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# Renal disease and the surgical patient: Minimizing the impact

## ABSTRACT

Chronic kidney disease (CKD) is common in patients scheduled for surgery and increases the risk of postoperative acute kidney injury, major adverse cardiac events, and death. Acute kidney injury is a common complication of cardiac and noncardiac surgery and negatively affects both short- and long-term outcomes. If we can detect underlying CKD and other risk factors for acute kidney injury before surgery, we may in theory be able to give preventive therapies and improve perioperative outcomes.

## KEY POINTS

Many patients undergoing surgery have CKD—up to 30% in some cardiac surgery populations.

CKD is a risk factor for perioperative complications including acute kidney injury and death.

Although challenging, early detection of renal injury is crucial to improving outcomes in this patient population. New biomarkers are being investigated.

Preoperative assessment and perioperative management of renal dysfunction may reduce the risk of adverse postoperative outcomes.

**C**HRONIC KIDNEY DISEASE (CKD) is estimated to affect 14% of Americans, but it is likely underdiagnosed because it is often asymptomatic.<sup>1,2</sup> Its prevalence is even higher in patients who undergo surgery—up to 30% in cardiac surgery.<sup>3</sup> Its impact on surgical outcomes is substantial.<sup>4</sup> Importantly, patients with CKD are at higher risk of postoperative acute kidney injury (AKI), which is also associated with adverse outcomes. Thus, it is important to recognize, assess, and manage abnormal renal function in surgical patients.

## WHAT IS THE IMPACT ON POSTOPERATIVE OUTCOMES?

CKD is defined in various ways, making it difficult to derive exact numbers about its impact on surgical outcomes. The definition (Table 1) and categories (Table 2) devised by the Kidney Disease Improving Global Outcomes (KDIGO) program are now the most widely accepted.<sup>5,6</sup>

### Cardiac surgery outcomes

In cardiac surgery patients, CKD is strongly correlated with higher postoperative inpatient and 30-day mortality rates, both all-cause and cardiovascular.<sup>7–10</sup> It is a strong predictor of death in the first 30 days after surgery, with a 35% to 43% higher risk of death for every 10 mL/min/1.73 m<sup>2</sup> of preoperative decrease in estimated glomerular filtration rate (GFR).<sup>10</sup>

Moreover, in patients undergoing coronary artery bypass grafting (CABG), the worse the renal dysfunction, the higher the long-term mortality rate. Patients with moderate (stage 3) CKD had a 3.5 times higher odds of in-hospital mortality compared with patients with normal renal function, rising to 8.8 with se-

**TABLE 1**

**Criteria for chronic kidney disease**

**Markers of kidney damage**

(≥ 1 present for > 3 months)

Albuminuria

(albumin excretion rate ≥ 30 mg/day; albumin-creatinine ratio ≥ 30 mg/g)

Urinary sediment abnormalities

Electrolyte and other abnormalities due to tubular disorders

Abnormalities detected by histology

Structural abnormalities detected by imaging

History of kidney transplant

**Decreased glomerular filtration rate (GFR)**

(present for > 3 months)

GFR < 60 mL/min/1.73 m<sup>2</sup> (GFR categories G3a to G5)

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**AKI is a common complication of surgery, especially cardiac surgery**

vere (stage 4) and to 9.6 with dialysis-dependent (stage 5) CKD.<sup>11</sup>

The mechanisms linking CKD with negative cardiac outcomes are unclear, but many possibilities exist. CKD is an independent risk factor for coronary artery disease and shares underlying risk factors such as hypertension and diabetes. Cardiac surgery patients with CKD are also more likely to have diabetes, left ventricular dysfunction, and peripheral vascular disease.

**Noncardiac surgery outcomes**

CKD is also associated with adverse outcomes in noncardiac surgery patients, especially at higher levels of renal dysfunction.<sup>12–14</sup> For example, in patients who underwent major noncardiac surgery, compared with patients in stage 1 (estimated GFR > 90 mL/min/1.73 m<sup>2</sup>), the odds ratios for all-cause mortality were as follows:

- 0.8 for patients with stage 2 CKD
- 2.2 in stage 3a
- 2.8 in stage 3b
- 11.3 in stage 4
- 5.8 in stage 5.<sup>14</sup>

The association between estimated GFR and all-cause mortality was not statistically

significant ( $P = .071$ ), but statistically significant associations were observed between estimated GFR and major adverse cardiovascular events ( $P < .001$ ) and hospital length of stay ( $P < .001$ ).

