# Prevention of Cardiac Surgery-Associated Acute Kidney Injury
## A Review of Current Strategies

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KEYWORDS

- Acute kidney injury • Prevention • Perioperative care • Inflammation
- Cardiac surgery • Randomized controlled trial

KEY POINTS

- Most large randomized controlled trials in cardiac surgery-associated acute kidney injury have been negative.
- Encouraging results have been shown with administration of glucocorticoids preoperatively, leukocyte filtration, and inhaled nitric oxide intraoperatively, and implementation of a postoperative Kidney Disease: Improving Global Outcomes bundle of care.
- Future trials should use more precise phenotyping of patients to more accurately identify subgroups of patients most likely to benefit from various interventions.

## INTRODUCTION

Cardiac surgery is one of the most common surgical procedures performed worldwide.[1] Technological advances and protocolized perioperative patient care have resulted in major improvements in clinical outcomes, including mortality. Despite these improvements, multiple postoperative complications, including atrial fibrillation, myocardial infarction, and stroke, remain common after cardiac surgery, and are associated with significant morbidity and mortality.[2]

Acute kidney injury (AKI) is a common and often devastating complication of cardiac surgery. The reported incidence of cardiac surgery-associated AKI (CS-AKI) depends on the characteristics of the patient population, as well as on the definition used for

AKI. Mild forms of CS-AKI occur in up to 30% of patients undergoing cardiac surgery,[3] whereas CS-AKI requiring dialysis occurs in only approximately 1% of patients, but is associated with a markedly increased risk of death.[4–6] Patients who recover from an episode of CS-AKI remain at greatly increased risk of incident and progressive chronic kidney disease.[3,7–9]

Various consensus-based definitions have been proposed for AKI, and are summarized in **Table 1**. Known risk factors for CS-AKI include advancing age, diabetes mellitus, preoperative chronic kidney disease (often defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m$^2$), and type of surgery, with open chamber procedures and reoperations corresponding with a higher risk of AKI. Among these risk factors, chronic kidney disease likely has the greatest prognostic value.[4,7,10]

Numerous studies have attempted to determine the factors and mechanisms that cause CS-AKI. Pathways that have been proposed include the systemic inflammatory response, hemolysis-induced injury, as well as ischemia–reperfusion injury caused by oxidative stress perioperatively.[3,7,11–13] It is likely that a combination of more than one of these factors, together with patient-related predisposing risk factors, is responsible for CS-AKI in any given patient.

| Table 1 | | |
|---|---|---|
| **Consensus-based definitions have been proposed for AKI** | | |
| | **Definitions of AKI Incidence and Severity** | |
| **Classification** | **Based on Changes in SCr** | **Based on Changes in UOP** |
| RIFLE | Definition: Increase in SCr ≥1.5× or decrease in GFR ≥25% within 7 d<br>Risk (R): Increase in SCr ≥1.5× or decrease in GFR ≥25%<br>Injury (I): Increase in SCr ≥2× or decrease in GFR ≥50%<br>Failure (F): Increase in SCr ≥3× or decrease in GFR ≥75%, or SCr >4 mg/dL with an acute increase >0.5 mg/dL | Definition: UOP <0.5 mL/kg per hour for ≥6 h<br>Risk (R): UOP <0.5 mL/kg per hour for ≥6 h<br>Injury (I): UOP <0.5 mL/kg per hour for ≥12 h<br>Failure (F): UOP <0.3 mL/kg per hour for ≥24 h or anuria for ≥12 h |
| AKIN | Definition: Increase in SCr ≥0.3 mg/dL or ≥1.5x within <48h<br>Stage 1: Increase in SCr ≥0.3 mg/dL or ≥1.5×<br>Stage 2: Increase in SCr ≥2×<br>Stage 3: Increase in SCr ≥3×, or SCr >4 mg/dL with an acute increase >0.5 mg/dL, or RRT | Definition: UOP <0.5 mL/kg per hour for ≥6 h<br>Stage 1: UOP <0.5 mL/kg per hour for ≥6 h<br>Stage 2: UOP <0.5 mL/kg per hour for ≥12 h<br>Stage 3: UOP <0.3 mL/kg per hour for ≥24 h or anuria for ≥12 h |
| KDIGO | Definition: Increase in SCr ≥0.3 mg/dL within 48 h or ≥50% within 7 d<br>Stage 1: Increase in SCr ≥0.3 mg/dL or ≥1.5×<br>Stage 2: Increase in SCr ≥2×<br>Stage 3: Increase in SCr ≥3×, or SCr >4 mg/dL, or RRT | Definition: UOP <0.5 mL/kg per hour for ≥6 h<br>Stage 1: UOP <0.5 mL/kg per hour for ≥6 h<br>Stage 2: UOP <0.5 mL/kg per hour for ≥12 h<br>Stage 3: UOP <0.3 mL/kg per hour for ≥24 h or anuria for ≥12 h |

RIFLE was adopted in 2004 by the Acute Dialysis Quality Initiative. AKIN was adopted in 2007 by the Acute Kidney Injury Network. KDIGO was adopted in 2012 by the KDIGO AKI Work Group.

