Review

Update on clinical trials for the prevention of acute kidney injury in patients undergoing cardiac surgery

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KEYWORDS: Acute kidney injury; Clinical trials; Cardiac surgery; Diagnosis; Prevention; Treatment

Abstract

BACKGROUND: Effective therapeutic agents for the prevention and treatment of acute kidney injury (AKI) after cardiac surgery remain elusive despite the tremendous advances in surgical techniques, technology, and understanding of disease processes. Recent developments and their effect on the incidence of AKI after cardiac surgery are discussed.

DATA SOURCES: Published clinical trials in PubMed, strength of evidence assessed by the guidelines of the American Family Physicians.

CONCLUSIONS: The definition of AKI has changed, and the focus of interventions has shifted from treatment to prevention to recovery from AKI. Antioxidants and biological agents have been added to classic armaments of hydration and diuretics in addition to tighter metabolic control to prevent AKI. Although the treatment options remain unsatisfactory, a lot of progress nevertheless continues to be made in the prevention and treatment of AKI.

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The Acute Kidney Injury Network (AKIN) has proposed the term acute kidney injury (AKI) to represent the entire spectrum of acute renal failure, replacing all previous terminology to describe acute alterations in serum creatinine levels or urine output. AKI is now defined as an increase in serum creatinine levels of 0.3 mg/dL or greater (≥26.4 μmol/L) or an increase to 50% or more from baseline within 48 hours or urine output less than 0.5 mL/kg/h for more than 6 hours. Clinical trials are now applying the new definition of AKI, rather than the classic hard end points of dialysis or death, as a measure of primary outcomes. Using the AKIN criteria, AKI has been reported to occur in 30% to 40% of patients undergoing cardiac surgery. The true incidence of AKI is difficult to estimate because of the varying definitions used in different studies. The incidence of AKI also varies with the severity of baseline cardiac and renal function and the types of cardiac surgery performed. Although data are limited, patients with pre-existing chronic kidney disease, those with impaired cardiac function, and those undergoing thoracic aortic aneurysm surgery (vs cardiac valve or coronary artery bypass surgery) are at higher risk for AKI. AKI is an independent risk factor for in-hospital mortality, progression to end-stage renal disease, and reduced long-term survival. Recently, the severity of AKI has been reported to be a major determinant of short- and long-term mortality. Patients with AKI requiring renal replacement therapies have mortality rates in excess of 40% to 50%. Even mild elevation of serum creatinine levels after

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cardiac surgery has been associated with significant increases in mortality. Correspondingly, a postoperative decline in the estimated glomerular filtration rate (GFR) was also associated with an increase in 30-day mortality. A graded relationship has been demonstrated between the duration of AKI and mortality, suggesting that the gap between association and causation may be narrowing. Evolving theories of the mechanisms of AKI have led to innovative therapeutic targets, but the outcomes of novel therapies have not been uniformly satisfactory. We provide an update on recent clinical trials and some of the innovative approaches that are under investigation to prevent AKI in patients undergoing cardiac surgery.

Methods

We conducted searches for published clinical trials on the prevention of AKI in human patients undergoing cardiac surgery by querying PubMed, the National Institute of Health's repository for peer-reviewed primary research reports in the life sciences. The strength of evidence was assessed by using the guidelines of the American Family Physicians. The strength of evidence was labeled using an ABC rating scale in which level A refers to a high-quality RCT and meta-analysis; level B (other evidence) refers to a well-designed nonrandomized clinical trial, lower quality RCTs, clinical cohort and case-controlled studies, high-quality historical uncontrolled studies, or well-designed epidemiologic studies with compelling findings; and level C refers to a consensus view point or expert opinion. The focus of the review is primarily on RCTs to prevent AKI after cardiac surgery; however, several nonrandomized, subject-related trials have also been included to complement the understanding of the issues concerned. We have elected to exclude level C studies because of their weaker level of evidence.

Results

Pharmacologic and nonpharmacologic interventions have been investigated in trials studying the prevention and treatment of AKI. Nonpharmacologic interventions include close monitoring and adjustment of volume status, avoidance of nephrotoxins, and modifications in surgical techniques such as off-pump bypass or hypothermia. The results of the interventions are discussed under separate subentities.