The association of CKD with major adverse outcomes and death in both cardiac and noncardiac surgical patients demonstrates the importance of understanding this risk, identifying patients with CKD preoperatively, and taking steps to lower the risk.

**■ WHAT IS THE IMPACT OF ACUTE KIDNEY INJURY?**

AKI is a common and serious complication of surgery, especially cardiac surgery. It has been associated with higher rates of morbidity, mortality, and cardiovascular events, longer hospital length of stay, and higher cost.

Several groups have proposed criteria for defining AKI and its severity; the KDIGO criteria are the most widely accepted.<sup>15</sup> These define AKI as an increase in serum creatinine concentration of 0.3 mg/dL or more within 48 hours or at least 1.5 times the baseline value within 7 days, or urine volume less than 0.5 mL/kg/hour for more than 6 hours. There are 3 stages of severity:

- Stage 1—an increase in serum creatinine of 1.5 to 1.9 times baseline, an absolute increase of at least 0.3 mg/dL, or urine output less than 0.5 mL/kg/hour for 6 to 12 hours
- Stage 2—an increase in serum creatinine of 2.0 to 2.9 times baseline or urine output less than 0.5 mL/kg/hour for 12 or more hours
- Stage 3—an increase in serum creatinine of 3 times baseline, an absolute increase of at least 4 mg/dL, initiation of renal replacement therapy, urine output less than 0.3 mL/kg/hour for 24 or more hours, or anuria for 12 or more hours.<sup>15</sup>

Multiple factors associated with surgery may contribute to AKI, including hemodynamic instability, volume shifts, blood loss, use of heart-lung bypass, new medications, activation of the inflammatory cascade, oxidative stress, and anemia.

**AKI in cardiac surgery**

The incidence of AKI is high in cardiac surgery. In a meta-analysis of 46 studies ( $N =$

TABLE 2

**Defining the severity of chronic kidney disease**

Stage	GFR, mL/min/1.73 m <sup>2</sup>	Descriptor
G1	≥ 90	Normal or high
G2	60–89	Mildly decreased <sup>a</sup>
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	< 15	Kidney failure

  

Albuminuria	AER, mg/day	ACR, mg/g	Descriptor
A1	< 30	< 30	Normal to mildly increased
A2	30–300	30–300	Moderately increased <sup>b</sup>
A3	> 300	> 300	Severely increased

<sup>a</sup> In the absence of evidence of kidney damage, neither GFR category G1 nor G2 meets the criteria for chronic kidney disease.

<sup>b</sup> Includes the nephrotic syndrome (AER usually > 2,200 mg/day).

ACR = albumin-creatinine ratio equivalent; AER = albumin excretion rate; GFR = glomerular filtration rate

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242,000), its incidence in cardiopulmonary bypass surgery was about 18%, with 2.1% of patients needing renal replacement therapy.<sup>16</sup> However, the incidence varied considerably from study to study, ranging from 1% to 53%, and was influenced by the definition of AKI, the type of cardiac surgery, and the patient population.<sup>16</sup>

Cardiac surgery-associated AKI adversely affects outcomes. Several studies have shown that cardiac surgery patients who develop AKI have higher rates of death and stroke.<sup>16–21</sup> More severe AKI confers higher mortality rates, with the highest mortality rate in patients who need renal replacement therapy, approximately 37%.<sup>17</sup> Patients with cardiac surgery-associated AKI also have a longer hospital length of stay and significantly higher costs of care.<sup>17,18</sup>

Long-term outcomes are also negatively affected by AKI. In cardiac surgery patients with AKI who had completely recovered renal function by the time they left the hospital, the 2-year incidence rate of CKD was 6.8%, significantly higher than the 0.2% rate in patients who did not develop AKI.<sup>19</sup> The 2-year

survival rates also were significantly worse for patients who developed postoperative AKI (82.3% vs 93.7%). Similarly, in patients undergoing CABG who had normal renal function before surgery, those who developed AKI postoperatively had significantly shorter long-term survival rates.<sup>20</sup> The effect does not require a large change in renal function. An increase in creatinine as small as 0.3 mg/dL has been associated with a higher rate of death and a long-term risk of end-stage renal disease that is 3 times higher.<sup>21</sup>

### ■ WHAT ARE THE RISK FACTORS FOR ACUTE KIDNEY INJURY?

The etiology of AKI is complex and multifactorial. Risk factors can be divided into patient- and surgery-associated risk factors (Table 3).