*Abbreviations:* KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease; SCr, serum creatinine; UOP, urine output.

Although CS-AKI is an important problem on its own, it is also an excellent model for studying novel therapeutic agents and strategies for AKI prevention in humans in general. Accordingly, many randomized controlled trials (RCTs) have been performed to investigate strategies for prevention of CS-AKI. In this review, we summarize these various strategies, including their rationale and their findings.

## METHODS

We searched Medline via Pubmed and the Cochrane Database of Systematic Reviews via Ovid for RCTs investigating strategies targeting CS-AKI in patients undergoing cardiac surgery. We restricted our search to, double-blind RCTs published since January 1, 2000, that enrolled a minimum of 100 adult patients (>18 years of age). Studies focused on contrast-induced nephropathy, and those studying patients undergoing emergency cardiac surgery were excluded. We categorized the therapeutic strategies into 3 groups according to the time period of therapeutic intervention: preoperative, intraoperative, and postoperative.

The following information was extracted from each article: study design (including blinding and use of placebo), mean age, sample size, type of surgery (coronary artery bypass grafting, valve, or combined surgery), AKI definition used, intervention, and outcome.

## PREOPERATIVE INTERVENTIONS

A variety of preoperative interventions have been studied for prevention of CS-AKI, including corticosteroids, remote ischemic preconditioning (RIPC), N-acetylcysteine (NAC), and statins. Major RCTs conducted in this area that included 100 or more patients are summarized in **Table 2**.

### *Corticosteroids*

#### *Rationale*
Cardiac surgery and cardiopulmonary bypass (CPB) invariably cause an acute systemic inflammatory response syndrome (SIRS).[11,14] Release of key cytokines, including IL-6, IL-8, complement C3/C4, and tumor necrosis factor-$\alpha$ are characteristic of SIRS and may contribute importantly to postoperative AKI.[7,11,15,16] Corticosteroids are potent anti-inflammatory drugs. In the cardiac surgery setting, corticosteroids have been extensively investigated in preventing both renal and extrarenal postoperative complications.

#### *Findings*
A 2011 Cochrane database systematic review on the use of steroids in cardiac surgery included 54 relatively small RCTs (total of 3615 patients). It concluded that corticosteroids had no beneficial effect on CS-AKI.[17] After this review, 2 large RCTs were conducted: The DExamethasone in Cardiac Surgery (DECS) (N = 4494),[18] and the Steroids In caRdiac Surgery (SIRS) (N = 7507).[19] Both studies concluded that steroids had no protective effect on AKI postoperatively. The DECS trial used the Failure stage of the Risk, Injury, Failure, Loss, and End-stage renal disease criteria for diagnosing AKI and the SIRS trial used Kidney Disease: Improving Global Outcomes (KDIGO) stage 3.[18,19] A recent meta-analysis that included both of these large RCTs found that steroids had no beneficial effect on prevention of CS-AKI in more than 16,000 cardiac surgical patients. Specifically, KDIGO stage 3 AKI occurred with an incidence of 2.7% (172 of 6330 patients) in the steroid group and in 3.3% (207 of 6336 patients) in the control group (relative risk, 0.83; 95% confidence interval,

**Table 2**
**RCTs of preoperative therapeutic interventions for prevention of CS-AKI**

| Trial | Multicenter | Double Blinded | No. of Patients | Cardiac Surgery Type | Intervention | AKI Definition | Major Findings |
|---|---|---|---|---|---|---|---|
| Yared et al,[92] 2000, USA | No | Yes | 235 | CABG, valve | Dexamethasone | RRT | Dexamethasone did not decrease the incidence of CS- AKI ($P$ = .25) |
| Dieleman et al,[18] 2012, Netherlands | Yes | Yes | 4494 | CABG, valve, combined | Dexamethasone | RIFLE stage F | Dexamethasone did not decrease the incidence of CS- AKI (RR, 0.7; 95% CI, 0.44–1.14) |
| Whitlock et al,[19] 2015, Int | Yes | Yes | 7507 | CABG, valve, combined | Methyl-prednisolone | KDIGO stage 3 | Methylprednisolone did not decrease the incidence of CS-AKI (RR, 0.91; 95% CI, 0.79–1.05) |
| Rahman et al,[93] 2010, UK | No | Yes | 162 | CABG | RIPC | ≥0.5 mg/dL SCr increase | RIPC did not decrease the incidence of CS- AKI ($P$ = .56) |
| Zimmerman et al,[28] 2011, USA | No | Yes | 118 | CABG, valve, combined | RIPC | KDIGO (any stage) | RIPC decreased the incidence of CS-AKI (RR, 0.43; 95% CI, 0.24–0.76) |
| Candilio et al,[94] 2015, UK | No | Yes | 178 | CABG, valve | RIPC | RIFLE stage F | RIPC did not decrease the incidence of CS- AKI ($P$ = .06) |
| Hausenloy et al,[26] 2015, UK | Yes | Yes | 1612 | CABG | RIPC | KDIGO (any stage) | RIPC did not decrease the incidence of CS-AKI ($P$ = .98) |
| Meybohm et al,[27] 2015, Germany | Yes | Yes | 1385 | CABG, valve, combined | RIPC | ≥200% SCr increase or RRT | RIPC did not decrease the incidence of CS-AKI (RR, 0.82; 95% CI, 0.52–1.30) |
| Zarbock et al,[95] 2015, Germany | Yes | Yes | 240 | CABG, valve, combined | RIPC | KDIGO (any stage) | RIPC decreased the incidence of CS-AKI in all KDIGO stages ($P$ = .02) |
| Burns et al,[36] 2005, Canada | No | Yes | 295 | CABG | NAC | ≥0.5 mg/dL SCr increase or ≥25% SCr increase, RRT | NAC did not decrease the incidence of CS-AKI (RR, 1.03; 95% CI, 0.72–1.46) or RRT ($P$ = .26) |

