of care needed to maximize both the survival and the well-being of the patients. Thereafter, this optimal dose of renal care could be refined according to special patient characteristics. Finally, we can consider that such optimized care might also allow an improvement in later prognosis.

In conclusion, the findings of the two present studies represent a step forward in the description of early mortality in dialysis patients and the understanding of factors able to influence it. Moreover, they show the crucial multidimensional nature of the adequacy of predialysis renal care in preventing premature patient death in the early dialysis period by revealing the effect of the number and timing of nephrology consultations during the predialysis period. These noteworthy results are likely to help in controlling the excessive mortality that affects dialysis patients worldwide, for which only marginal progress has been recorded for two decades.

DISCLOSURE
The authors declared no competing interests.

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Propofol as a panacea for acute kidney injury?

Lindsey L. Huddleston[1] and Kathleen D. Liu[2,3]

Yoo and colleagues report a small but provocative randomized clinical trial to prevent acute kidney injury in the setting of cardiopulmonary bypass surgery. Their article describes a trial of 112 patients undergoing valvular surgery with cardiopulmonary bypass who were randomized to receive sevoflurane (an inhaled anesthetic) or propofol for general anesthesia. The use of propofol was associated with a significant decrease in the rate of postoperative acute kidney injury.

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Acute kidney injury (AKI) remains a significant cause of morbidity and mortality after cardiac surgery with cardiopulmonary bypass (CPB). Although the incidence of AKI severe enough to require dialysis in the postoperative period is relatively rare (<5%), milder degrees of AKI (for example, KDOQI or AKIN stage 1 disease, defined as an absolute increase in serum creatinine of 0.3 mg/dl or a relative increase in serum creatinine of more than 50%[1]) are much more common, with an incidence as high as 40% following coronary artery bypass grafting or valvular surgery.[2] Even these small changes in serum creatinine are associated with longer intensive care unit and hospital stays and are independent risk factors for mortality.[3] In addition, the annual rates of AKI after cardiac surgery are probably increasing. A recent cohort study examining trends in AKI after cardiac surgery found an increase in the annual rates of AKI from 4.5% in

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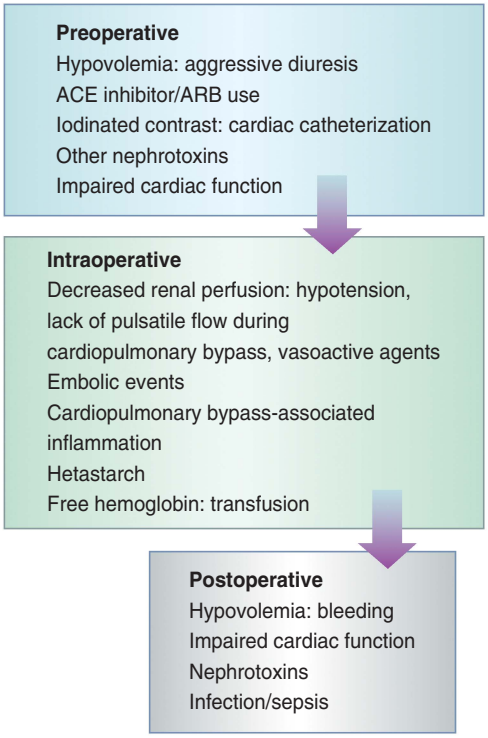

Figure 1 | Potentially modifiable risk factors for CPB-associated AKI. Although some risk factors for AKI are not modifiable (for example, chronic kidney disease), other risk factors are amenable to intervention or optimization prior to surgery (for example, delaying surgery after cardiac catheterization, optimizing cardiac function in the perioperative period). In their randomized clinical trial, Yoo *et al.*[10] hypothesize that CPB-associated inflammation can be reduced by the use of propofol as an anesthetic agent. ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CPB, cardiopulmonary bypass.

1999 to 12.8% in 2008.[4] The significant contribution to morbidity and mortality and the potentially increasing rate, coupled with limited treatment options, make prevention of AKI a major focus in the perioperative care of cardiac surgery patients.