#### Cardiac surgery

CKD is a risk factor not only after cardiac surgery but also after percutaneous procedures. In a meta-analysis of 4,992 patients with CKD who underwent transcatheter aortic valve replacement, both moderate and severe CKD increased the odds of AKI, early stroke, the

**The most important patient risk factors are age > 75 and CKD**

**TABLE 3**

**Risk factors for acute kidney injury in surgical patients**

<b>Cardiac surgery</b>	<b>Noncardiac surgery</b>
<b>Patient factors</b>	
Age > 75	Age ≥ 59
Chronic kidney disease	Body mass index ≥ 32 kg/m <sup>2</sup>
Diabetes mellitus (type 1 > type 2)	Peripheral vascular occlusive disease
Anemia	Hepatic disease, especially chronic kidney disease
Congestive heart failure	Chronic obstructive pulmonary disease
Left ventricular dysfunction	African American race
Pulse pressure > 40 mm Hg	Hypertension
Prior myocardial infarction	Diabetes
Angiotensin-converting enzyme inhibitors (but evidence conflicting)	
<b>Surgical factors</b>	
Urgent surgery	Emergency surgery
Duration of procedure	High-risk surgery (intrathoracic, intraperitoneal, suprainguinal vascular, with potential for large blood loss or large fluid shifts)
Cardiopulmonary bypass > 2 hours	
Intra-aortic balloon pump use	Total vasopressor dose
Multiple inotrope use	Vasopressor infusion
Off-pump coronary artery bypass grafting (vs on-pump)	Diuretic administration

Adapted from information in references 7, 15, 17, 23–27, 30–32, 34.

**Although AKI  
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outcomes  
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need for dialysis, and all-cause and cardiovascular mortality at 1 year.<sup>22,23</sup> Increased rates of AKI also have been found in patients with CKD undergoing CABG surgery.<sup>24</sup> These results point to a synergistic effect between AKI and CKD, with outcomes much worse in combination than alone.

In cardiac surgery, the most important patient risk factors associated with a higher incidence of postoperative AKI are age older than 75, CKD, preoperative heart failure, and prior myocardial infarction.<sup>19,25</sup> Diabetes is an additional independent risk factor, with type 1 conferring higher risk than type 2.<sup>26</sup> Preoperative use of angiotensin-converting enzyme (ACE) inhibitors may or may not be a risk factor for cardiac surgery-associated AKI, with some studies finding increased risk and others finding reduced rates.<sup>27,28</sup>

Anemia, which may be related to either patient or surgical risk factors (eg, intraoperative blood loss), also increases the risk of AKI in cardiac surgery.<sup>29,30</sup> A retrospective study of CABG surgery patients found that intraoperative hemoglobin levels below 8 g/dL were associated with a 25% to 30% incidence of AKI, compared with 15% to 20% with hemoglobin levels above 9 g/dL.<sup>29</sup> Additionally, having severe hypotension (mean arterial pressure < 50 mm Hg) significantly increased the AKI rates in the low-hemoglobin group.<sup>29</sup> Similar results were reported in a later study.<sup>30</sup>

Among surgical factors, several randomized controlled trials have shown that off-pump CABG is associated with a significantly lower risk of postoperative AKI than on-pump CABG; however, this difference did not translate into any long-term difference in mortality

rates.<sup>31,32</sup> Longer cardiopulmonary bypass time is strongly associated with a higher incidence of AKI and postoperative death.<sup>33</sup>

### Noncardiac surgery

AKI is less common after noncardiac surgery; however, outcomes are severe in patients in whom it occurs. In a study of 15,102 noncardiac surgery patients, only 0.8% developed AKI and 0.1% required renal replacement therapy.<sup>34</sup>

Risk factors after noncardiac surgery are similar to those after cardiac surgery (Table 3).<sup>34–36</sup> Factors with the greatest impact are older age, peripheral vascular occlusive disease, chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy, high-risk surgery, hepatic disease, emergent or urgent surgery, and high body mass index.

