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Perioperative Acute Kidney Injury: An Under-Recognized Problem

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The incidence of perioperative acute kidney injury (AKI) is more common than previously recognized, especially in high-risk patients undergoing higher risk procedures. The growing number of patients who develop perioperative AKI is related, in part, to the aging population and increase in the number of individuals with chronic comorbidities, particularly those with premorbid chronic kidney disease. Despite the acceptance of standardization in the definition of AKI, clinicians routinely underdiagnose it and fail to appreciate that it is associated with considerable morbidity and mortality. Unfortunately, few, if any, preemptive therapies have proven effective in preventing AKI. Timely diagnostic methods using evolving biomarkers raises the prospect of detection of kidney damage before the onset of irreversible loss of function, but remain under investigation. Clear evidence supporting any therapeutic intervention except renal replacement therapy remains elusive. Renal replacement therapy is indicated for select patients with progressive AKI; however, the ideal timing, method, and application of it remain under debate. It is fundamental to identify patients at risk for AKI. The Kidney Disease: Improving Global Outcomes guidelines suggest preventive strategies that include avoidance of nephrotoxic agents and hyperglycemia, optimization of hemodynamics, restoration of the circulating volume, and institution of functional hemodynamic monitoring. Clear evidence in support of this approach, however, is lacking. Recently, the perioperative administration of dexmedetomidine and the provision of remote ischemic preconditioning have been studied to potentially limit the development of perioperative AKI. This review discusses accepted standard definitions of AKI, highlights associated risk factors for its development, and provides an overview of its epidemiology and pathology. It emphasizes potential preventive strategies, the possible role of emerging biomarkers in defining its presence more expeditiously before irreversible injury, and current recommended guidelines and therapeutic approaches. The ultimate goal of this article is to bring to the attention of clinicians the seriousness of this potentially preventable or modifiable perioperative complication. (Anesth Analg 2017;125:1223–32)

The considerable morbidity and mortality associated with perioperative acute kidney injury (AKI) is well documented,[1] but AKI remains an underdiagnosed and misunderstood disease. The development of consensus criteria (Risk, Injury, Failure, Loss, End Stage Renal Disease [RIFLE] criteria [2004]; Acute Kidney Injury Network [AKIN] criteria [2007]; Kidney Disease: Improving Global Outcomes [KDIGO] criteria [2012]) has drawn more attention toward this serious clinical condition. AKI has been diagnosed increasingly over the past 2 decades. An estimated 2%–18% of hospitalized patients[2,3] and between 22% and 57% of intensive care unit patients develop AKI during their hospital admission.[4,5]

AKI does not always progress to renal failure requiring renal replacement therapy (RRT). Full recovery to baseline function may not occur. Even small acute increases in creatinine concentration, historically viewed as trivial, can result in short- and long-term complications including infections and bleeding,[6,7] chronic kidney disease (CKD),[8] end-stage renal disease, cardiovascular diseases,[9,10] and death.[11] It is noteworthy that development or progression of chronic disorders after an episode of AKI has major socioeconomic and public health effects.[12,13] A recent large-scale cohort study of 10,518 patients with no history of CKD undergoing major surgery observed a 30-day mortality of 1.9% in patients not suffering from AKI, compared with 31% in those with AKI.[14] Despite research efforts, outcomes of perioperative AKI and its related long-term sequelae have remained largely unaltered.[15] Since treatment options are limited, reliable risk assessment, prevention, and symptomatic relief remain the mainstay of improving patient outcomes.[16]

The purpose of this review is to discuss the definition, epidemiology, risk factors, prevention, and subsequent management of AKI during the perioperative period in different surgical settings, with a special emphasis on early diagnosis and the emerging role of new biomarkers.

DEFINITION AND DIAGNOSIS

Terms such as acute renal failure, acute kidney disease, acute kidney syndrome, or AKI have been used in the past to describe kidney dysfunction arising from acute conditions.

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AKI diagnosis and research was plagued by dozens of different and inconsistent definitions. Ultimately, in 2004, the Acute Dialysis Quality Initiative released the RIFLE criteria, which replaced the term "acute renal failure" and introduced the term "AKI" to indicate the reversibility of the acute condition.[17] Subsequently, the RIFLE criteria rapidly gained wide acceptance to define AKI. They were based on changes in serum creatinine (sCr) from baseline or urine output. The diagnostic system differentiates 3 severity grades (risk, injury, failure) and 2 outcome classes (loss, end-stage renal disease) (Table 1). At the time of its introduction, the concept of AKI was attractive because it included patients without actual structural kidney damage but with functional impairment. This group of patients may benefit significantly from early therapeutic interventions. Despite strengths of the RIFLE classification, the obvious discrepancy between increases in sCr concentration and decreases in estimated glomerular filtration rate (GFR) remained problematic.[18] In 2007, the AKIN suggested a modification of the RIFLE criteria, in an attempt to improve their sensitivity.[15] The bar for diagnosing AKI was significantly lowered (for details see Table 1). In 2012, the Acute Kidney Injury Working Group of KDIGO released the latest classification system with the aim of unifying the RIFLE and AKIN criteria.[19] Figure 1 displays the current AKI diagnosing criteria.