Currently, no pharmacologic interventions have demonstrated effectiveness in prevention of AKI after cardiac surgery. This is probably secondary to the complicated pathogenesis of AKI after CPB, which has not been fully elucidated. It is thought to be multifactorial, with contributing factors including preoperative risk, hemodynamic disturbances during surgery, ischemia–reperfusion injury (IRI), hemodilution, and the proinflammatory state induced by surgery and CPB.[5] While the etiology of AKI after CPB is complex, there are multiple distinct targets in the perioperative period for potential interventions (Figure 1). One of these is to decrease or attenuate the inflammatory response provoked by CPB during the intraoperative period. During and after CPB, both neutrophils and vascular endothelial cells are activated, and upregulation of adhesion factors occurs. This inflammatory response is caused by a combination of reaction to contact of cells with the artificial bypass circuit, non-pulsatile blood flow, IRI, and surgical stress. Inflammatory markers including interleukin-6, interleukin-8, and tumor necrosis factor-α increase in circulation compared with baseline when measured immediately after CPB. In addition, hypotension, hypothermia, hemodilution, and non-pulsatile blood flow can all contribute to ischemia, which also leads to activation of renal endothelial cells and potentiates the inflammatory response.[6] Previous studies have shown that corticosteroids, leukocyte filter utilization, and miniaturized extracorporeal circuits decrease the inflammatory response after CPB; however, none of these factors have been associated with a decrease in the incidence of perioperative AKI.[7]

Given the lack of therapies to prevent CPB-associated AKI, there is interest in identifying other intraoperative strategies to prevent AKI. Anesthetic agents have been extensively investigated for their role in prevention of IRI and myocardial protection. Halogenated anesthetics such as isoflurane and sevoflurane have been shown to increase postischemic myocardial function after ischemic injury in animal models. This is thought, in part, to be related to a reduced number of neutrophils and platelets in the coronary vasculature in animals exposed to halogenated anesthetics before ischemic insult.[8] Propofol, a widely used intravenous anesthetic agent, has also been shown to have anti-inflammatory properties and to reduce IRI. In recent studies using animal models for IRI, propofol has been shown to reduce inflammatory markers to a greater extent than sevoflurane.[9]

Yoo *et al.*[10] (this issue) report the results of a randomized clinical trial examining the effect of propofol anesthesia on the incidence of AKI following valvular heart surgery with CPB. The authors hypothesized that propofol would reduce inflammation after CPB compared with sevoflurane and consequently be associated with lower rates of postoperative AKI. One hundred twelve patients scheduled to undergo valvular heart surgery were randomized to receive either propofol or sevoflurane anesthesia. The patients were well matched in regard to preoperative comorbidities and risk of development of AKI (based on both EuroSCORE and Cleveland Clinic assessments). Intraoperative anesthetic and management of CPB were standardized, and patients in both groups had similar CPB and aortic cross-clamping times and similar hemodynamics. The authors found a significant reduction in the occurrence of AKI in the group randomized to receive propofol (37.5% versus 10.7%, $P = 0.001$).

It is worth commenting on the selection of anesthetic technique for the two treatment arms. In general, anesthetic technique is not protocolized, and the investigators did an excellent job standardizing care across the two arms. However, a few elements of the experimental design are notable. The authors chose to use sevoflurane as their comparison anesthetic agent to propofol. Since its introduction, the safety profile of sevoflurane has been questioned secondary to potential nephrotoxic properties. Sevoflurane is metabolized into two products that are potentially nephrotoxic: inorganic fluoride ions and compound A (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether). However, numerous studies in animals and human subjects have failed to demonstrate fluoride-induced nephrotoxicity despite high concentrations of fluoride ions.[11] Compound A has been shown to be nephrotoxic in rats, causing necrosis of the tubules at the corticomedullary junction. Despite the nephrotoxicity seen in rats, numerous studies have demonstrated the safety of sevoflurane and the absence of kidney injury when it is administered at low flow rates, even for prolonged periods of time in humans.[12] Thus, sevoflurane is an acceptable choice for comparison with propofol in the study conducted by Yoo *et al.*[10] and probably did not produce any nephrotoxicity that would have confounded their results.

Although propofol has historically been avoided in cardiac surgery patients, its use is becoming more widespread. Although the dosing and administration of propofol in their protocol was reasonable for this specific patient population, future studies to replicate the results of Yoo *et al.*[10] may be limited, especially in elderly patient populations and patients with more comorbid conditions, in whom administration of propofol could cause profound hemodynamic instability. Practical limitations such as the inability to measure propofol levels to ensure adequate amnesia and anesthesia and the potential for propofol to be absorbed into and clog the bypass circuit may further limit its widespread use.

A couple of caveats to the study are also worth noting. First, the overall rate of AKI was 37.5% in the control arm, which is similar to the rate observed in a recent large cohort study of patients undergoing cardiac surgery in the United States.[2] However, the population studied in this clinical trial was relatively healthy, as those with chronic kidney disease were excluded by design and the proportion of patients with diabetes, hypertension, and congestive heart failure was low. Thus, although there are no predictive models for milder forms of AKI, the predicted occurrence of AKI is probably lower than the 37.5% incidence observed in the control arm. Second, as others have demonstrated in simulation studies, given the small sample size, it is likely that the very large treatment effect observed is an overestimate of the actual effect that would be found in a larger patient population simply due to chance.[13] Finally, the proposed impact of propofol on AKI is attenuation of the inflammatory response in the setting of IRI. However, a similar effect has not been seen in other patient populations in whom IRI is thought to contribute to AKI, for example, cirrhotic patients who undergo liver resection. In a recent randomized controlled trial, Song *et al.* found no difference in postoperative renal function in cirrhotic patients who underwent liver resection randomized to receive sevoflurane or propofol as the principal anesthetic.[14]