| Source | Int | RCT | No. of Patients | Procedures | Intervention | AKI Definition | Result |
|---|---|---|---|---|---|---|---|
| Sisillo et al,[96] 2008, Italy | No | Yes | 254 | CABG, valve, combined | NAC | ≥25% SCr increase | NAC did not decrease the incidence of CS-AKI (RR, 1.60; 95% CI, 0.98–2.63) |
| Mannacio et al,[97] 2008, Italy | No | Yes | 200 | CABG | Rosuvastatin | Postoperative SCr of ≥2.5 mg/dL | Rosuvastatin did not decrease the incidence of CS-AKI (RR, 0.33; 95% CI, 0.03–3.19) |
| Billings et al,[39] 2016, USA | No | Yes | 615 | CABG, valve, combined | Atorvastatin | ≥0.5 mg/dL SCr increase or RRT | Atorvastatin did not decrease the incidence of CS-AKI (RR, 1.06; 95% CI, 0.78–1.46) |
| Park et al,[40] 2016, Korea | No | Yes | 200 | Valve | Atorvastatin | AKIN (any stage) | Atorvastatin did not decrease the incidence of CS-AKI according to all AKIN stages (P = .404 and P = .817, respectively) |
| Zheng et al,[41] 2016, China | Yes | Yes | 1922 | CABG, valve, combined | Rosuvastatin | KDIGO (any stage) | Rosuvastatin increased the incidence of CS-AKI (21% vs 17.5%; P = .005) |
| Haase et al,[48] 2009, Germany | No | Yes | 100 | CABG, valve, combined | Bicarbonate | ≥25% SCr increase | Bicarbonate decreased the incidence of CS-AKI (RR, 0.43; 95% CI, 0.19–0.98) |
| Haase et al,[49] 2013, Germany | Yes | Yes | 350 | CABG, valve, combined | Bicarbonate | ≥0.5 mg/dL SCr increase or ≥25% SCr increase | Bicarbonate increased the incidence of CS-AKI (RR 1.60; 95% CI 1.04–2.45) |
| McGuinness et al,[98] 2013, Australia | Yes | Yes | 427 | CABG, valve, combined | Bicarbonate | ≥0.5 mg/dL SCr increase or ≥25% SCr increase | Bicarbonate did not decrease the incidence of CS-AKI (P = .58) |

*Abbreviations:* AKIN, Acute Kidney Injury Network; CABG, coronary artery bypass grafting; CI, confidence interval; Int, international; KDIGO, Kidney Disease Improving Global Outcome; NAC, *N*-acetylcysteine; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease; RR, relative risk; SCr, serum creatinine.

0.68–1.01; $P = .07$; $I^2 = 0\%$).[20] Of note, a major limitation in the definition used for AKI in the DECS trial was the failure to consider renal replacement therapy (RRT), which could have resulted in misclassification. A post hoc analysis of the DECS trial that assessed AKI requiring RRT found that dexamethasone was indeed effective in preventing CS-AKI (relative risk, 0.44; 95% confidence interval, 0.19–0.96).[21] This study illustrates the need for careful consideration of appropriate end points in RCTs that assess AKI prevention, and particularly the need for inclusion of RRT in the definition of AKI.[22]

### Bottom line

Taken in aggregate, there is currently insufficient evidence to recommend routine prophylactic administration of steroids to patients undergoing cardiac surgery for prevention of AKI. Furthermore, a one-size-fits-all approach with respect to steroids (as well as other interventions) fails to take into account the heterogeneity of patient and surgical factors that predispose to AKI. Carefully conducted subgroup analyses may reveal key characteristics that identify patients most likely to benefit from steroids and other interventions.