Perioperative fluid resuscitation

Maintaining adequate hydration and optimal mean arterial pressure, avoiding hypotension, and minimizing exposure to nephrotoxic agents are general strategies that help diminish renal damage in hospitalized patients. Preoperative cardiac catheterization is frequently performed 24 to 72 hours before scheduled cardiac surgery and is associated with a 16% to 48% incidence of AKI. Although hydration reduces the risk of contrast-induced AKI in patients undergoing coronary angioplasty, its role in the prevention of AKI after cardiac surgery remains uncertain. A meta-analysis of 20 studies concluded that surgical patients receiving perioperative hemodynamic optimization had a decreased risk of AKI and death. However, efforts at preoperative hemodynamic optimization by the routine use of pulmonary artery catheters in aortic surgery were not effective in preventing postoperative cardiac and renal complications.

Maintaining adequate hydration and optimal mean arterial pressure, avoiding hypotension, and minimizing exposure to nephrotoxic agents are general strategies that help diminish renal damage in hospitalized patients. Preoperative cardiac catheterization is frequently performed 24 to 72 hours before scheduled cardiac surgery and is associated with a 16% to 48% incidence of AKI. Although hydration reduces the risk of contrast-induced AKI in patients undergoing coronary angioplasty, its role in the prevention of AKI after cardiac surgery remains uncertain.
<table>
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<td>Does not decrease mortality or dialysis requirement*</td>
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<td>No significant difference in AKI requiring dialysis*</td>
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<td>Postoperative</td>
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<td>Erythropoietin</td>
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<td>B</td>
<td>Not effective</td>
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<td></td>
<td>Postoperative</td>
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| ACE = angiotensin-converting enzyme; AKI = acute kidney injury; HES = hydroxyethyl starch; IABP = intra-arterial balloon pump; ICU = intensive care unit; N = no; SOE = strength of evidence; Y = yes.
of solute diuresis, stimulation of endogenous natriuretic peptide release, decrease in sympathetic activity, inactivation of the renin-angiotensin system, and attenuation of oxidant generation, as mentioned previously. In a recent systematic review of the comparative safety of colloids, AKI and a dose-dependent increase in mortality were observed in patients with severe sepsis or septic shock who were receiving hydroxyethyl starch (HES).\textsuperscript{25} Impaired coagulation and clinical bleeding were frequently reported after hydroxyethyl starch infusion, especially in patients undergoing cardiac surgery. In head-to-head randomized comparisons of different types of HES, observed effects on coagulation and renal function were similar, whereas albumin displayed a more favorable safety profile than did HES. Even third-generation HES 130/0.4, despite its low molecular weight, was associated with increased risk of death and a requirement for dialysis.\textsuperscript{23} In a multicenter randomized double-blind trial of 6,997 patients in the ICU, resuscitation with 4% albumin was not superior to normal saline in improving survival, despite a trend for favorable response with albumin in patients with sepsis.\textsuperscript{24} Although there may be a lack of consensus about the superiority of a specific fluid type, it may not be prudent to restrict fluid in the preoperative period in an otherwise asymptomatic patient undergoing cardiac surgery. When prescribing fluid therapy, one must be cognizant of the unfavorable link between positive fluid balance and adverse outcomes.

**Perioperative glycemic control**

Glucose homeostasis is disturbed preoperatively for many nondiabetic patients undergoing cardiac surgery. Cardiopulmonary bypass exacerbates the catabolism and disturbed glucose homeostasis, which is also induced to a lesser degree by surgery without cardiopulmonary bypass. Perioperative hyperglycemia is associated with increased mortality, surgical complications, and AKI. In a prospective randomized controlled study of 1,548 patients undergoing cardiac surgery, intensive insulin therapy to maintain blood glucose levels at or less than 110 mg/dL in the ICU reduced overall in-hospital mortality by 34\%, bloodstream infections by 46\%, AKI requiring dialysis by 41\%, and median number of red blood cell transfusions by 50\%.\textsuperscript{25} Furthermore, retrospective analysis of 1,050 patients undergoing cardiac surgery found that maintaining intra- and postoperative blood glucose levels between 80 and 110 mg/dL may be associated with a significant reduction in AKI in nondiabetic patients.\textsuperscript{26} Hyperglycemia induces oxidative stress and inhibits sodium-glucose transporters in the renal proximal tubules and stimulates reactive oxygen species.\textsuperscript{27,28} However, in a prospective multicenter randomized clinical trial of 6,104 critically ill surgical and nonsurgical patients, a blood glucose target level of 180 mg/dL resulted in lower mortality than did a target of 81 to 108 mg/dL.\textsuperscript{29} The detrimental effects of perioperative hyperglycemia have prompted the Society for Thoracic Surgeons to issue guidelines for blood glucose management during cardiac surgery, recommending blood glucose levels less than 180 mg/dL.\textsuperscript{30}