In sum, Yoo *et al.*[10] conducted an elegant trial with a well-founded physiologic background and careful experimental design that allowed control of confounding variables and feasibility of replication in larger patient populations. While the results are provocative, limitations include the small sample size and a relatively healthy population that may not be generalizable to the entire cardiac surgery patient population. Prior prospective[15,16] and retrospective[17] studies have not shown a benefit with propofol (versus inhaled anesthetics) for AKI in the setting of cardiac surgery. However, given the observed large treatment effect and the limited options in treatment and prevention of AKI in the cardiac surgery setting, the trial conducted by Yoo *et al.*[10] warrants repeating and should be repeated before adoption of the routine use of propofol for anesthesia in cardiac surgery.

DISCLOSURE

LLH declared no competing interests. KDL has been a member of a Data Safety Monitoring Board for CytoPherx and a member of the Clinical Events Adjudication Committee for Astute. She has previously done consulting work for AbbVie, Chemocentryx, and Complexa. She owns stock in Amgen. She has received reimbursement for travel from the American Thoracic Society and the American Society of Nephrology. She has received gifts of reagents for biomarker assays from Abbott and CMIC. None of these conflicts of interest is relevant to the material discussed here.

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Insulin resistance in chronic kidney disease: a step closer to effective evaluation and treatment

Ian H. de Boer[1] and Rajnish Mehrotra[1]

Accurate measurements are needed to target insulin resistance in chronic kidney disease (CKD). Among older men with and without moderate CKD, Jia and colleagues compared insulin resistance estimated from glucose and insulin concentrations obtained while fasting or during an oral glucose tolerance test vs. insulin resistance measured by the gold-standard hyperinsulinemic euglycemic clamp and tested associations of each with mortality. These findings move forward the study of insulin resistance in CKD and generate new questions for future work.

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In 1931, Professor Wilhelm Falta published the theory that decreased sensitivity of target cells to the physiologic actions of insulin—in other words, insulin resistance—leads to the development of diabetes mellitus.[1] Insulin is the central hormone regulating glucose homeostasis and signaling the body that it has entered the fed state. After a meal, pancreatic β-cells secrete insulin in response to increased blood nutrient concentrations. Insulin then suppresses hepatic glycolysis and gluconeogenesis, inhibits lipolysis in adipose tissue, and stimulates skeletal muscle to take up glucose, all actions that shift nutrients from the circulation into cells (Figure 1). When the liver, adipose tissue, and muscle are resistant to these effects, the pancreas may secrete more insulin, thereby maintaining euglycemia at the expense of hyperinsulinemia. The failure of pancreatic β-cells to compensate for insulin resistance leads to overt type 2 diabetes. As decreased physical activity and obesity have led to widespread insulin resistance in developed countries, Falta's theory has proved correct, and an epidemic of diabetes has ensued.

Over time, it has become clear that insulin also has important effects beyond regulation of energy homeostasis. In particular, insulin resistance is closely coupled with mitochondrial dysfunction, generation of reactive oxygen species, endothelial dysfunction, and other cardiovascular risk factors (Figure 1). Though causal relationships among these processes are difficult to disentangle, insulin resistance may contribute to these harmful processes. Human studies suggest that these effects may be clinically relevant, with multiple observational cohort studies reporting associations of insulin resistance with increased risks of cardiovascular events and death.[2,3] Of additional interest to nephrologists, insulin has direct effects on multiple cells in the kidney. Induction of insulin resistance in podocytes leads to glomerulosclerosis in animal models, and insulin resistance is associated with albuminuria and the development of chronic kidney disease (CKD) in observational human studies.[4]

Building on work performed in the 1960s, DeFronzo and colleagues published a series of articles from 1978 to 1983 documenting severe insulin resistance in hemodialysis patients, specifically those without overt diabetes.[5] These studies used a technique called the hyperinsulinemic euglycemic clamp to directly measure whole-body glucose uptake in response to an insulin stimulus. Using the euglycemic clamp and related techniques, DeFronzo and others demonstrated that end-stage renal disease patients are very insulin resistant, that the site of insulin resistance is localized to skeletal muscle, and that insulin resistance partially improves with dialysis.[5] Recent studies have identified specific uremic toxins that may mediate this effect, including gut-derived molecules such as *p*-cresyl sulfate.[6] These observations, coupled with the epidemiology of insulin resistance and cardiovascular disease described above,

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