Surgical risk factors include total vasopressor dose administered, use of a vasopressor infusion, and diuretic administration.<sup>34</sup> In addition, intraoperative hypotension is associated with a higher risk of AKI, major adverse cardiac events, and 30-day mortality.<sup>37</sup>

Noncardiac surgery patients with postoperative AKI have significantly higher rates of 30-day readmissions, 1-year progression to end-stage renal disease, and mortality than patients who do not develop AKI.<sup>35</sup> Additionally, patients with AKI have significantly higher rates of cardiovascular complications (33.3% vs 11.3%) and death (6.1% vs 0.9%), as well as a significantly longer length of hospital stay.<sup>34,36</sup>

### ■ CAN WE DECREASE THE IMPACT OF RENAL DISEASE IN SURGERY?

Before surgery, practitioners need to identify patients at risk of AKI, implement possible risk-reduction measures, and, afterward, treat it early in its course if it occurs.

The preoperative visit is the ideal time to assess a patient's risk of postoperative renal dysfunction. Laboratory tests can identify risks based on surgery type, age, hypertension, the presence of CKD, and medications that affect renal function. However, the basic chemistry panel is abnormal in only 8.2% of patients and affects management in just 2.6%, requiring the clinician to target testing to patients at high risk.<sup>38</sup>

Patients with a significant degree of renal dysfunction, particularly those previously undiagnosed, may benefit from additional preoperative testing and medication management. Perioperative management of medications that could adversely affect renal function should be carefully considered during the preoperative visit. In addition, the postoperative inpatient team needs to be informed about potentially nephrotoxic medications and medications that are renally cleared. Attention needs to be given to the renal impact of common perioperative medications such as nonsteroidal anti-inflammatory drugs, antibiotics, intravenous contrast, low-molecular-weight heparins, diuretics, ACE inhibitors, and angiotensin II receptor blockers. With the emphasis on opioid-sparing analgesics, it is particularly important to assess the risk of AKI if nonsteroidal anti-inflammatory drugs are part of the pain control plan.

Nephrology referral may help, especially for patients with a GFR less than 45 mL/min. This information enables more informed decision-making regarding the risks of adverse outcomes related to kidney disease.

### ■ WHAT TOOLS DO WE HAVE TO DIAGNOSE RENAL INJURY?

Several risk-prediction models have been developed to assess the postoperative risk of AKI in both cardiac and major noncardiac surgery patients. Although these models can identify risk factors, their clinical accuracy and utility have been questioned.

#### Biomarkers

Early diagnosis is the first step in managing AKI, allowing time to implement measures to minimize its impact.

**Serum creatinine testing** is widely used to measure renal function and diagnose AKI; however, it does not detect small reductions in renal function, and there is a time lag between renal insult and a rise in creatinine. The result is a delay to diagnosis of AKI.

Biomarkers other than creatinine have been studied for early detection of intraoperative and postoperative renal insult. These novel renal injury markers include the following:

**Neutrophil gelatinase-associated lipocalin (NGAL).** Two studies looked at plasma NGAL as an early marker of AKI in patients

**Serum creatinine is used to diagnose AKI, but it does not detect small reductions in renal function**



with CKD who were undergoing cardiac surgery.<sup>39,40</sup> One study found that by using NGAL instead of creatinine, postoperative AKI could be diagnosed an average of 20 hours earlier.<sup>39</sup> In addition, NGAL helped detect renal recovery earlier than creatinine.<sup>40</sup> The diagnostic cut-off values of NGAL were different for patients with CKD than for those without CKD.<sup>39,40</sup>

**Other novel markers** include:

- Kidney injury marker 1
- N-acetyl-beta-D-glucosaminidase
- Cysteine C.

Although these biomarkers show some ability to detect renal injury, they provide only modest discrimination and are not widely available for clinical use.<sup>41</sup> Current evidence does not support routine use of these markers in clinical settings.

## ■ CAN WE PROTECT RENAL FUNCTION?

Interventions to prevent or ameliorate the impact of CKD and AKI on surgical outcomes have been studied most extensively in cardiac surgery patients.

**Aspirin.** A retrospective study of 3,585 cardiac surgery patients with CKD found that preoperative aspirin use significantly lowered the incidence of postoperative AKI and 30-day mortality compared with patients not using aspirin.<sup>42</sup> Aspirin use reduced 30-day mortality in CKD stages 1, 2, and 3 by 23.3%, 58%, and 70%, respectively. On the other hand, in the Perioperative Ischemic Evaluation (POISE) trial, in noncardiac surgery patients, neither aspirin nor clonidine started 2 to 4 hours preoperatively and continued up to 30 days after surgery altered the risk of AKI significantly more than placebo.<sup>43</sup>

**Statins** have been ineffective in reducing the incidence of AKI in cardiac surgery patients. In fact, a meta-analysis of 8 interventional trials found an increased incidence of AKI in patients in whom statins were started perioperatively.<sup>44</sup> Erythropoietin was also found to be ineffective in the prevention of perioperative AKI in cardiac surgery patients in a separate study.<sup>45</sup>

The evidence regarding other therapies has also varied.