**Preoperative contrast agent exposures and use of angiotensin-converting enzyme inhibitors and statins**

Patients undergoing cardiac surgery are often exposed to procedures using contrast agents before and after surgery. Investigation of the effect of cardiac angiography timing, contrast agent dose, and preoperative renal function on AKI after coronary artery bypass grafting (CABG) in 395 patients demonstrated that the risk of perioperative AKI was significantly greater if the patients received more than 1.5 mL/kg contrast dye, had angiography performed within 5 days of operation, or had impaired preoperative kidney function.\textsuperscript{11} The risk of AKI after CABG was inversely and modestly related to the time between cardiac catheterization and CABG, with the highest incidence in those operated on 1 day or less after cardiac catheterization, despite otherwise being of low-risk profile. Whether delaying elective CABG for more than 24 hours after exposure to contrast agents (when feasible) has the potential for decreasing AKI after CABG remains to be evaluated in future studies.\textsuperscript{31} The incidence of AKI was reported to decrease significantly from 50.2\% to 33.7\% when cardiac surgery was undertaken in a subsequent hospitalization after the cardiac operation,\textsuperscript{12} as was the incidence of poststernotomy mediastinitis.\textsuperscript{13} Clinicians may limit the degree of severity of AKI after cardiac surgery by allowing adequate time for renal recovery after a preoperative insult.

The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the perioperative period of cardiac surgery remains controversial. In a retrospective analysis of 1,358 adult patients who underwent cardiac surgery, the preoperative use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers was associated with an increased risk of AKI.\textsuperscript{32} Others have reported that the chronic preoperative use of renin-angiotensin system inhibitors did not affect postoperative renal function or increase the risk of postoperative AKI after off-pump CABG.\textsuperscript{33} A prospective observational study of 536 patients found that preoperative angiotensin-converting enzyme inhibitors decreased the incidence of postoperative AKI after CABG.\textsuperscript{34} In the absence of more definitive evidence, discontinuing these drugs the day before surgery may be prudent.

The use of statins to prevent AKI remains uncertain. Preoperative statin use was not associated with a reduction in the incidence of AKI in patients undergoing on-pump surgery.\textsuperscript{35} A more recent retrospective analysis of prospectively collected data from 324 patients in an ongoing clinical trial found that early postoperative statin use was associated with a lower incidence of AKI among both long-term statin users and statin-naive patients undergoing cardiac surgery.\textsuperscript{36}

**Perioperative anemia and transfusions**

There is evidence to suggest that low preoperative and intraoperative hemoglobin levels and perioperative red blood cell transfusions are independently associated with...
AKI. One study found that patients undergoing cardiac surgery who had significant comorbidities (EuroSCORE ≥ 4) and who had hemoglobin levels less than 11 g/dL had a higher incidence of postoperative adverse events. In a study of 920 consecutive patients who underwent on-pump cardiac surgery, the odds ratio (OR) for AKI was 1.16 per gram per deciliter decrease in hemoglobin levels. There appears to be a direct relationship between plasma free hemoglobin levels and the duration of cardiopulmonary bypass time and AKI in patients undergoing cardiac surgery.46 Advance targeted transfusion in anemic patients reduced perioperative anemia and erythrocyte transfusions but did not affect the incidence of AKI.41 However, blood transfusions postoperatively in pediatric patients undergoing cardiac surgery were not beneficial and were associated with an increased incidence of AKI and prolonged hospital stays.42,43 After adjustment for the use of miniaturized circuits and for the year of surgery, no significant association between the incidence of AKI, dialysis, and aprotinin was noted. Red blood cell transfusions were associated with an increased risk of AKI and dialysis (ORs, 95% confidence interval [CI], 1.64 [1.12 to 2.41] and 2.07 [1.13 to 3.73]), respectively, as were fresh frozen plasma transfusions (ORs, 2.28 [1.68 to 3.09] and 3.11 [1.95 to 4.97]), respectively. Platelet transfusions were also associated with an increased risk of dialysis (OR, 2.20 [1.21 to 4.01]). In contrast to the unfavorable findings of the effect of transfusions in observational studies in cardiac surgery in humans, red blood cell transfusion during cardiopulmonary bypass in pigs prevented the reductions in creatinine clearance, loss of nitric oxide bioavailability, platelet activation, inflammation, and epithelial cell injury attributable to cardiopulmonary bypass. However, it did not prevent the development of significant intrarenal vasoconstriction and endothelial dysfunction.44