INCIDENCE AND EPIDEMIOLOGY

Until recently, the lack of a standard definition for AKI resulted in large variations in reported incidence and mortality. Therefore, the review focuses on data published after release of the RIFLE criteria in 2004. In the United States, the overall incidence of AKI is estimated at 2147 cases per million population per year.[20] This translates to approximately 600,000 AKI patients annually. It can be assumed that 10% to 20% of these patients progress to late-stage CKD, resulting in up to 120,000 cases of CKD in addition to the population at risk for end-stage renal failure.[21] The incidence of AKI in hospitalized patients increased continuously from 4.9% in 1983[22] to 7.2% in 2002[23] and to 20% in 2012.[24] A recent analysis of 19,249 acute care hospitalizations reported an AKI incidence of 22.7% over a 1-year period.[24] In critically ill patients, AKI is even more common, and could affect up to 60%.[13] A systematic review identified 24 studies including over 71,000 patients in which the RIFLE classification was used to define AKI.[25] The overall mortality rate was 18.9% in the "risk" class, 36.1% in the "injury" class, and 46% in the "failure" class compared with 6.9% mortality in patients not suffering from AKI.

Approximately 30%–40% of all cases of AKI cases occur after surgery. The incidence of AKI in surgical patients ranges from 18% to 47%.[26–28] Some surgical patient populations deserve special consideration because they are exposed to distinct risk factors inherent to the type of surgery. AKI is most common among cardiac surgery patients, in whom cardiopulmonary bypass (CPB) is used. These patients face a unique combination of renal stressors. Rates of AKI for elective patients are in the range of 15%, with 2% requiring RRT.[29] But also in noncardiac surgery, AKI occurred in approximately 1% of those patients with preoperative normal kidney function.[30] Certain noncardiac surgery procedures pose a particular high risk:

- gastric bypass surgery for morbid obesity is associated with an 8.5% incidence of AKI[31];
- one-third of the patients receiving liver transplant experience postoperative AKI, with 17% requiring RRT[32];
- patients with preexisting CKD showed a significantly increased AKI risk than the average 1%.

Patients who develop AKI during the course of surgery demonstrate an 8-fold increased risk for the progression to CKD.[21]

PATHOPHYSIOLOGY

The development of perioperative AKI is not caused by 1 single factor but is precipitated by a variety of insults. Hypoperfusion and inflammation are the major mechanisms affecting renal function.

Hypovolemia frequently develops in the perioperative period and may reduce the mean arterial pressure (MAP), resulting in renal hypoperfusion. Initially, the kidneys are able to maintain the GFR through activation of the sympathetic nervous system, which includes the excretion of antidiuretic hormone and angiotensin-II. Persistent hypoperfusion precipitates a decrease in GFR secondary to vasoconstriction of both afferent and efferent arterioles. This compensatory effect depends on the autoregulatory capabilities of the kidneys and is reduced in patients with chronic renal impairment.[33] Systemic inflammation, a uniform response of the organism to the trauma of surgery, leads to tubular injury causing AKI.[34] Tubular damage is caused by microcirculatory dysfunction, better leukocyte migration, and endothelial dysfunction.[35]

Irrespective of the acute effects of hypoperfusion and inflammation, the patient's preoperative clinical condition, intraoperative risk factors, and perioperative conditions impact on renal function.

Risk Factors for the Development of AKI

A number of risk factors predispose for AKI. However, patient-related factors are more strongly associated with mortality than the type of surgery (Table 2).

Table 1. Definitions of AKI

AKI Stage	SCr Criteria	UO Criteria
RIFLE R (risk)	Increase sCr × 1.5 or GFR decrease >25%	UO < 0.5 mL/kg/h for 6 h
RIFLE I (injury)	Increase sCr × 2.0 or GFR decrease >50%	UO < 0.5 mL/kg/h for 12 h
RIFLE F (failure)	Increase sCr × 3.0 or GFR decrease >75% or sCr > 4 mg/dL	UO < 0.5 mL/kg/h for 24 h or anuria for 12 h
RIFLE L (loss)	Complete loss of kidney function for >4 wk	
RIFLE E (ESKD)	ESKD for >3 mo	
AKIN stage 1	Increase sCr of ≥ 0.3 mg/dL or increase ≥150%–200% from baseline	UO < 0.5 mL/kg/h for more than 6 h
AKIN stage 2	Increase sCr > 200%–300% from baseline	UO < 0.5 mL/kg/h for more than 12 h
AKIN stage 3	Increase sCr > 300% from baseline or sCr ≥ 4.0 mg/dL with acute increase ≥0.5	UO < 0.3 mL/kg/h or anuria for 12 h

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; RIFLE, Risk, Injury, Failure, Loss, End Stage Renal Disease; sCr, serum creatinine; UO, urine output.