**N-acetylcysteine** in high doses reduced the incidence of AKI in patients with CKD

stage 3 and 4 undergoing CABG.<sup>46</sup> Another meta-analysis of 10 studies in cardiac surgery patients published recently did not show any benefit of N-acetylcysteine in reducing AKI.<sup>47</sup>

**Human atrial natriuretic peptide**, given preoperatively to patients with CKD, reduced the acute and long-term creatinine rise as well as the number of cardiac events after CABG; however, it did not reduce mortality rates.<sup>48</sup>

**Renin-angiotensin system inhibitors**, given preoperatively to patients with heart failure was associated with a decrease in the incidence of AKI in 1 study.<sup>49</sup>

**Dexmedetomidine** is a highly selective alpha 2 adrenoreceptor agonist. A recent meta-analysis of 10 clinical trials found it beneficial in reducing the risk of perioperative AKI in cardiac surgery patients.<sup>50</sup> An earlier meta-analysis had similar results.<sup>51</sup>

**Levosimendan** is an inotropic vasodilator that improves cardiac output and renal perfusion in patients with systolic heart failure, and it has been hypothesized to decrease the risk of AKI after cardiac surgery. Previous data demonstrated that this drug reduced AKI and mortality; however, analysis was limited by small sample size and varying definitions of AKI.<sup>52</sup> A recent meta-analysis showed that levosimendan was associated with a lower incidence of AKI but was also associated with an increased incidence of atrial fibrillation and no reduction in 30-day mortality.<sup>53</sup>

**Remote ischemic preconditioning** is a procedure that subjects the kidneys to brief episodes of ischemia before surgery, protecting them when they are later subjected to prolonged ischemia or reperfusion injury. It has shown initial promising results in preventing AKI. In a randomized controlled trial in 240 patients at high risk of AKI, those who received remote ischemic preconditioning had an AKI incidence of 37.5% compared with 52.5% for controls ( $P = .02$ ); however, the mortality rate was the same.<sup>54</sup> Similarly, remote ischemic preconditioning significantly lowered the incidence of AKI in nondiabetic patients undergoing CABG surgery compared with controls.<sup>55</sup>

**Fluid management.** Renal perfusion is intimately related to the development of AKI, and there is evidence that both hypovolemia and excessive fluid resuscitation can in-

**Preventive interventions have been studied, but none has been proven effective**

crease the risk of AKI in noncardiac surgery patients.<sup>56</sup> Because of this, fluid management has also received attention in perioperative AKI. Goal-directed fluid management has been evaluated in noncardiac surgery patients, and it did not show any benefit in preventing AKI.<sup>57</sup> However, in a more recent retrospective study, postoperative positive fluid balance was associated with increased incidence of AKI compared with zero fluid balance. Negative fluid balance did not appear to have a detrimental effect.<sup>58</sup>

## RECOMMENDATIONS

No prophylactic therapy has yet been shown to definitively decrease the risk of postoperative AKI in all patients. Nevertheless, it is important to identify patients at risk during the preoperative visit, especially those with CKD. Many patients undergoing surgery have CKD, placing them at high risk of developing AKI in the perioperative period. The risk is particularly high with cardiac surgery.

Serum creatinine and urine output should be closely monitored perioperatively in at-risk patients. If AKI is diagnosed, practitioners need to identify and ameliorate the cause as early as possible.

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TABLE 4

### Recommendations for perioperative prevention and management of acute kidney injury

Use isotonic crystalloids rather than colloids for volume expansion in the absence of hemorrhagic shock

Use vasopressors in conjunction with fluids to manage vasomotor shock in patients at risk of acute kidney injury

Use protocol-based management of hemodynamics and oxygenation parameters in high-risk patients in perioperative setting or patients in septic shock

Target a total energy intake of 20 to 30 kcal/kg/day in patients with acute kidney injury

Avoid nephrotoxic medications such as aminoglycosides

Use renal dosing for medications

Adapted from information in reference 15.

Recommendations from KDIGO for perioperative prevention and management of AKI are listed in Table 4.<sup>15</sup> These include avoiding additional nephrotoxic medications and adjusting the doses of renally cleared medications. Also, some patients may benefit from preoperative counseling and specialist referral.

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