Antioxidants

N-acetylcysteine, a precursor of intracellular glutathione, scavenges reactive oxygen species and has been shown to decrease kidney injury.45 N-acetylcysteine may be an effective oxygen free radical scavenger during cardiac surgery and has been reported to lower the oxidative burst response of neutrophils during cardiopulmonary bypass. However, in prospective randomized clinical trials, intravenous N-acetylcysteine did not prevent postoperative renal dysfunction, interventions, complications, or mortality in high-risk patients undergoing CABG with cardiopulmonary bypass.46 It also was not effective in the prevention of AKI in patients with chronic renal insufficiency who were undergoing cardiac surgery.47 Recent meta-analyses have also failed to demonstrate a significant positive N-acetylcysteine effect across studies.48 Current evidence does not support the role of N-acetylcysteine in the prevention of AKI in patients undergoing cardiac surgery.

Do other antioxidants, such as uric acid, have a role in AKI in cardiac surgery? Emerging data suggest that levels of serum uric acid, the most abundant antioxidant in the body, may have a role in AKI in cardiac surgery, albeit in a negative way. Serum uric acid levels greater than 7 mg/dL were associated with a 40-fold (OR, 39.1; 95% confidence interval [CI], 11.6 to 131.8) increased risk of AKI, higher postoperative serum creatinine values, and longer hospital lengths of stay and duration of mechanical ventilation support in patients undergoing cardiac surgery.49 In a prospective, double-blind, parallel-design, placebo-controlled, randomized pilot trial of 26 hyperuricemic patients undergoing cardiac surgery, preoperative lowering of serum uric acid levels by urate oxidase (rasburicase) was associated with decreased renal parenchymal injury as measured by urine NGAL levels.50 In a small clinical trial, prophylactic vitamin E and allopurinol were given as antioxidants, and serum uric acid levels were not measured; no beneficial effect was seen on the incidence of AKI in patients undergoing cardiac surgery.51 There was also no effect on the incidence of AKI in patients undergoing cardiac surgery from the early intravenous infusion of antioxidant supplements such as selenium, zinc, vitamin C, and vitamin B1.52

Diuretics

Another important tool in fluid management are diuretics. Theoretically, diuretics may decrease the severity of AKI by preventing tubule obstruction and decreasing oxygen consumption by inhibition of the Na-K-2Cl co-transporter. However, data on diuretic use in the intensive care setting is controversial, with 1 study reporting a significant increase in the risk of death or nonrecovery of renal function associated with its use,53 whereas data from a prospective multiple-center multinational epidemiologic study did not show a higher mortality with its use in patients with severe AKI.54 In a prospective randomized clinical trial of patients undergoing cardiac surgery, prophylactic infusion of furosemide (0.5 μg/kg/min, starting at the beginning of surgery and continuing for 48 hours) was associated with an increased incidence of AKI and deterioration of renal function.55 Similarly, a recent prospective randomized clinical trial of high-risk patients undergoing cardiac surgery did not demonstrate a benefit of prophylactic diuretic use to prevent AKI.56 Routine postoperative diuretic administration has not been shown to prevent AKI or offer renal protection in cardiac surgery.57 Therefore, diuretics are not recommended for the prevention or treatment of AKI, although they remain a valuable tool for correcting volume overload.

Vasodilators: fenoldopam, dopamine

Fenoldopam is a selective dopamine-1 agonist that has been used for the prevention of AKI in small trials with variable results. Small studies using fenoldopam have demonstrated a reduction of renal dysfunction. In a prospective, randomized, double-blind, placebo-controlled
study, administration of fenoldopam at the onset of cardiopulmonary bypass and maintaining it for the first 12 postoperative hours was associated with a reduced incidence of AKI in patients undergoing cardiac surgery. Pooled estimates from 2 separate meta-analyses of randomized and case-matched studies also showed that fenoldopam consistently and significantly reduced the need for renal replacement therapy and reduced hospital mortality. A potential complication of fenoldopam is the occurrence of systemic hypotension, which may offset its beneficial effect of renal vasodilation. Indeed, a multicenter nonrandomized prospective study failed to conclusively demonstrate the benefits of fenoldopam in the prevention of AKI in high-risk patients undergoing cardiac surgery. Similarly, Bove et al reported that in patients with chronic kidney disease who underwent cardiac surgery, fenoldopam did not reduce the rate of AKI or the need for dialysis. More recently, high-dose fenoldopam during cardiopulmonary bypass appeared to decrease AKI (as measured by NGAL and cystatin C levels) in pediatric patients undergoing cardiac surgery. An appropriately powered trial is required to confirm the conflicting data regarding fenoldopam and AKI in cardiac surgery.

