKI (OR 0.41, 95% CI 0.23–0.74; p = 0.003). However, a higher rate of hypotensive episodes (27.5%) and/or use of vaso-pressors (18.8%) was also found and there was no effect on RRT, survival, and length of ICU/hospital stay [101]. Because the number of the enrolled patients was small, large, multicenter, and appropriately powered trials are needed to confirm the favorable results in regard to the reduction of AKI risk. It should be noted that when fenoldopam is used, careful dose adjustment is necessary to reduce its potential adverse effects.

Mannitol

Mannitol, an osmotic diuretic, is widely used in the priming fluid for CPB to reduce the incidence of renal dysfunction, but studies so far have been inconclusive. Patients with preoperative plasma creatinine <130 μM or with sCr between 130 and 250 μM were randomized to receive 0.5 g/kg of mannitol or an equivalent volume of Hartmann's solution in the pump prime. There were no differences between the groups in plasma creatinine or change in creatinine from baseline, urine output, or urinary retinol binding protein and microalbumin during the early postoperative period [102, 103]. In a recent study on mannitol treatment of CSA-AKI, mannitol infusion increased urine flow, accompanied by an increase in renal blood flow and the renal blood flow/cardiac output ratio as well as a decrease in renal vascular resistance. Mannitol did not affect filtration fraction or renal oxygenation, which suggested balanced increases in perfusion/filtration and oxygen demand/supply [104]. Mannitol is probably a safe routine priming fluid for cardiac surgery patients, whether or not they have established mild renal dysfunction. The therapeutic role of mannitol in regard to CSA-AKI needs to be studied further.

Atrial Natriuretic Peptide and BNP

The favorable physiologic profile of atrial natriuretic peptide (ANP)/BNP suggests that infusion of ANP or BNP may have an important role in the prevention or treatment of CSA-AKI. In that ANP and BNP uniquely block the RAA system and at the same time induce renal arterial vasodilatation, ANP or BNP may be used to promote diuresis in cardiac surgery patients with volume overload, and avoid the use of high doses of diuretics, such as furosemide. ANP and BNP are homeostatic hormones mainly secreted from the human heart. The natriuretic and diuretic actions of ANP and BNP are caused by renal hemodynamic and direct tubular actions. Biological activity of endogenous ANP decreases during CPB. ANP increases transcapillary filtration pressure within the glomerulus and the medullary vasa recta blood flow. In addition, continuous low-dose infusion of ANP inhibits the RAA system, decreases systemic vascular resistance, and compensates for the adverse effects of CPB [105]. Almost all related studies have shown a renoprotective effect of ANP in cardiac surgery patients, with increased creatinine clearance and urine volume and reduced usage of conventional diuretics, whether preoperatively with normal renal function or with impaired function or with left ventricular dysfunction [106, 107].

With BNP infusion in CPB patients, plasma cGMP levels are increased and plasma ANP levels decreased. At the same time, the peak increase in sCr and plasma CyC level is attenuated, creatinine clearance is maintained, urine output increased, and the incidence of AKI decreased [108]. A meta-analysis showed that BNP infusion significantly reduced the length of ICU/hospital stay, but did not decrease the incidence of RRT or mortality [109]. In a systematic review, BNP resulted in a 10% reduction in the incidence of AKI [110]. The safety and potential benefits of nesiritide, the recombinant human BNP, in CABG patients were documented in the prospective randomized NAPA study [111]. In another prospective randomized trial of nesiritide in high-risk cardiac surgery patients, nesiritide did not prevent

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dialysis or all-cause mortality; however, it did reduce the incidence of AKI (defined as an absolute increase in sCr of ≥0.3 mg/dl from baseline, or a percentage increase in sCr >50% from baseline within 48 h) compared with controls (2.2 vs. 22.4%; p = 0.004) [112]. Large, multicenter, prospective, randomized controlled trials should be performed to assess the therapeutic potential of agents such as nesiritide in preventing and treating AKI in the cardiovascular surgical setting.

N-Acetylcysteine

Patients are often exposed to contrast media with cardiac catheterization and cardiac surgery in series. This double insult has implications for the incidence of CSA-AKI and also prophylaxis to delay the surgery after the catheterization if clinically feasible. Many studies have shown NAC to have a protective effect on contrast-induced AKI (CI-AKI) when administered before the onset of renal insult [113]. A prospective trial found that in patients with CKD III–IV undergoing cardiac catheterization, hydration with sodium bicarbonate is not more effective than hydration with sodium chloride and oral NAC for CI-AKI (9.8 vs.8.4%) [114]. Another study which performed a randomized comparison of two preventive strategies showed that in 320 patients with baseline renal insufficiency scheduled to undergo catheterization, the incidence of CI-AKI in the sodium bicarbonate group was not different from the normal saline group, and NAC did not reduce CI-AKI in the two study arms [115]. A meta-analysis concluded that combination prophylaxis with NAC and sodium bicarbonate substantially reduced the occurrence of CI-AKI by 35% (RR 0.65, 95% CI 0.40–1.05) and should be strongly incorporated for all high-risk patients [116]. Although based on the existing evidence the overall benefit of NAC is not consistent or overwhelming, in 2012, Kidney Disease: Improving Global Outcomes (KDIGO) suggests using oral NAC, together with intravenous isotonic crystalloids, in patients at increased risk of CI-AKI (grade 2D) [117].