### Remote Ischemic Preconditioning

### Rationale

RIPC involves brief induction of ischemia and reperfusion to distal tissues, usually by using a sphygmomanometer in the upper arm or leg. This ischemia–reperfusion could result in protection from future ischemia–reperfusion injury, because the first episode of ischemia–reperfusion leads to the release and activation of anti-inflammatory cytokines and oxidative stress scavengers. RIPC has shown promising results in animal models as well as various clinical settings.[23–25] Therefore, unsurprisingly, RIPC has been advocated as a strategy for prevention of CS-AKI.

### Findings

Multiple RCTs have been conducted to investigate the effect of RIPC on CS-AKI, and have shown inconsistent results.[23,26–28] One trial conducted in 120 patients found that RIPC decreased the incidence of CS-AKI, as diagnosed by KDIGO stage 1.[28] However, the 2 largest trials (each included >1500 patients) concluded that RIPC did not affect the incidence of more severe CS-AKI (KDIGO stage 3).[26,27] Two meta-analyses concluded that RIPC compared with a sham intervention did not lead to differences in postoperative serum creatinine levels, incidence of AKI, need for RRT, or probability of death.[29,30]

### Bottom line

RIPC, at least for the time being, cannot be recommended for prevention of CS-AKI.

### N-Acetylcysteine

### Rationale

NAC is a precursor of intracellular glutathione, a tripeptide antioxidant that scavenges reactive oxygen species. NAC has been shown to prevent or attenuate AKI in animal models.[31–33] Early studies in humans also suggested a protective effect of NAC in the setting of contrast nephropathy,[34] although a more recent study of 4993 patients found no effect on major adverse kidney events at 90 days.[35]

### Findings

Several small RCTs have evaluated the efficacy of NAC in preventing CS-AKI. The largest study randomly assigned 148 individuals to NAC and 147 individuals to

placebo, and found that NAC did not prevent postoperative renal dysfunction.[36] Recent meta-analyses have also failed to demonstrate a significant protective effect of NAC in preventing CS-AKI.[37,38]

### Bottom line
Use of NAC for the prevention of CS-AKI is not supported by current evidence.

## Statins

### Rationale
The 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, also known as statins, attenuate inflammation and oxidative stress, 2 of the possible underlying mechanisms responsible for CS-AKI.

### Findings
Three recent large RCTs found that high-dose perioperative administration of atorvastatin compared with placebo did not decrease the incidence of CS-AKI, either in patients naive to statins or in patients already taking statins.[39–41] Several meta-analyses of RCTs have also been performed to evaluate the effects of statins given in the preoperative and postoperative period on the incidence of CS-AKI, and none have shown beneficial effects of these drugs.[42–44] Noteworthy, a meta-analysis by Putzu and colleagues[45] found that preoperative statins were associated with a possible increased risk of AKI postoperatively.

### Bottom line
These results do not support the initiation of statin therapy to prevent CS-AKI.

## Sodium Bicarbonate

### Rationale
At neutral or alkaline pH, free ferric ions precipitate as insoluble ferric hydroxide, which is excreted as an inert complex in the urine. A higher urinary pH also reduces the generation of injurious hydroxyl radicals and lipid peroxidation.[46] In a murine model of acute renal failure induced by bilateral renal artery occlusion, animals that received sodium bicarbonate to increase the renal tubular pH were protected against tubular injury.[47] Thus, urinary alkalinization with sodium bicarbonate might protect against CS-AKI.

### Findings
One RCT that enrolled 100 patients found that the administration of sodium bicarbonate attenuated the severity of CS-AKI, as indicated by a smaller increase in urinary neutrophil gelatinase-associated lipocalin postoperatively.[48,49] A study by the same group a couple of years later in 350 patients showed that bicarbonate administration resulted in a greater incidence of CS-AKI.[49] Hence, whether administering intravenous sodium bicarbonate prevents CS-AKI remains uncertain, however, because published RCTs have yielded discordant results. Moreover, 3 meta-analyses, the largest of which included more than 1000 patients from 5 RCTs, did not demonstrate any benefit of sodium bicarbonate administration.[50–52]

### Bottom line
The use of perioperative administration of sodium bicarbonate for the prevention of CS-AKI is questionable. Larger studies are needed to determine its potential efficacy. It is possible that sodium bicarbonate could be particularly helpful to a subpopulation

of patients undergoing cardiac surgery who have longer CPB times, and thus more hemolysis and release of free hemoglobin (Hb) and iron.[13,53]

## INTRAOPERATIVE MEASURES

A variety of intraoperative interventions have been studied for prevention of CS-AKI, including off-pump surgery, leukocyte filtration, inotropes and volatile anesthetics. Major RCTs conducted in this area that included 100 or more patients are summarized in Table 3.