Dopamine stimulates dopamine-1 and dopamine-2 receptors and thereby decreases renal vascular resistance and enhances diuresis and natriuresis. In a prospective study, the continuous infusion of dopamine was ineffective and was not superior to placebo in preventing AKI in patients undergoing cardiac surgery, a finding that was also supported by systematic review of clinical trials. Furthermore, there is concern about potential toxicity, including tachycardia, arrhythmias, myocardial ischemia, and intestinal ischemia. Thus, dopamine cannot be recommended as a renal protective agent and is better avoided. Infusion of sodium nitroprusside (a nitric oxide donor) during cardiopulmonary bypass was associated with lower serum creatinine values and AKI in a prospective randomized pilot study in patients undergoing cardiac surgery. Inspired nitric oxide has been reported to modulate oxidative stress markers in patients undergoing cardiac surgery. These results need validation in large clinical trials before they can be recommended for routine clinical practice.

Natriuretic peptides

Natriuretic peptides are the natural antagonist of the renin-angiotensin system and are involved in the regulation of sodium and water balance and arterial pressures. Natriuretic peptides increase the GFR by selective dilation of the afferent arterioles and constriction of the efferent arterioles without affecting renal blood flow. However, their application in clinical practice to prevent AKI has yielded mixed results despite promising early results in noncardiac patients and cardiac patients undergoing surgery. Natriuretic peptides failed to demonstrate a beneficial effect on dialysis-free survival or reduction in the need for dialysis in acute tubular necrosis. A prospective randomized clinical trial could not demonstrate a benefit for prophylactic use of nesiritide on the incidence of dialysis or death in patients undergoing high-risk cardiac surgery despite reducing the incidence of AKI per AKIN criteria. Others have also reported attenuated serum creatinine response to prophylactic natriuretic peptides in patients undergoing CABG. Disappointingly, a follow-up study reported that the renal protection provided by nesiritide in the immediate postoperative period was not associated with improved long-term survival in patients undergoing high-risk cardiovascular surgery. On the basis of this evidence, natriuretic peptides cannot be recommended for routine use in the broad population of patients with AKI who are undergoing cardiac surgery.

On-pump vs off-pump surgery

Efforts to decrease complications associated with the use of the heart-lung machine have included the investigation of the impact of on-pump vs off-pump cardiac surgical procedures on the primary composite end point of death or complications (reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure) before discharge or within 30 days after surgery. Significant differences were not observed for the 30-day primary end point; however, the rate of the 1-year composite outcome was higher for off-pump than for on-pump CABG (9.9% vs 7.4%; P = .04). The proportion of patients with fewer grafts completed than originally planned was higher with off-pump CABG than with on-pump CABG (17.8% vs 11.1%; P < .001). Similarly, no major differences in 30-day outcomes were observed when high-risk patients were randomized to off-pump vs on-pump coronary artery bypass surgery. The use of centrifugal pumps to produce pulsatile flow during cardiopulmonary bypass in patients undergoing cardiac surgery did not result in significant differences in postoperative AKI, endothelial activation, or inflammatory response compared with patients who underwent cardiopulmonary bypass with nonpulsatile pumps. There was also no long-term benefit with off-pump procedures with regard to major adverse cardiac and cerebrovascular events, including all-cause mortality, acute myocardial infarction, and cardiac arrest with successful resuscitation, low cardiac output syndrome and cardiogenic shock, stroke, and coronary reintervention. Because the previous studies lacked sufficient power to accurately assess moderate but clinical differences in rates of death, myocardial infarction, stroke, and renal failure, 4,752 patients at 79 centers in 19 countries were randomly assigned to undergo off-pump or on-pump CABG. There was no significant difference between off-pump and on-pump CABG with respect to the 30-day rate of death, myocardial infarction, stroke, or need for dialysis; however, the incidence of AKI was significantly reduced in the off-pump group.