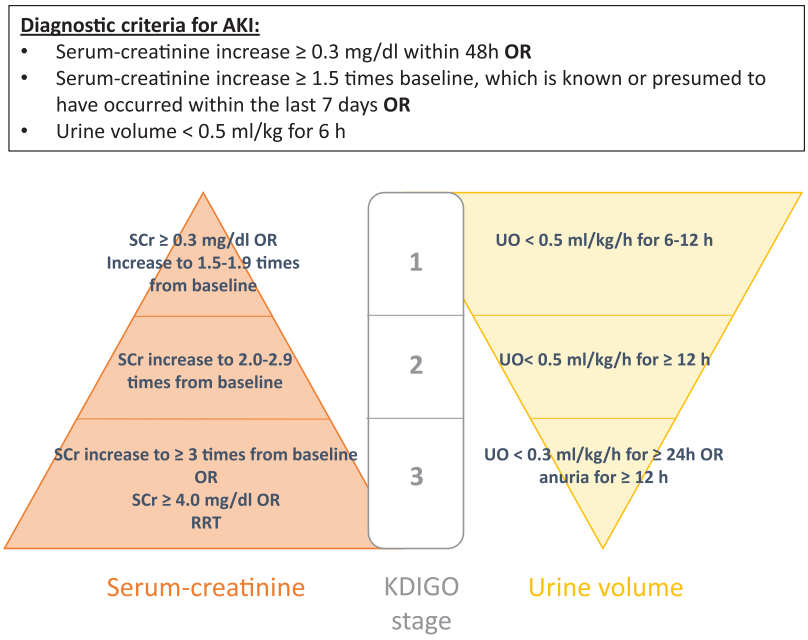

Figure 1. AKI diagnostic criteria. KDIGO criteria for the diagnosis of AKI. AKI indicates acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy; sCr, serum creatinine; UO, urine output.

Table 2. Risk Factors for the Development of Postoperative AKI

Preoperative Risk Factors	Intraoperative Risk Factors
Age	Duration of surgery
Female sex	Intraperitoneal surgery
Body mass index	Repair of abdominal aortic aneurysm
Hypertension	Intraoperative hypotension
Chronic kidney disease	Transplantation of solid nonrenal organs
Insulin-requiring diabetes mellitus	Transfusion of packed red blood cells
Chronic obstructive pulmonary disease	Intraabdominal hypertension
Peripheral vascular disease	Length of cardiopulmonary bypass (cardiac surgery)
Cerebrovascular disease	Cross-clamp time (cardiac surgery)
Congestive heart failure	Hemodilution (cardiac surgery)
Sepsis	Use of intraaortic ballon pump
Ascites	Type of cardiac surgical procedure
	Nephrotoxic agents (eg, antibiotics, contrast agents)

Abbreviation: AKI, acute kidney injury.

Preoperative Risk Factors. The ageing society combined with the growing number of comorbidities displays a tremendous burden. Comorbidities (eg, CKD, diabetes mellitus, chronic obstructive pulmonary disease, and cardiovascular disease) are strongly associated with the development of AKI.[36–38] The most important patient-related factor is the preoperative level of kidney function. In cardiac surgery, rates of AKI requiring RRT approach 30% in patients with preexisting CKD.[36] Older obese female patients are particularly susceptible to developing AKI.[39,40] A recent study demonstrated a strong statistical association between body mass index (BMI) and perioperative AKI after cardiac surgery.[41] The odds of AKI increased by 26.5% per 5 kg/m^2 BMI. The authors claimed that BMI influenced AKI in part by oxidative stress. It is important to take into account that drugs with nephrotoxicity such as angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, aminoglycosides, and nonsteroidal antiinflammatory drugs increase the development of AKI.

Intraoperative Risk Factors. Cardiac surgery facilitated by CPB has the highest risk followed by general, thoracic, orthopedic, vascular, and urological surgery.[42] Patients with sepsis who undergo surgery or those requiring emergency procedures have higher rates of postoperative AKI when compared with elective procedures.[37]

CPB and aortic cross clamping, ischemia reperfusion injury, low cardiac output, prolonged periods of hypotension, use of vasopressors, and inotropic support are associated with the development of AKI. CPB is associated with systemic inflammatory response, coagulopathy, and embolism. The perioperative risk of AKI increases with longer duration of CPB. Avoiding CPB by off-pump techniques may reduce AKI and long-term renal outcomes.[43–46] A recent meta-analysis of 27,806 patients from 22 observational and randomized trials of patients undergoing on-pump versus off-pump cardiac surgical procedures[47] observed a 43% risk reduction for AKI associated with off-pump surgery (odds ratio: 0.57, 95% confidence interval [CI], 0.43–0.76), suggesting off-pump coronary artery bypass as a viable alternative for high-risk patients. Prospective studies are warranted to arrive at definitive conclusions. The most important strategy in cardiac surgical patients is the use of risk-predicting models[36,39,48] to detect high-risk patients preemptively to allow timely initiation of preventive strategies.