### *On-Pump Versus Off-Pump Coronary Artery Bypass Grafting*

#### *Rationale*
The use of the CPB results in a systemic inflammatory response influencing the function of multiple organs throughout the body, including the kidneys, lungs, and the heart itself. Contact of blood with foreign surfaces such as the CPB circuit, the use of cardiotomy suction, blood–air interface, and surgical trauma and stress are regarded as the main pathophysiologic determinants of this condition.[14] Consequently, the effect of on-pump versus off-pump CPB on postoperative outcomes, including AKI, has been an area of active investigation.

#### *Findings*
The 3 largest RCTs to date (the CORONARY, GOPCABE, and ROOBY studies) that investigated on-pump versus off-pump CPB enrolled nearly 10,000 patients in total.[54–56] The CORONARY study enrolled 4752 patients and found no significant difference in the incidence of postoperative AKI requiring RRT between patients undergoing on-pump versus off-pump CPB.[54] A detailed analysis showed that off-pump surgery did decrease the incidence of mild AKI at 30-days (defined as a relative increase in serum creatinine of >50% or an absolute increase of ≥0.3 mg/dL), but the beneficial effects on renal function did not persist at 1 year of follow-up.[57] Further, neither the ROOBY nor the GOPCABE study showed any renoprotective effects of off-pump compared with on-pump CABG surgery.[55,56]

#### *Bottom line*
There are conflicting findings regarding the efficacy of off-pump CABG on decreasing the risk of CS-AKI, but consistent findings regarding lack of efficacy in preventing moderate to severe CS-AKI.

### *Leukocyte Filtration*

#### *Rationale*
There is evidence from both animal and human studies that neutrophils and other leukocytes accumulate in the kidneys in the setting of AKI and play an important role in mediating tubular injury.[58] The application of leukocyte filters and cytokine filtration techniques has therefore been researched in several studies of CS-AKI prevention.

#### *Findings*
A recent meta-analysis of 6 RCTs that enrolled a total of 374 patients concluded that leukocyte filters did indeed protect against CS-AKI (odds ratio, 0.18; 95% confidence interval, 0.05–0.64).[6] However, caution is necessary in interpreting these results, because the sample sizes of the studies were relatively small, and the definitions used for CS-AKI varied from study to study.

**Table 3**
**RCTs of intraoperative therapeutic interventions for prevention of CS-AKI**

| Trial | Multicenter | Double Blinded | No. of Patients | Cardiac Surgery Type | Intervention | AKI Definition | Primary Outcome |
|---|---|---|---|---|---|---|---|
| Shroyer et al,[55] 2009, USA | Yes | No | 2203 | CABG | Off-pump surgery | RRT | Off-pump CABG did not decrease the incidence of RRT (RR, 0.90; 95% CI, 0.37–2.20) |
| Lamy et al,[54] 2012, Int | Yes | No | 4752 | CABG | Off-pump surgery | RIFLE stages R, I and F, and RRT | Off-pump CABG did not decrease the incidence of RRT (HR, 1.04; 95% CI, 0.61–1.76). Off-pump CABG did decrease the incidence of RIFLE stage R (HR, 0.87; 95% CI, 0.76–0.98) |
| Diegeler et al,[56] 2013, Germany | Yes | No | 2539 | CABG | Off-pump surgery | RRT | Off-pump CABG did not decrease the incidence of RRT (HR, 0.80; 95% CI, 0.49–1.29) |
| Lemma et al,[99] 2012, Italy | Yes | No | 693 | CABG | Off-pump surgery | RIFLE stage I | Off-pump CABG did not decrease the incidence of CS-AKI ($P = .15$) |
| Mentzer et al,[100] 2007, USA | No | Yes | 303 | CABG | BNP | Peak increase in SCr | BNP decreased the incidence of CS-AKI ($P<.001$) |
| Sezai et al,[101] 2011, Japan | No | Yes | 504 | CABG | ANP | $\geq$0.3 mg/dL SCr increase or RRT | ANP decreased the incidence of CS-AKI ($P = .001$) |
| Cogliati et al,[102] 2007, Italy | No | Yes | 193 | CABG, valve, combined | Fenoldopam | Postoperative SCr >2 mg/dL or $\geq$0.7 mg/dL SCr increase | Fenoldopam decreased the incidence of CS-AKI ($P = .004$) |
| Bove et al,[65] 2014, Italy | Yes | Yes | 667 | CABG, valve, combined | Fenoldopam | RRT | Fenoldopam did not decrease the incidence of RRT ($P = .47$) |