However, there is no solid evidence to indicate that there is a benefit from prophylactic administration of NAC to prevent AKI or reduce mortality following cardiac surgery [118]. Nigwekar and Kandula [119] carried out a meta-analysis which included 12 randomized controlled trials with 1,324 patients and found that use of NAC was not associated with a reduction in AKI (OR 0.89, 95% CI 0.68–1.15), need for RRT, or mortality after cardiovascular surgery [119]. Adabag et al. [120] performed a similar systematic review which included 10 trials with 1,163 patients and had similar results, including no reduction in the incidence of AKI in the NAC group (35 vs. 37% in the placebo group; p = 0.24).

Overall then, no single agent has been shown to prevent CSA-AKI and no pharmacologic strategy has demonstrated clear efficacy in the prevention of early CSA-AKI [121]. Some of the newer drugs, like nesiritide and fenoldopam, have shown evidence of renoprotection, but good-quality, large-population trials of individual or combinations of agents are needed to detect clinically relevant differences in outcomes. Future studies regarding the pharmacologic prevention of CSA-AKI should use important clinical endpoints including need for RRT, length of hospitalization, and mortality.

Prophylactic and Therapeutic Blood Purification

Different forms of RRT such as intermittent hemodialysis, continuous hemofiltration, or hybrid forms are now available for application in cardiac surgery patients. The underlying disease, its severity and stage, clinical and hemodynamic status, the resources available, and different costs of therapy may all influence the choice of the RRT strategy [122]. In addition, it is not known whether RRT modalities can eliminate significant amounts of clinically relevant inflammatory mediators in CSA-AKI. KDIGO, in 2012, suggests using continuous

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RRT, rather than standard intermittent RRT, for hemodynamically unstable patients (grade 2B) [117].

The optimal time to initiate RRT in CSA-AKI remains uncertain. It is difficult to define starting criteria. As claimed in the majority of previous studies, accepted indications of RRT include: fluid overload, overt uremia, hyperkalemia, and severe metabolic acidosis. Furthermore, the presence of any other organ failure accompanied by AKI may be a valid criterion for RRT. In 2012, the KDIGO guideline on renal support for AKI suggests initiating RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist (not graded) [117]. One study evaluated the effect of prophylactic hemofiltration on postoperative renal function in 124 consecutive patients with moderate preoperative renal dysfunction. The results showed that the patients with intraoperative prophylactic hemofiltration had better protection of renal function than the patients in the group without prophylactic hemofiltration [123]. A retrospective observational multicenter study enrolled data from 24 Spanish hospitals with 203 patients with AKI-RRT after cardiac surgery. The study patients were divided into two groups based on the time RRT was initiated: before (early-RRT group) or after the third day (late-RRT group) after cardiac surgery. The late-RRT group had significantly higher in-hospital mortality (80.4 vs. 53.2%; p < 0.001), longer adjusted hospital stays by 11.6 days (95% CI 1.4–21.9), and higher increases in creatinine at discharge than early-RRT patients, although the early group had worse renal function (creatinine and oliguria) in the immediate postoperative period (24–48 h) and prior to surgery [124]. These results suggest that RRT should be initiated as soon as possible when AKI with diuretic resistance occurs in patients after cardiac surgery. Due to the limited number of related studies, the impact of early initiation of RRT on CSA-AKI outcome remains uncertain.

Clear guidelines on RRT durations are still lacking. One study designed to evaluate continuous veno-venous hemofiltration (CVVH) for the treatment of cardiogenic shock in conjunction with acute renal failure after cardiac surgery found that a CVVH duration of <50 h over 72 h was associated with a higher mortality risk (>50 h; OR 0.009, 95% CI 0.04–0.93; p = 0.01). This study suggests that CVVH should be continued as long as possible during the first 3 days [125]. In 2012, KDIGO guidelines suggest discontinuing RRT when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care (not graded). Furthermore, KDIGO also suggests not using diuretics to enhance kidney function recovery or to reduce the duration or frequency of RRT (grade 2B) [117].

Ultrafiltration (UF), including three types of UF techniques, conventional UF (CUF), modified UF (MUF), and zero-balance UF (Z-BUF), is currently considered a standard method to remove excess water administered during CPB in pediatric populations. It is increasingly being employed intraoperatively and postoperatively in complex adult cardiac surgery patients with renal impairment and fluid overload. UF in this setting minimizes the adverse effects of hemodilution, such as tissue edema and the need for blood transfusion. The benefits from hemoconcentration include lower requirement for blood products, and the reduction of SIRS [126]. The effect of UF on the incidence and outcome of CSA-AKI in adult cardiac surgery patients remains to be determined.

Conclusion

AKI continues to be a common and important complication of cardiac surgery and is associated with increased mortality, complications, and length of hospital stay. Effective clinical protocols for the prevention and optimal management have yet to be defined. Clinical strategies that stress prevention rather than treatment remain the mainstay of effective

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management of patients at high risk for AKI. Strategies to prevent CSA-AKI include: careful risk prediction with adjustment in overall clinical management, early diagnosis, less extensive/invasive surgical procedures, optimal CPB techniques, and optimal support of cardiovascular function and oxygen delivery during surgery and postoperatively. Potential favorable pharmacologic interventions include use of natriuretic peptides, such as nesiritide, and use of dopamine agonists, such as fenoldopam. The prompt, judicious application of RRT may also improve outcomes [127].

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Disclosure Statement

All the authors declare that they have no competing interests.

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