In vascular surgery, factors that prolong the duration of renal ischemia and intraoperative hypotension are key determinants of postoperative AKI. Newer techniques, such as endovascular aneurysm repair, may be superior to conventional approaches preventing AKI development.[49] In abdominal surgery, 1 major problem is intraabdominal hypertension. While the transient increase of intraabdominal pressure during laparoscopic surgery with a reduction of urinary output is not predictive for postoperative AKI,[50,51] longer periods of elevated intraabdominal pressure

resulting from fluid overload with diffuse edema of the intestinal wall frequently cause an abdominal compartment syndrome. The related compression of the renal vasculature induces renal ischemia and the development of AKI.[52,53]

Perioperative Conditions

Prolonged episodes of hypotension decrease renal perfusion and result in AKI in patients with impaired autoregulation.[54] A MAP in the range of 60–75 mm Hg was accompanied by improved oxygen saturation and GFR and prevented AKI.[55] Moreover, the duration of hypotensive episodes should thus be kept as short as possible.[56] To this date, it is not known which vasopressor is most effective in the prevention of AKI. Guidelines recommend to use primarily norepinephrine for restoration of MAP. In an experimental model, it has been demonstrated that norepinephrine effectively increases global and medullary pressure resulting in higher diuresis.[57] However, an optimal perfusion pressure for individual patients cannot be specified because the autoregulatory range of renal perfusion is dependent on underlying diseases and premorbid conditions.

Nephrotoxic agents such as antihypertensive drugs (angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers), antibiotics (eg, aminoglycosides), nonsteroidal antiinflammatory drugs, or loop diuretics are well known to induce AKI. Additionally, a significant number of patients are exposed to contrast agents, promoting the development of contrast-induced AKI. The development of contrast-induced AKI depends on factors such as type and dose of contrast agent, underlying CKD, age, or hydration status.[58,59]

Significant anemia lowers oxygen supply to tissues as a consequence of the reduced oxygen-carrying capacity of the blood. Subsequent renal hypoxia is a contributing factor in the development of AKI. Studies revealed that preoperative anemia with hemoglobin levels <8 mg/dL is associated with an up to 4-fold increased risk of AKI.[60,61] Similarly the transfusion of packed red blood cells correlates with AKI,[62–64] giving rise to serious concerns about how to manage anemia.

Emerging Role of Damage Markers

SCr and urine output are functional biomarkers changing late during the development of AKI. However, both markers are constrained by limitations. SCr changes only become evident after 50% of the total renal mass is compromised, resulting in late GFR declines. Transient changes will never become evident although damage has occurred. Urine output does not allow an early detection of renal dysfunction, although recent literature shows a significant association of low urine output and adverse outcomes in adults[65] and pediatric patients.[66] Therefore, current research activities aim to identify new biomarkers, which are released before sCr increases and/or urinary output declines (Figure 2).[67–69] Meanwhile, studies have shown that new biomarkers can detect subclinical AKI in the presence of early tubular damage but before the emergence of filtration dysfunction.[67,68]

The production and release of possible biomarkers of early tubular stress is triggered by surgical trauma, CPB, or other noxious events. Different biomarkers relate to different aspects of kidney function and different mechanisms of injury. They might help to detect AKI earlier in its course, identify the underlying etiology, and even tailor-specific therapeutic interventions. Several issues have to be addressed before these biomarkers can be introduced into daily clinical routine. The most important ones are the lack of sensitivity that is related to the etiological heterogeneity of AKI, and the lack of specificity that seems related to extrarenal causes for fluctuations in serum or urine concentrations of the biomarkers.[70] Renal biomarker performance was most promising when well-defined kidney injury, such as exposure to radiocontrast agents or after particular operations, was examined.[71] In more heterogeneous populations with variable onset of kidney injury biomarkers perform less well. Recently, Mårtensson and Bellomo[72] called for the use of biomarker panels instead of single molecules in addition to clinical risk models to augment the robustness of predicting postoperative AKI.

Neutrophil-gelatinase–associated lipocalin (NGAL), tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor binding protein 7 (IGFBP7) are promising[73] and have been introduced into clinical medicine. NGAL is almost undetectable in the urine of healthy individuals. After ischemic or nephrotoxic insults, a significant increase in plasma and urine occurs, prompting the notion that NGAL is the "troponin" of the kidneys.[74] However, the etiology of AKI is multifactorial and not limited to ischemia. Studies investigating the predictive performance of NGAL are controversial, with some judging the performance as near ideal while others considered it useless.[75,76] Explanations for the divergent results are poor performance of the gold standard sCr and urine output as well as the timing of biomarker assessment and preexisting comorbidities, because NGAL can predict AKI only in patients with prior normal kidney function.[77] Furthermore, a variety of NGAL isoforms are released from different tissues[78] and current point of care tests are not able to distinguish between these. Therefore, the clinical utility of NGAL has been challenged.