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**Table 3**
**(*continued*)**

| Trial | Multicenter | Double Blinded | No. of Patients | Cardiac Surgery Type | Intervention | AKI Definition | Primary Outcome |
|---|---|---|---|---|---|---|---|
| Lahtinen et al,[103] 2011, Finland | No | Yes | 200 | CABG, valve, combined | Levosimendan | ≥50% SCr increase or RRT | Levosimendan did not decrease the incidence of CS-AKI (RR, 1.02; 95% CI, 0.37–2.84) |
| Landoni et al,[68] 2017, Int | Yes | Yes | 506 | CABG, valve, combined | Levosimendan | RIFLE stages R, I, F and RRT | Levosimendan did not decrease the incidence of any RIFLE stage or RRT (*P* = .18; .98; .49, and .27, respectively) |
| Mehta et al,[69] 2017, Int | Yes | Yes | 882 | CABG, valve, combined | Levosimendan | RRT | Levosimendan did not decrease the incidence of RRT (RR, 0.54; 95% CI, 0.24–1.24) |
| Lei & Berra,[72] 2018, China | No | Yes | 244 | Multiple valve | NO | KDIGO stage 1 | NO decreased the incidence of CS-AKI (RR, 0.78; 95% CI, 0·62–0.97) |

*Abbreviations:* ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; Int, international; KDIGO, Kidney Disease Improving Global Outcome; NO, nitric oxide; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease; RR, relative risk; SCr, serum creatinine.

### Bottom line

Additional research is needed to evaluate the efficacy of leukocyte filters for the prevention of CS-AKI.

## Vasodilators and Inotropes

### Rationale

Renal vasodilators, including natriuretic peptide, fenoldopam, and levosimendan, have been found to increase renal blood flow in a rat model.[59] Natriuretic peptide consists of atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide. Atrial natriuretic peptide and brain natriuretic peptide, administered as human analogues, may have renoprotective properties, including anti-inflammatory effects and the reduction of renal ischemia–reperfusion injury via upregulation of intrarenal angiotensin II.[60] Fenoldopam, a dopamine 1 receptor partial agonist, may reverse renal hypoperfusion and have anti-inflammatory effects in humans.[61] Levosimendan is an adenosine triphosphate–sensitive potassium channel opener that could improve renal perfusion in the vasoplegic state after cardiac surgery by inducing mesangial cell relaxation. In animal models, administration of levosimendan before injury significantly improved renal tubular ischemia–reperfusion injury.[59]

### Findings

Two meta-analyses assessed pooled data from 9 small RCTs of intraoperative administration of natriuretic peptides for prevention of CS-AKI. These trials, which enrolled nearly 1000 patients, found a significantly decreased incidence of postoperative AKI in patients who received natriuretic peptides.[51,62,63] A meta-analysis of RCTs performed in patients undergoing cardiac surgery and other major surgery indicated that fenoldopam led to a lower risk of AKI, but not RRT or death.[64] However, these studies also had small sample sizes and were of variable quality. Recently, a large multicenter, double-blind, RCT failed to show any renoprotective effects or survival benefits of fenoldopam infusion in patients undergoing cardiac surgery. Fenoldopam was even related to increased rates of hypotension.[65] Meta-analyses of small sized RCTs concluded that levosimendan resulted in a significant decrease in the incidence of AKI after cardiac surgical procedures.[63,66,67] However, the 2 largest RCTs conducted to date, failed to report any beneficial effects of levosimendan in preventing severe AKI (defined as need for RRT) in patients undergoing cardiac surgery.[68,69]

### Bottom line

Natriuretic peptides seem to have some protective effects on CS-AKI, but large RCTs are still needed to confirm this effect. There is no definite evidence that fenoldopam nor levosimendan protects against postoperative AKI.

## Nitric Oxide

### Rationale

During hemolysis in cardiac surgery, Hb is released into the circulation in the form of oxyhemoglobin (Oxy-Hb). Nitric oxide (NO) is a potent vasodilator, which relaxes vascular smooth muscle, and NO depletion by plasma Oxy-Hb produces vasoconstriction, impairs tissue perfusion, and causes inflammation in animal models.[70] Consequently, plasma Oxy-Hb facilitates development of AKI by intrarenal oxidative reactions.[71] The administration of exogenous NO gas oxidizes plasma Oxy-Hb to methemoglobin and might thus prevent CS-AKI.

### Findings

In a randomized clinical trial in China of 217 adults with rheumatic valve disease undergoing elective, multiple valve replacement surgery, administration of 80 parts per million of NO during and after prolonged CPB reduced the incidence of CS-AKI and improved renal function at a follow-up of 1 year after surgery.[72]

### Bottom line

NO intraoperatively seems to decrease the incidence of AKI in a Chinese population undergoing cardiac surgery. More trials are necessary to establish its use in Caucasians and those with calcific vessel or valve disease.

## POSTOPERATIVE MEASURES

A variety of postoperative interventions have been studied for prevention of CS-AKI, including a KDIGO-based bundle of care, several resuscitation strategies, restrictive packed red blood cell (pRBC) transfusions, and strict glycemic control. Major RCTs conducted in this area that included 100 or more patients are summarized in **Table 4**.