Intra-aortic balloon pump

The intra-aortic balloon pump (IABP) increases coronary perfusion and is commonly used in cardiac surgery.
Although preoperative use of the IABP improves outcomes in high-risk cardiac patients, it can lead to a decrease in blood flow below the descending aorta and cause ischemic complications. Interestingly, several studies report that renal hemodynamics improve with IABP support, although improvement in creatinine clearance could not be demonstrated. In fact, in clinical studies, preoperative IABP use was identified as 1 of the characteristics most strongly associated with postoperative severe AKI. Another important aspect is the use of aseptic common with high-risk patients undergoing off-pump cardiac surgery. Prospective randomized trials also support the finding that preoperative IABP use improves outcomes and has a beneficial effect on renal function, especially compared with the use of postoperative IABP. Postoperative IABP has been most commonly associated with a high incidence of AKI. Another important aspect is the use of linear vs pulsatile perfusion with IABP use, the latter being associated with reduced endothelial activation and AKI.

Erythropoietin-stimulating agents

Patients undergoing cardiac surgery are at risk for ischemia- or hypoxia-induced adverse events; thus, it is not surprising that the hypoxia-inflammation link has become a therapeutic target to improve perioperative outcomes. Several investigators have hypothesized a protective effect of erythropoietin against ischemic and cytotoxic renal damage and observed that patients aggressively treated with erythropoietin demonstrated a slower progression of AKI. Erythropoietin has proliferative and antiapoptotic effects in ischemia-reperfusion models in the brain, and cell cultures can mobilize stem cells and increase the plasma levels and the renal expression of vascular endothelial growth factor in a dose-dependent manner. Erythropoietin may have a direct action on polymorphonuclear leukocytes to decrease systemic inflammation and oxidative stress. In a small pilot trial of 71 patients, prophylactic administration of 300 U/kg intravenous erythropoietin was reported to prevent AKI and improve postoperative renal function. However, in the EARLYARF trial to prevent AKI in critically ill patients, early intervention with erythropoietin did not affect the outcome of AKI.

Comments and Conclusions

The treatment options for AKI after cardiac surgery remain unsatisfactory. The suboptimal clinical results achieved with therapeutic agents that were deemed promising in vitro and in animal models point to the complexity of the mechanisms of AKI in patients undergoing cardiac surgery. The initiating event in AKI appears to be vasoconstriction related to imbalance between the vasoconstrictors and vasodilators, with subsequent impairment of renal blood flow autoregulation, hyperfusion, hypoxia, oxidative stress, and activation of the inflammation cascade. The players involved are only beginning to be discovered, and investigators are exploring therapeutic targets with sodium bicarbonate, ketanserin, beta-erythropoietin, remote ischemic preconditioning, and dose-escalated intra-aortic infusion of allogeneic bone marrow–derived multipotent stromal cells to prevent and treat AKI. The Critical Care Nephrology Working Group of the European Society of Intensive Care Medicine has published expert opinions on the prevention of AKI and protection of renal function in the ICU, which are mostly in accordance with what has been reviewed in this article. For clinicians, the approach to preventing AKI begins with identification of high-risk patients, minimization of potential ischemic and toxic injury, administration of sodium bicarbonate for emergency procedures that use contrast agents, maintenance of fluid balance and avoidance of starch preparations, optimization of glycemic control, minimization of blood product transfusions, and careful consideration of the use of IABP and novel therapeutic agents in select patient groups (Table 1). Effective treatment options in established AKI remain elusive. The delayed development of effective therapies is greatly related to the inability to diagnose AKI in the early phase when intervention could potentially alter the prognosis of affected patients. Despite the availability of many biomarkers, including NGAL and interleukin-18 to detect early AKI, the lack of established cutoff values has impeded their clinical implementation. Novel methods such as promoting regeneration of injured renal tubular cells and preservation of mitochondrial function by opening mitochondrial or plasmalemmal adenosine-5′-triphosphate–sensitive potassium channels and closure of the mitochondrial permeability transition pore are gaining momentum. In a randomized single-blind controlled pilot trial, ischemic preconditioning at a remote site prevented AKI in patients undergoing cardiac surgery.

What is a clinician to do when prophylactic measures fail to prevent AKI and current therapies have unproven efficacy to treat AKI? Shared decision making between cardiac surgeons, intensivists, and nephrologists may provide the best plan of action. There is ample evidence of the benefits of early renal replacement therapy in critically ill patients. In patients with severe AKI undergoing cardiac surgery, early and aggressive continuous renal replacement therapies have been shown to improve survival. For patients treated with continuous renal replacement therapies, the actuarial 1- and 5-year survival rates were 53% and 52%, respectively. Only a small percentage (2.2%) of patients who survive require long-term renal support. It is therefore evident that despite being unsatisfactory, a lot of progress nevertheless continues to be made in the prevention and treatment of AKI. Stay tuned.
References