Cell cycle arrest of renal tubular epithelial cells is involved in the pathogenesis of AKI,[79] suggesting that cell cycle arrest–related proteins could aid early AKI detection (Figure 3). The cell cycle consists of 2 phases. The interphase—which is mainly the preparatory phase for DNA synthesis—consists of the gap-1 (G1), synthesis (S), and gap-2 (G2) phase. During the mitotic (M) phase the cell divides. In case of tubular stress, renal tubular epithelial cells arrest in G1 phase to avoid DNA damage during division of cells.[80] TIMP-2 and IGFBP7 are released during G1 arrest and are detectable very early during development of AKI.[71,73] It appears that TIMP-2 and IGFBP7 predict mortality, renal recovery, and severity of AKI.[81]

In analogy to the "angina pectoris" concept for myocardial ischemia, the "renal angina" concept was introduced in 2010 to identify patients at high risk for AKI. In contrast to acute coronary syndromes, AKI does not show any visceral symptoms. Therefore, the "renal angina" concept combines comorbidities with clinical conditions and biomarkers. According to this concept, the measurement of damage biomarkers in patients with certain comorbidities and clinical conditions considerably improves the negative predictive value of these markers.[82] The combination of TIMP-2*IGFBP7 has recently been recommended for the diagnosis of AKI in an appropriate patient population

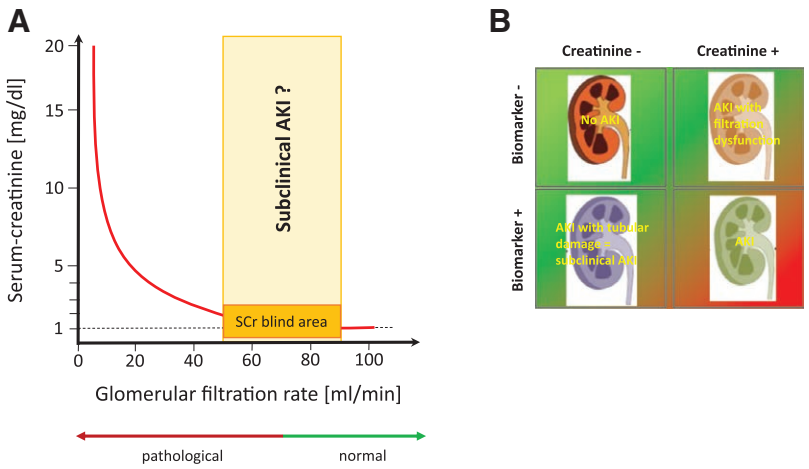

Figure 2. Subclinical and clinical AKI. A, GFR and sCr relationship. SCr changes become apparent when GFR is reduced by 50%. There is a creatinine blind area where changes are not apparent but subclinical AKI may have occurred. B, Diagnosis of AKI based on functional (sCr) and damage markers (new biomarkers). The use of damage biomarkers allows an early diagnosis of subclinical AKI. AKI indicates acute kidney injury; GFR, glomerular filtration rate; sCr, serum creatinine.

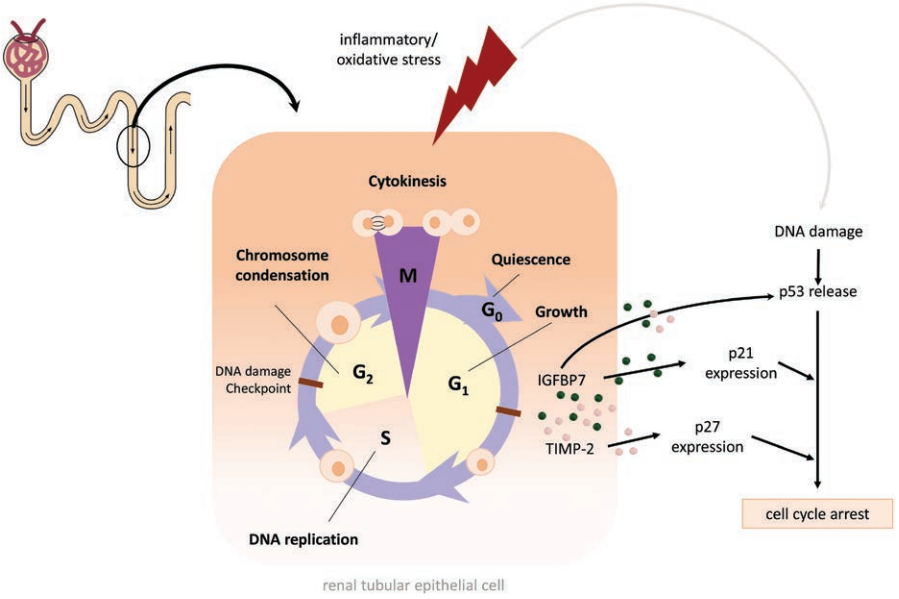

Figure 3. Cell cycle and [TIMP-2]*[IGFBP7]. Inflammatory or oxidative stress results in DNA damage of renal tubular epithelial cells. This leads to a release of TIMP-2 and IGFBP7. TIMP-2 enhances the expression of p27; IGFBP7 conducts an expression of p53 and p21 all leading to G_1-cell cycle arrest. G_0 indicates gap_0 phase = rest phase; G_1, gap_1 phase = cell grow phase; G_2, gap_2 phase = cell grow phase; IGFBP7, insulin-like growth factor binding protein 7; M, mitotic phase; p, protein; S, DNA synthesis phase; TIMP-2, tissue inhibitor of metalloproteinases-2.

(intensive care unit patients, age ≥21 years with 1 further risk factor for AKI, after cardiac bypass or other major high-risk surgery or with sepsis).[83] Based on current evidence it is important to note that the measurement of biomarkers should be restricted to patients at high risk for the development of AKI, but may not be useful in patients with already established AKI. In these patients, furosemide stress test might be more meaningful.[84]

OPTIONS TO PREVENT AKI

Despite some progress, the search for strategies to prevent the development of AKI remains in the introductory stage.