### Kidney Disease: Improving Global Outcomes–Based Bundle of Care

#### Rationale

Because of the multifactorial nature of CS-AKI, it is likely that a combination of interventions, rather than a single intervention, is needed to result in meaningful reductions in the incidence of CS-AKI.

#### Findings

The PrevAKI RCT was a single-center trial that investigated the use of KDIGO guidelines in the prevention of postoperative AKI in high-risk patients who were identified using a urinary (TIMP-2)/(IGFBP7) ratio of greater than 0.3.[73] The investigators assessed the effect of a KDIGO bundle of care, consisting of optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and prevention of hyperglycemia, among patients undergoing cardiac surgery. Implementation of the KDIGO bundle of care decreased the incidence and severity of AKI after cardiac surgery in these high-risk patients.[73]

#### Bottom line

The results from this single-center trial are promising. However, an adequately powered multicenter trial is needed to confirm whether implementation of a KDIGO-based bundle of care is effective in reducing CS-AKI.

### Fluid Management Strategies

#### Rationale

Fluid management in the perioperative setting is complex and controversial. Fluid overload and hypovolemia are each associated with worse outcomes, including AKI, among patients undergoing cardiac surgery.

#### Findings

A multicenter, double-blind, double-crossover RCT known as the SPLIT Trial assessed the use of a buffered crystalloid solution compared with saline in 2278 patients who were admitted to the intensive care unit and who required fluid therapy (50% of these were cardiac surgery patients). They found similar rates of postoperative AKI in both fluid management strategies.[74] These results require additional investigation, however, because saline resuscitation in other settings, including critical

**Table 4**
**RCTs of postoperative therapeutic interventions for prevention of CS-AKI**

| Trial | Multicenter | Double Blinded | No. of Patients | Cardiac Surgery Type | Intervention | AKI Definition | Primary Outcome |
|---|---|---|---|---|---|---|---|
| Meersch et al,[73] 2017, Germany | No | No | 276 | CABG, valve, combined | KDIGO-based approach | KDIGO stage 1–3 | The KDIGO-based approach decreased the incidence of CS-AKI (OR, 0.48; 95% CI, 0.29–0.80) |
| Young et al,[74] 2015, Australia | Yes | Yes | 2278 | NS | Crystalloid vs saline resuscitation | RIFLE stage R, I, F | Crystalloids vs saline did not decrease the incidence of AKI (RR, 1.04; 95% CI, 0.80–1.36) |
| Hajjar et al,[104] 2010, Brazil | Yes | No | 502 | CABG, valve, combined | Restrictive (Ht ≥24%) threshold for pRBC transfusion | RRT | Restrictive vs liberal threshold for pRBC transfusion did not decrease the incidence of RRT (P = .99) |
| Murphy et al,[105] 2015, UK | Yes | No | 2007 | CABG, valve, combined | Restrictive (Hb <7.5 g/dL) threshold for pRBC transfusion | AKIN stages 1–3 | Restrictive vs liberal threshold for pRBC transfusion did not decrease the incidence of CS-AKI (P>.05) |
| Mazer et al,[81] 2017, Int | Yes | No | 5243 | CABG, valve, combined | Restrictive (Hb <7.5 g/dL) threshold for pRBC transfusion | RRT | Restrictive vs liberal threshold for pRBC transfusion did not decrease the incidence of RRT (HR,0.84; 95% CI, 0.60–1.19) |
| Steiner et al,[83] 2015, USA | Yes | No | 1098 | CABG, valve, combined | Fresh (≤10 d) vs old pRBC (≥21 d) | SCr change | Fresh vs old pRBC did not decrease the incidence of CS-AKI (P = .72) |
| Desai et al,[86] 2012, USA | No | No | 189 | CABG | Tight (90–120 mg/dL) vs liberal (121–180 mg/dL) glucose ranges | RIFLE stage F | Tight vs liberal glucose control did not decrease the incidence of CS-AKI (absolute difference 2.2%; 95% CI, −5% to 8%) |
| Umpierrez et al,[87] 2015, USA | Yes | No | 302 | CABG, valve | Tight (100–140 mg/dL) vs liberal (141–180 mg/dL) glucose ranges | ≥50% SCr increase | Tight vs liberal glucose control did not decrease the incidence of CS-AKI (P = .08). |

*Abbreviations:* CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; Ht, hematocrit; Int, international; KDIGO, Kidney Disease Improving Global Outcome; NS, not specified; OR, odds ratio; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease; RR, relative risk; SCr, serum creatinine.

illness, has been shown to result in higher rates of AKI as compared with balanced solutions.[75]

Noteworthy, concerns have been raised regarding administration of higher molecular weight hydroxyethyl starches as part of fluid resuscitation in various settings, including cardiac surgery, because this approach seems to be associated with a higher incidence of AKI requiring RRT.[76,77]

### Bottom line
Additional studies are needed to investigate the effects of resuscitation using normal saline versus balanced solutions (eg, Ringer's lactate) on the incidence of CS-AKI. Hydroxyethyl starches are contradicted in cardiac surgery.