Pharmacological Interventions

Development of successful pharmacological interventions to prevent and manage AKI has been limited. Table 3 provides an overview of the different types and classes of pharmacological agents that have been studied extensively.

Dexmedetomidine, a highly selective α-2 agonist, has been introduced into perioperative practice due to its sedative, analgesic, and anxiolytic effects. Other beneficial effects such as reduced norepinephrine release, improved hemodynamic stability, and balancing of the myocardial oxygen supply/demand ratio could be demonstrated, prompting the presumption of beneficial effects on renal function. Animal studies demonstrated cytoprotection during renal ischemia and inhibition of hypoxemia-induced apoptosis of proximal tubular cells.[85] The renoprotective properties of dexmedetomidine were confirmed in recent clinical trials in cardiac surgery, demonstrating a significant reduction of AKI in patients with preoperative normal or mild impairment of kidney function.[86–88] In a randomized placebo-controlled trial in 200 patients undergoing valvular heart surgery, the incidence of AKI and a composite of major morbidity end points during the first 48 postoperative hours[89] were significantly improved when dexmedetomidine was compared with placebo (14% vs 33%; odds ratio [OR], 0.33; 95% CI, 0.164–0.667; P = .002). The authors concluded that preemptive dexmedetomidine infusion provides sympatholysis, which might be beneficial for preventing AKI. Another trial demonstrated a dose-dependent effect of dexmedetomidine with the lowest increase in NGAL in the group treated with the higher dexmedetomidine dose, suggesting a beneficial effect on structural AKI.[90] Use of

Table 3. Pharmacologic Prevention of Perioperative AKI

Vasoactive Agents and Diuretics	Cryoprotective Therapy
Dopamine	Dexmedetomidine[a]
Fenoldopam	Proinflammatory cytokines
Theophylline	Steroids
Recombinant atrial natriuretic peptide	*N*-acetylcysteine
Angiotensin-converting enzyme inhibitor	Intensive glucose control by insulin infusion
Angiotensin-II receptor antagonists	HMG-CoA reductase inhibitors (statins)
Furosemide	Sodium bicarbonate

Abbreviations: AKI, acute kidney injury; HMG-CoA, 3-hydroxy-3-methylglutaryl -coenzyme.
[a]Promising pharmacologic option, more evidence needed.

dexmedetomidine to prevent AKI appears promising, but data remain insufficient to make a clear recommendation.

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are used to primarily reduce cholesterol levels in the prevention of cardiovascular diseases and may reduce the incidence of AKI due to their pleiotropic effects. However, recently published data did not support this hypothesis.[91,92] Billings et al[92] randomized 615 patients undergoing cardiac surgery to receive atorvastatin or placebo before, during, and after surgery. Among all participants, AKI occurred in 20.8% in the atorvastatin group versus 19.5% in the placebo group (relative risk, 1.06 [95% CI, 0.78–1.46]; $P = .75$). The study was stopped for futility but the pretreatment of 416 patients with statin may have influenced the outcome. A recent population-based study examined over 200,000 major surgical procedures, and arrived at different conclusions.[93] AKI was found in 1.9% of the patients and 0.5% required RRT during the first 14 postoperative days. The 30-day mortality rate was 2.8%. Statin use was associated with a 16% lower odds of postoperative AKI (OR, 0.84), 17% lower odds of RRT (OR, 0.83), and 21% lower odds of mortality (OR, 0.79). The results showed, according to the authors, beneficial effects of perioperative statin use on important renal complications after major surgery. A general recommendation regarding statin use for AKI cannot be made or refuted, because evidence from prospective trials is lacking.[16]

Sodium bicarbonate was thought to have protective effects on the kidneys through urinary alkalization.[94] However, large randomized controlled trials demonstrated no beneficial effects of sodium bicarbonate.[95,96]

Taken together, apart from dexmedetomidine to date no pharmacologic treatment that has been tested in clinical trials holds promise for the prevention of AKI in perioperative patients.

KDIGO Guidelines

The KDIGO guidelines propose a bundle of preventive strategies for patients at high risk for the development of AKI. This bundle includes discontinuation and avoidance of nephrotoxic agents, alternatives to radio contrast agents, maintenance of volume status and perfusion pressure, maintenance of normoglycemia, monitoring of sCr and urine output, and functional hemodynamic monitoring.[97] Until now it has not been unequivocally proven that implementing the KDIGO bundle improves renal outcomes, but initial evidence has recently been presented. A single-center, randomized controlled clinical trial (PrevAKI) demonstrated that biomarker-guided implementation of the KDIGO guidelines as compared with standard care significantly reduced the occurrence of AKI in cardiac surgery patients (absolute risk reduction, 16.6% [95 CI, 5.5%–27.9%]; $P = .004$; intervention described in Figure 4).[98]

As previously mentioned, the application of nephrotoxic agents is associated with AKI. Surgical patients are frequently exposed to contrast agents or antiinflammatory drugs. Avoidance of these agents prevents AKI.

To prevent arterial hypotension and related drops in renal blood flow, intravascular volume status has to be optimized. The choice of intravenous fluids plays an important role in the development of AKI. Frequently, isotonic saline 0.9% is regarded as first-line treatment. However, it contains unphysiologically high amounts of chloride, causing hyperchloremic acidosis and renal vasoconstriction, resulting in a reduced GFR[99] and a higher incidence of AKI.[100] A chloride restrictive infusion regimen is therefore associated with a significantly reduced incidence of moderate and severe AKI.[101] Thus, balanced crystalloid solutions with electrolyte compositions compared with plasma should be preferred for volume resuscitation.

Arterial hypotension is a frequent result of hypovolemia, but also occurs in association with multiple other etiologies. AKI is associated with intraoperative hypotension in a graded fashion.[56,102] A large retrospective cohort study of 5127 patients undergoing noncardiac surgery observed AKI when MAP during surgery was <60 mm Hg for more than 20 minutes and <55 mm Hg for more than 10 minutes (adjusted OR, 2.34 [95% CI, 1.35–4.05]).[56]

Tight glycemic control has been shown to significantly reduce AKI in critically ill patients.[103] Subsequently, it has been ruled out in cardiac surgery patients that tight glycemic control is superior to continuous perioperative insulin therapy in terms of AKI incidence and mortality. This has been underlined by several well-conducted clinical trials.[104,105]

Remote Ischemic Preconditioning

Ischemic preconditioning was first described in animals with myocardial infarction in 1986.[106] Subsequently, it could be demonstrated that protective effects of brief periods of ischemia were not locally limited to the organ or tissue receiving the preconditioning stimulus, but were also detectable in remote tissues.[107–109] This phenomenon has been termed remote ischemic preconditioning (RIPC). RIPC is an effective and uncomplicated maneuver to trigger the endogenous protection against hypoxic injuries. It consists of transient episodes of sublethal ischemia, followed by reperfusion. The RIPC stimulus is applied to a remote tissue before the subsequent and definitive ischemic injury to the target organ occurs.

Ischemia reperfusion injury is a significant clinical problem, and the kidney is particularly susceptible to it because of its high metabolic rate and complex vascular anatomy.[110] Twenty minutes of ischemia have been shown to cause irreversible kidney damage. To protect the kidney against an ischemia reperfusion injury, a RIPC stimulus is applied to a distant organ. Use of the