### Packed Red Blood Cell Transfusions

### Rationale
Anemia and transfusion of pRBCs are each associated with an increased risk of CS-AKI,[78,79] but direct causal relationships in this setting cannot be determined from observational studies owing to confounding by severity of illness. Thus, optimal transfusion thresholds can only be determined from RCTs. Additionally, a large retrospective cohort study (n = 2872) found that transfusion of older pRBCs is associated with worse outcomes postoperatively following cardiac surgery, including in-hospital, renal failure and sepsis.[80]

### Findings
The TRICs-III study is a recently published RCT that assessed the effects of a restrictive versus liberal threshold for transfusion of pRBCs in 5243 adults undergoing cardiac surgery. The restrictive transfusion group received pRBCs if their Hb concentration decreased to less than 7.5 g/dL, whereas the liberal transfusion group received pRBCs if their Hb concentration decreased to less than 9.5 g/dL. The investigators found that the incidence of AKI requiring RRT was similar in both groups.[81] A recent meta-analysis found similar results.[82] Of note, only 1 RCT (the RECESS trial) investigated the effects of storage time of pRBCs on outcomes after cardiac surgery.[83] This trial, which included 1098 patients, found that transfusion of pRBCs stored for 10 or fewer days was not superior to transfusion of pRBCs stored for 21 or more days with respect to severe organ dysfunction.[83]

### Bottom line
The use of a restrictive versus liberal threshold for perioperative pRBC transfusion does not affect the incidence of CS-AKI. Additionally, the storage duration of pRBCs does not seem to affect the incidence of CS-AKI.

### Glycemic Control

### Rationale
Perioperative hyperglycemia is associated with increased mortality, surgical complications, and AKI.[84] Mechanisms by which hyperglycemia could predispose patients to a greater susceptibility to AKI are not entirely clear; however, hyperglycemia is known to induce oxidative stress and also to inhibit sodium-glucose co-transporters in the renal proximal tubules.[85]

### Findings
Two RCTs (N = 189 and N = 302) assessed the effect of tight (100–140 mg/dL) versus liberal (141–180 mg/dL) glycemic control. These studies found no difference in the incidence of CS-AKI.[86,87]

***Bottom line***
Liberal glycemic control has the same effects on CS-AKI as tight glycemic control. Consequently, this has prompted the Society for Thoracic Surgeons to issue guidelines for blood glucose management after cardiac surgery, recommending targeting blood glucose levels of less than 180 mg/dL.[88]

## DISCUSSION

CS-AKI remains a complex and challenging problem. Numerous trials of various preoperative, intraoperative, and postoperative preventive measures have been attempted, yet the majority of RCTs were negative. Preliminary data suggest that a KDIGO-based bundle of care, which includes optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and prevention of hyperglycemia, might help to decrease the incidence of CS-AKI.[3,73] These strategies are low-cost and relatively easy to implement in clinical practice. Although these strategies are promising, larger studies are still needed to confirm these findings.

The use of anti-inflammatory interventions such as steroids, RIPC, statins, NAC, and urinary alkalization seems to be ineffective in preventing CS-AKI in the general cardiac surgery population. Post hoc analyses, however, have shown that certain subgroups of patients may benefit from some of these interventions, for example, corticosteroids.[21] Of all intraoperative measures that have been investigated, none except leukocyte filtration and inhaled NO has proven to be of benefit in protecting against CS-AKI. Yet, the positive findings related to these 2 interventions are based on RCTs that had small sample sizes; thus, additional research is needed to confirm these findings.

One important reason why the majority of RCTs may have been negative is because they assessed interventions aimed at a general cardiac surgical population. Future RCTs should include more precise phenotyping of patients to determine which patients are at the greatest risk of developing AKI, and as such would likely benefit most from the intervention, rather than a one-size-fits-all approach. Phenotyping could be performed through the use of clinical characteristics (eg, preoperative estimated glomerular filtration rate , diabetes mellitus), blood and urine biomarkers (eg, urinary [TIMP-2]/[IGFBP7] ratio, urinary neutrophil gelatinase-associated lipocalin, or plasma fibroblast growth factor-23),[10,13,89] immune characteristics,[90] or (epi)genetic markers.[91]

## SUMMARY

Thousands of patients have been enrolled in clinical trials assessing various therapeutic strategies for prevention of CS-AKI, and the vast majority of these studies have been negative. More comprehensive phenotyping of patients may yield higher success rates in future trials, and could be accomplished through a variety of approaches. Finally, implementation of a KDIGO bundle of care the and administration of inhaled NO intraoperatively represent promising therapeutic strategies. However, the efficacy of these strategies in preventing CS-AKI requires confirmation in larger, multicenter trials before they can be recommended for widespread implementation.

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