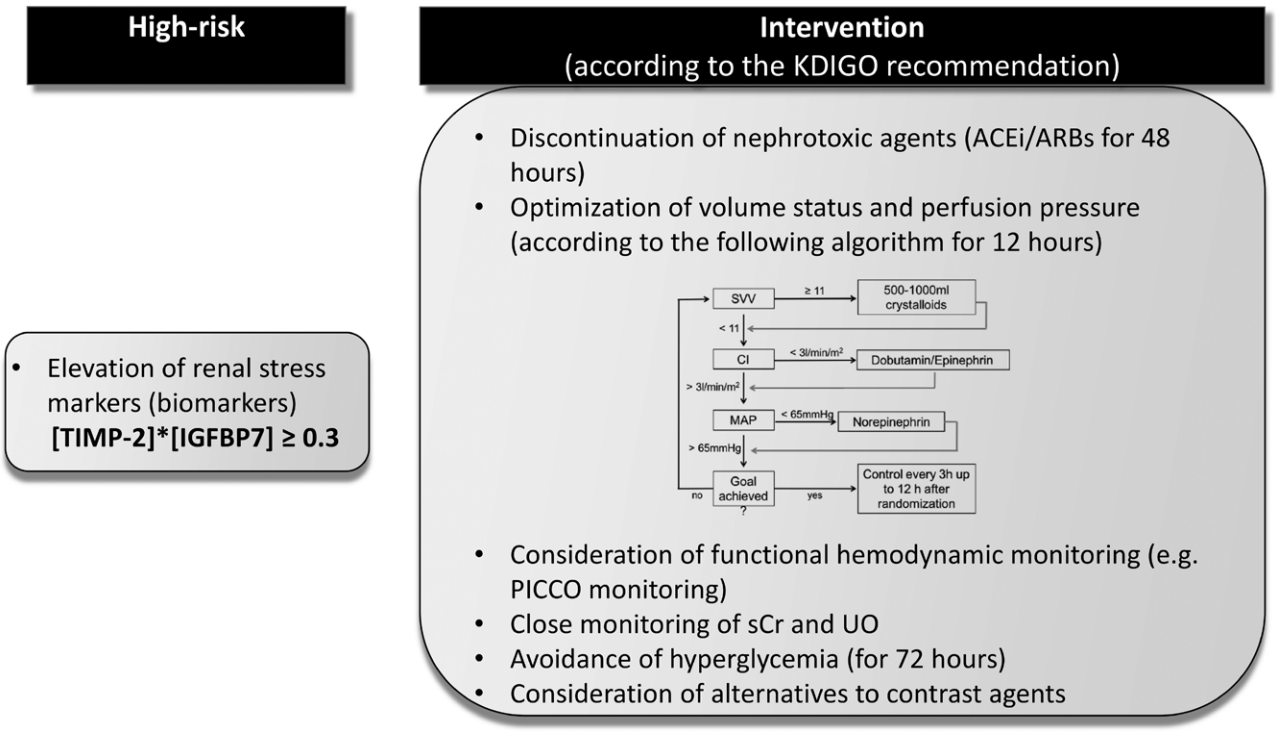

Figure 4. Preventive strategy performed in the PrevAKI trial (interventional arm). In the PrevAKI trial, patients at high risk for the development of AKI were defined using the biomarkers [TIMP-2]*[IGFBP7] ≥ 0.3. The interventional arm was treated according to the recommendation of the KDIGO guidelines (discontinuation of nephrotoxic agents, optimization of volume status and hemodynamics, consideration of functional hemodynamic monitoring, close monitoring of sCr and urine output, avoidance of hyperglycemia, and consideration of alternatives of radiocontrast agents). ACEi indicates angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin-II receptor blocker; CI, cardiac index; IGFBP7, insulin-like growth factor binding protein 7; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure; sCr, serum creatinine; SVV, stroke volume variation; TIMP-2, tissue inhibitor of metalloproteinases-2; UO, urine output.

upper limbs as remote tissue is the established method, as skeletal muscle is less susceptible to ischemia reperfusion injury compared with the kidney. Typically, a blood pressure cuff around the upper arm is inflated to a pressure of 30 mm Hg above the systolic blood pressure for a period of 5 minutes. Thereafter the pressure is released for 5 minutes. The inflation/deflation cycle is repeated 3 times. The underlying molecular mechanisms of RIPC are not fully understood, but the definitive protective step in RIPC signaling is the inhibition of opening of the mitochondrial permeability transition pore, which prevents cell death.[110]

Several clinical trials have been performed to investigate the effects of RIPC on kidney function especially in patients after cardiac surgery. Beneficial effects of RIPC on the occurrence of AKI in the postoperative period could be demonstrated in some randomized controlled trials[111,112] whereas others showed no effect.[113,114] The results of the trials are hard to compare due to the heterogeneity of the patient population and the use of different end points. However, in this context, it is important to mention that certain anesthetics such as propofol reverse the protective mechanisms of RIPC.[115] The use of propofol might be 1 possible explanation for the different study outcomes. In the face of contradictory study results, the fact that RIPC is easy to apply, does not impose additional costs, and is not associated with complications tips the balance in favor of RIPC,[114] and RIPC should be considered as part of the preventive management plan for high-risk patients.

Renal Replacement Therapy

In severe AKI, RRT is the only therapeutic option. RRT modalities include intermittent hemodialysis, as well as continuous and intermittent hemofiltration and hemodiafiltration. The ideal mode of RRT, timing of initiation, and duration remain open to investigation. The KDIGO guidelines recommend initiation of RRT when life-threatening fluid accumulation or significant imbalances (eg, acidosis, various electrolyte abnormalities, and uremic pericardial effusion) occur.[97] However, most patients develop severe AKI without life-threatening complications and the initiation of RRT primarily remains at the discretion of the intensivist. Starting RRT late during the course of AKI while awaiting life-threatening complications implies the possibility that at that time AKI is already irreversible. On the other hand, early institution of RRT imposes the additional risks and complications of an invasive therapeutic procedure, without being sure that there is sufficient therapeutic benefit.

In the past, several studies have addressed this issue but have not arrived at definitive conclusions, because of different definitions of "early" or "late" initiation of RRT.[116] Recently, 2 randomized controlled trials defining AKI via KDIGO criteria have been published.[117,118] The Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with AKI (ELAIN) trial compared a (biomarker supported) strategy of initiation of RRT at KDIGO stage 2 versus KDIGO stage 3. The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial compared the initiation at KDIGO stage 3 versus KDIGO stage 3 plus clinical indication. The results

of these studies demonstrate that early initiation at a moderate stage (KDIGO 2) improves patients' outcome while the initiation at a severe stage (KDIGO 3 and KDIGO 3 plus clinical indication) may be too late during AKI development. One could argue that patients with moderate AKI may have recovered without RRT and were unnecessarily exposed to an invasive procedure. However, an approach that addresses only high-risk patients identified by both clinical risk scores and modern biomarkers[82,118] allows for early initiation of RRT while at the same time avoiding its unnecessary execution.

CONCLUSIONS

The development of AKI is under-recognized but has significant potential consequences for perioperative patient outcomes. The pathophysiology of AKI is complex. Its prevention requires a multimodal approach. Effective preventive strategies rely on the identification of patients at high risk through the use of clinical scoring systems. The early detection of AKI with the use of damage biomarkers is gaining more acceptance and will probably be included in the next AKI guidelines. Drug treatment still does not play a role in the prevention of AKI, and renoprotective interventions remain limited to adherence to the KDIGO guidelines. Initial evidence suggests that RIPC may be effective for the prevention of AKI and can be considered in high-risk patients. If preventive strategies fail, early initiation of RRT at KDIGO stage 2 seems to offer advantages for high-risk patients.

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